Synthesis and binding properties of chiral macrocyclic barbiturate receptors: application to nitrile oxide cyclizations

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A series of chiral macrocyclic receptors containing a barbiturate binding domain based on two 2,6-diaminopyridine groups has been synthesized with the purpose of exploiting these for asymmetric 1,3-dipolar cycloadditions. Each macrocyclic host was built possessing an (*R*)-BINOL or a modified deoxycholate moiety as the chiral unit connected to the barbiturate binding domain with varying lengths of spacer. All the hosts with the exception of one were found to effectively bind a barbiturate–cinnamic acid conjugate with association constants in the order of 10^4 M^{-1} in $CDCl_3$. The 1,3-dipolar cycloaddition between several arylnitrile oxides and the cinnamate conjugates were examined in the presence of stoichiometric amounts of a chiral receptor affording two regioisomeric isoxazolines. Enantiomeric excesses of up to 30% were obtained in one case for the major regioisomer. In most cases, the enantiomeric excesses could be measured directly from the crude ^{1}H-NMR spectra owing to the diastereomeric interaction between the isoxazoline cycloadduct and the chiral receptor. The relatively low enantiofacial selectivities at the C=C double bond of the cinnamate were attributed to the non-planar orientation of the barbiturate–cinnamate conjugate with respect to the receptor, as previously noted for the binding of barbital† to an achiral macrocyclic host (S.-K., Chang, E. Fan, D. Van Engen and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 7640), directing the cinnamate unit away from the chiral unit.

Introduction

A principal binding mode between a substrate undergoing chemical transformation and an enzyme, involves recognition through multiple weak intermolecular interactions such as hydrogen bonding. This recognition event allows for a strong geometrically defined association of the substrate in the enzyme such that any activation or reaction with other active site functional groups becomes pseudo-intramolecular, thereby greatly increasing the rate of the process. Whereas, there is ample literature precedence concerning studies using synthetic receptors capable of binding ligands with high association constants *via* multiple hydrogen bonding (*i.e.* molecular recognition);[1] more spectacular applications include the design of such systems for promoting organic synthetic transformations.[2]

The application of such receptors would be highly advantageous.[3] The fixed orientation of the substrate in the receptor would allow organic reactions to become regioselective; the selectivity is not only determined by intrinsic directive properties of the substrate itself but also by its orientation in the receptor. This trait is a particularly important property of many enzymatic reactions. By designing a chiral receptor, it may also allow one face of the bound substrate to be shielded thus directing the desired reaction to occur at only one of the two enantiotopic faces of an achiral substrate. In other words, chirality is transferred from the receptor to the substrate.

An interesting host–guest system based on multiple hydrogen bonding is represented by Hamilton's previously reported complex of barbital **1** to the macrocyclic receptor or host, **2**, consisting of two 2,6-diaminopyridine units forming a cavity for **1** (Scheme 1).[4] The **2** : **1** complex, exhibiting six hydrogen bonding interactions as revealed by its X-ray crystal structure, was found to possess a strong association constant (2.5×10^5 M^{-1} in CH_2Cl_2).[4d] Because of this effective binding, numerous applications exploiting this host–guest system have therefore been put forth including models for transacylase enzymes,[4c,5] organic gels,[6] systems for the sensitive detection of barbiturates though fluorescence change, [4b,7] models for studying electron transport,[8] and others.[9]

In this work, we examine the possibility of employing chiral receptors containing the same binding motif as the macrocyclic receptor **2** for asymmetric synthesis. In particular, various macrocyclic chiral hosts **3a**–**c**, **4**, **5** and **6** have been synthesized for the first time incorporating a (*R*)-BINOL or a C3,C3′-disubstituted (*R*)-BINOL unit, as well as a modified deoxycholic acid, as illustrated in Fig. 1. The ability of these hosts to bind a barbiturate–cinnamic acid conjugate has then been examined. It is our expectation that upon binding, the orientation of the barbiturate conjugate in the chiral host will place the cinnamate moiety proximate to the chiral environment, hence shielding one face of the C=C double bond. To study this shielding effect, well-known 1,3-dipolar cycloadditions[10–12] employing arylnitrile oxides have been performed with a receptor bound cinnamate moiety, the results of which are discussed below.

Results and discussion

Synthesis of the chiral receptors and the barbiturate–cinnamic acid conjugate

The BINOL-macrocycles **3a**–**c** and **4** were synthesized employing a similar procedure reported for the preparation of receptor **2**. In these receptors, the length of the spacer between the binding motif and the chiral unit has been varied in order to identify a host with the best binding properties for the barbiturate–cinnamate conjugate, as well as with the appropriate length for the proper placement of the cinnamate moiety with respect to the chiral unit.

† The IUPAC name for barbital is 5,5-diethylbarbituric acid.

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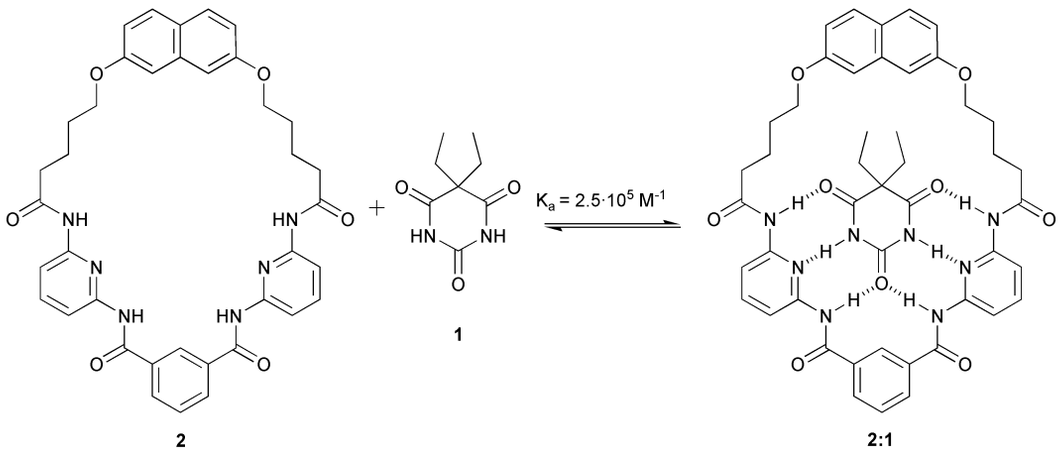
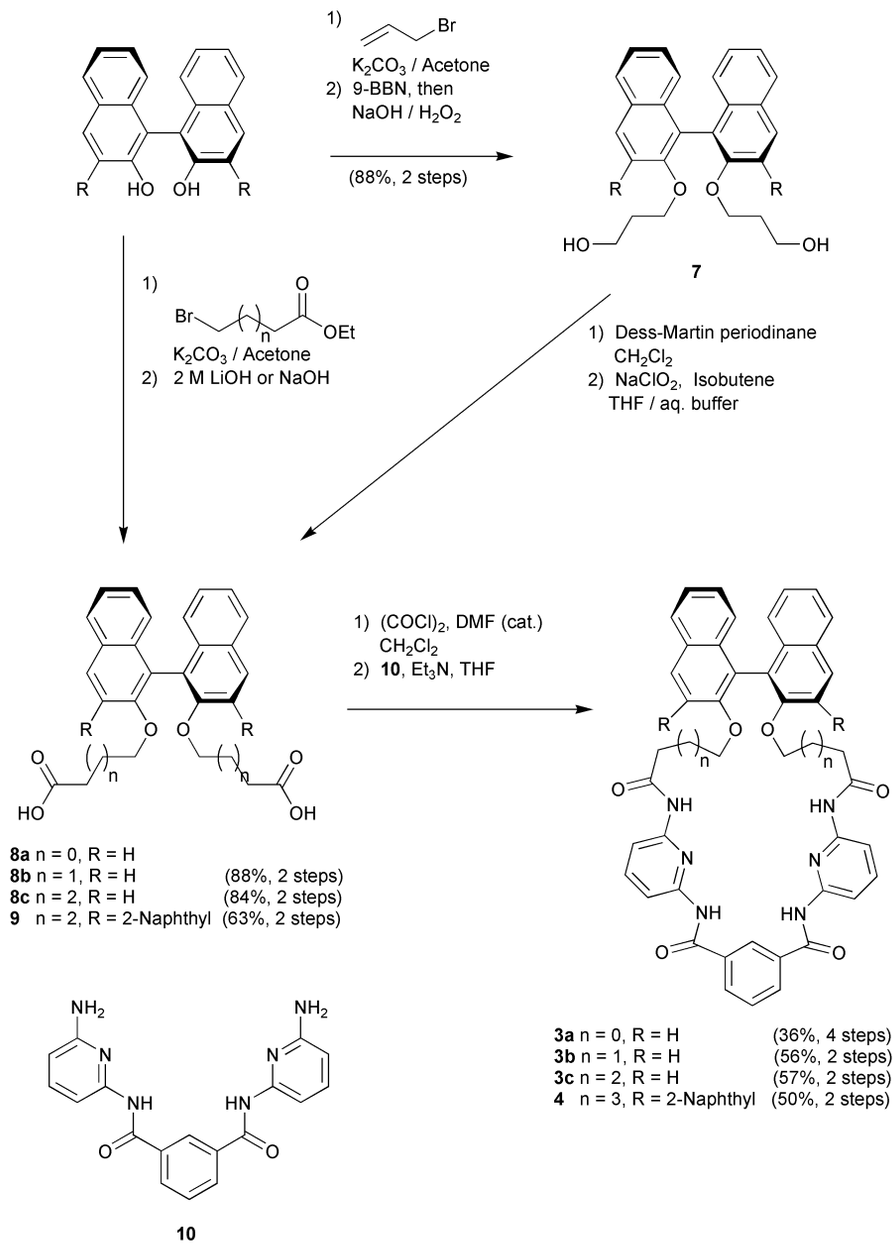
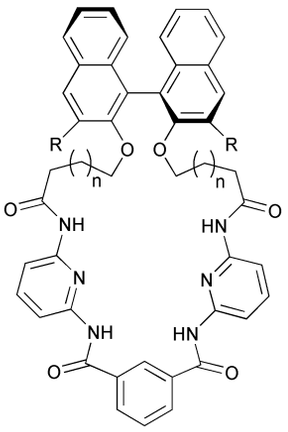


Scheme 1

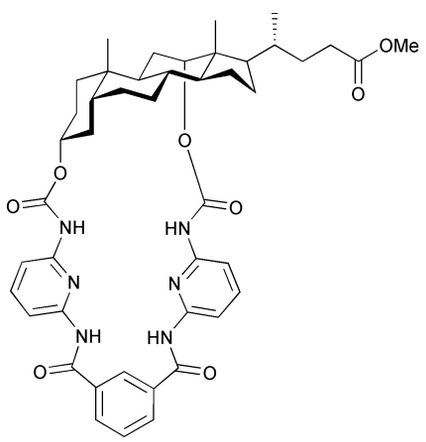


Scheme 2

Preparation of the diacid **8a** started with the diallylation of (*R*)-BINOL[13] with allyl bromide in the presence of potassium carbonate (Scheme 2). Subsequent hydroboration with 9-BBN and accompanying oxidation afforded the diol **7** in 88% overall yield for the two steps. Conversion of the diol to the dicarboxylic acid **8a** was achieved by oxidation to the dialdehyde using the Dess–Martin periodinane[14] and then finally to the diacid with sodium chlorite. The homologs of this diacid, **8b**



3a n = 0, R = H
3b n = 1, R = H
3c n = 2, R = H
4 n = 2, R = 2-Naphthyl



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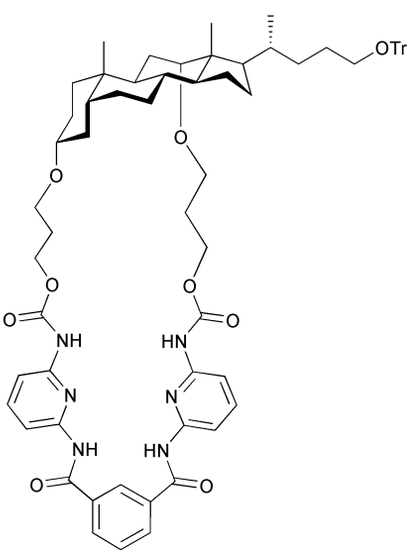

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Fig. 1 Chiral barbiturate binding macrocycles.

and **8c**, were easily prepared in two steps by alkylation of BINOL with ethyl 3-bromobutyrate or 5-bromovalerate, respectively, and then subsequent hydrolysis. Macrocyclization proved successful by first converting the diacids to their corresponding diacid chlorides (oxalyl dichloride, DMF, CH_2Cl_2) and then subjecting them to one equivalent of the readily available diamine **10**[4d] in THF under high dilution conditions in the presence of triethylamine. In this way, the crystalline chiral receptors **3a**–**3c** were secured in good yields from 36–57% for the two steps, after column chromatography. A similar sequence of events was used for the synthesis of the chiral host **4** embodying a 3,3′-dinaphthyl–BINOL unit, itself prepared in 6 steps from (*R*)-BINOL employing a Pd(0)-catalyzed Suzuki coupling reaction as the prime step.[15]

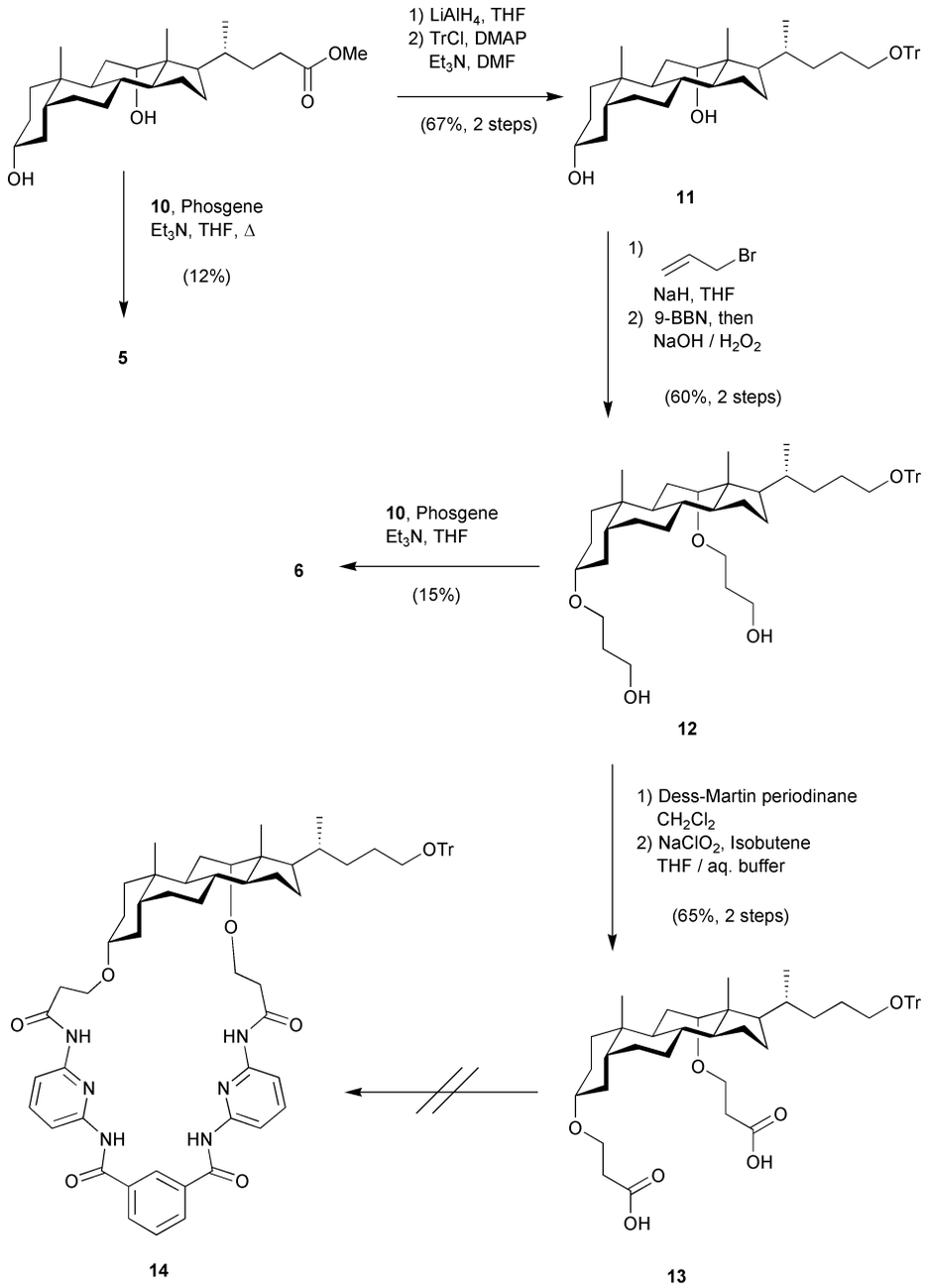
The spacial arrangement of the two secondary hydroxy groups in deoxycholic acid (distance = 6 Å)[16] suggested the possibility of exploiting this steroid for the generation of a chiral but non-*C*2-symmetrical macrocyclic barbiturate binding receptor. To achieve this goal, the corresponding methyl ester was reduced and tritylated to afford the monoprotected triol **11** (Scheme 3). Subsequent chain extension proceeded as previously described for the synthesis of the macrocycle **3a** affording the dicarboxylic acid **13**. Nevertheless, several attempts to promote the cyclization under high dilution conditions between the corresponding acid chloride of **13** with diamine **10** only led to trace amounts of the desired macrocycle **14**. Reversing the roles of the acylating agent, however proved more rewarding. Hence, treatment of the diamine **10** with phosgene and triethylamine followed by the slow addition of the diol **12** at room temperature resulted in a 15% yield of the macrocyclic dicarbamate **6**.[17] Encouraged by this result we could likewise extend this cyclization approach to the synthesis of the smaller macrocycle **5** in 12% yield in one step from methyl deoxycholate. In this latter case, it was necessary to slowly add the methyl deoxycholate to a refluxing solution of the phosgene-pretreated diamine in order to obtain the desired macrocycle. In contrast, fast addition of the steroid only led to a product composed of the diamine **10** coupled to two deoxycholate units according to ES-MS, whereas attempted ring formation at room temperature afforded no cyclic products signalling a high ring tension in this small macrocyclic structure. Effort was also made to prepare **5** by the direct coupling of the diamine **10** with the crystalline bis(imidazolylcarbonyl) functionalized deoxycholate,[18] although in vain.

With the chiral hosts in hand, the barbiturate–cinnamate substrates were then accessed from the readily available 5-isopropyl-, 5-methyl- and 5-phenyl- barbituric acids **15a**–**c** as shown in Scheme 4.[19] Introduction of a linker for the cinnamic acid was easily achieved by subjecting **15a**–**c** to aqueous formaldehyde under acidic conditions affording the primary alcohols **16a**,**c** in high yields, whereas the greater water solubility of **16b** resulted in a reduced yield.[20] Although base-promoted acylation with cinnamoyl chloride only led to concomitant deformylation, refluxing a THF solution of **16a**–**c** with excess acid chloride generated the desired esters **17a**–**c** in good yields of 82–90%.

Binding properties of the chiral receptors

Our first concern was whether the chiral hosts could effectively bind to complementary barbiturate substrates, being a prerequisite for the subsequent asymmetric dipolar cycloaddition studies. Titration experiments in $CDCl_3$ were therefore performed between the receptor and substrate measuring the characteristic large downfield shifts of the host's amide NH's (approx. 1.5 ppm) as a function of the barbiturate concentration. From the titration curve, the association constant (K_a) can therefore be extracted according to that previously reported.[4d] Although, there is some uncertainty associated with the measured values of K_a higher than 10^4 M^{-1} employing NMR techniques,[21] the precision is nevertheless adequate for our purposes, providing us with a general idea of the percentage of binding.

The association constants found are shown in Table 1. The known receptor **2** has previously been reported to bind barbital **1** with a K_a value of 2.5×10^5 M^{-1} in CH_2Cl_2.[4d] Through titration studies and curve fitting, it was satisfying to see that a similar result was also obtained with barbital and the host **3c** which displays the closest resemblance to **2**.[22,23] In spite



Scheme 3

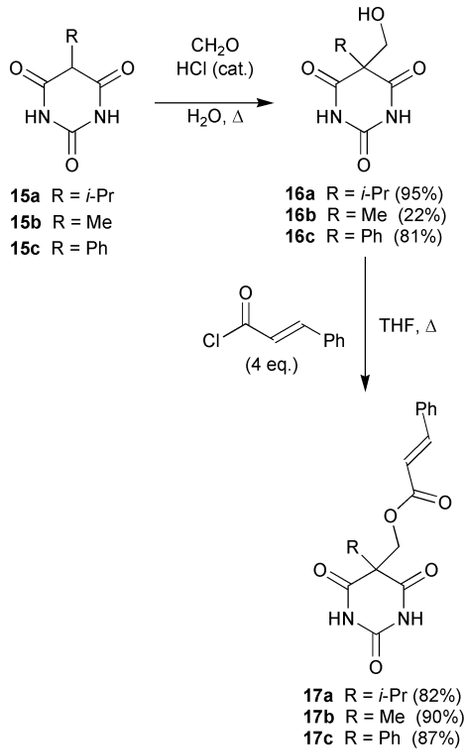
Table 1 Association constants for receptors **3a**–**3c**, **4** and **6** with barbiturate substrates

Receptor	Substrate	K_a (M^{-1})[a]
3a	**17a**	1.1×10^3
3b	**17a**	1.6×10^4
3c	**17a**	7.0×10^4
3c	**1**	2.2×10^5
4	**17a**	3.6×10^4
6	**17a**	5.2×10^4

[a] All association constants were measured employing titration experiments in $CDCl_3$.

of the fact that a small decrease in the K_a was noted for the barbiturate conjugate **17a** ($K_a = 7.0 \times 10^4$ M^{-1}), being the sterically most demanding of the three barbiturates synthesized, this value was still sufficiently high and encouraging for subsequent studies. Measurements made with this conjugate and receptors **3a** and **3b**, revealed a slight decrease in the binding constant, possibly owing to the smaller ring size and hence more rigid nature of these hosts. The deoxycholate containing macrocycle **6** also proved satisfactory, displaying an affinity for **3c** with $K_a = 5.2 \times 10^4$ M^{-1}.

It was somewhat surprising to see that the smaller counterpart to **6**, namely the receptor **5**, appears to bind two molecules of **3c**. This was demonstrated through the application of a standard protocol, the Job method, for the stoichiometry determination between a receptor (R) and its ligand (L).[1b] As illustrated in Fig. 2, the complexation stoichiometry is easily determined at the maximum, obtained by plotting at a fixed total concentration ([R] + [L]), the observed change in the chemical shift of the amide or carbamate protons ($\Delta\delta$(NH)) of the receptor, multiplied by the mole fraction, $x = [R]/([R] + [L])$, as a function of the mole fraction, x.[24] As seen with the receptor **3c**, the peaks of the curves are observed at a mole fraction of 0.5 indicating a 1 : 1 stoichiometry for the complex as expected. On the other hand, the macrocycle **5** reveals a maximum at approx. 0.38 suggesting that in this case two of the barbiturate conjugates are recognized and bound by the same receptor. As to the mode of this binding, we can only speculate that the small ring size and steric congestion of the deoxycholate



Scheme 4

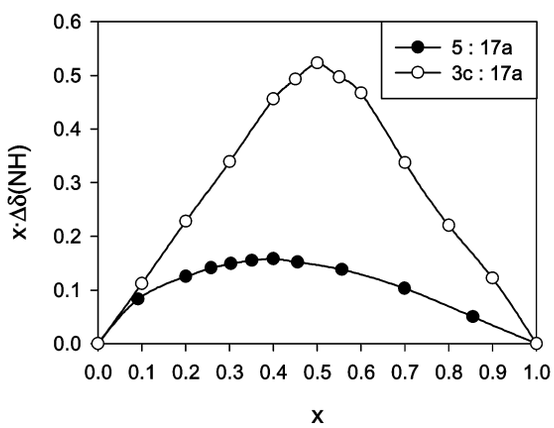


Fig. 2 Job plots of receptors **3c** and **5** with the barbiturate **17a**. See text for further discussion.

fragment in **5** arranges the two pyridyl units in a coplanar orientation upon binding rather than both occupying the same plane. Hence, each diaminopyridine unit binds separately to a barbiturate *via* a hydrogen bonding network consisting of only three contact points rather than the usual six.[25]

The barbiturate conjugates **17b** and **17c** proved to be only slightly soluble in either of the two solvents dichloromethane or deuteriochloroform. Whereas, the association constants were not measured with the above chiral receptors, we have noted that in the presence of one equivalent of the macrocycle **3c** a clear solution was obtained in the deuteriochloroform, suggesting complexation is also achieved with these barbiturates.

Studies of the nitrile oxide addition to the barbiturate–cinnamate conjugate in the presence of chiral receptors

To evaluate the ability of the synthetic receptors to transfer chirality to the barbiturate–cinnamic acid conjugate, 1,3-dipolar cycloadditions were studied between an arylnitrile oxide and the cinnamoyl group of **17a–c** in the presence of a stoichiometric quantity of the hosts **3a–c** and **4–6**.[10e,26] As the above titration experiments clearly demonstrated the ability of the conjugate to bind well to the prepared receptors, it was anticipated that the cinnamoyl fragment would be oriented in close proximity to the asymmetric unit, thereby shielding one of the two enantiotopic faces of the C=C double bond (Fig. 3).

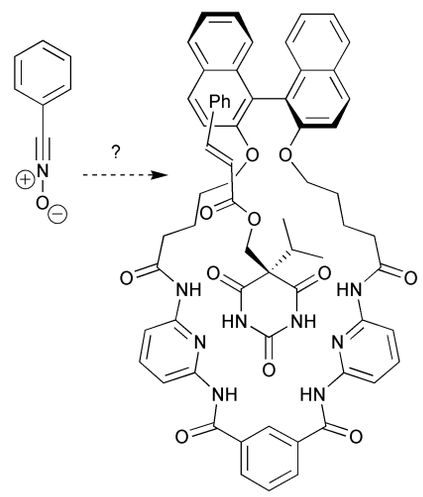
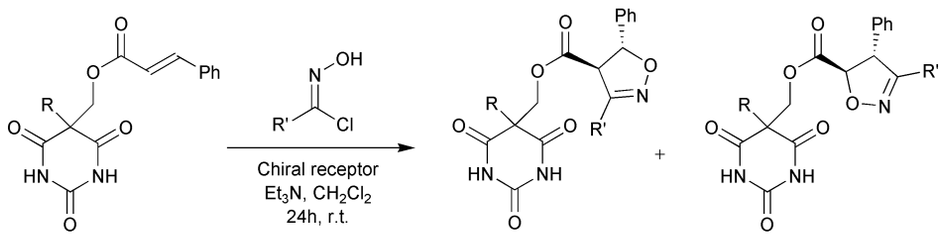


Fig. 3 Addition of benzonitrile oxide to a receptor bound cinnamate–barbiturate conjugate.

The results of this study are depicted in Table 2. The cycloaddition of the cinnamoyl derivative **17a** with benzonitrile oxide, generated *in situ* from the corresponding chlorooxime upon addition of one equivalent of triethylamine, performed well in the absence of a receptor affording a racemic mixture of the two regioisomeric 2-isoxazolines **18a** and **19a** in 95% yield and in a 5.5 to 1 ratio in favor of the 5-phenyl isomer **15a** (entry 1). This ratio is similar to the 4 : 1 ratio for similar isoxazolines prepared from the addition of benzonitrile oxide to methyl cinnamate in EtOAc.[27] Repetition of the cycloadditions in the presence of a chiral host was carried out by first premixing the receptor with the substrate and stirring for 15 min in CH_2Cl_2 allowing complexation to occur, followed by the addition of Et_3N and the chlorooxime. After stirring for 24 hours at room temperature the reaction was stopped and separation of products **18** and **19** from the receptor could be accomplished by flash chromatography. Typically 85–95% of the chiral host was recovered and a conversion of approximately 50–70% of the cinnamate conjugate was observed. Although, it was expected that the presence of the triethylamine would have some influence on the binding of the barbiturate to the host, it has previously been shown that small amounts of base do not significantly perturb the binding constants for these hydrogen bonding interactions.[9b]

In the reaction between cinnamate **17a** and benzonitrile oxide in the presence of receptor **3a** or **3b**, no enantioselective induction was observed in either of the products **18a** or **19a** as determined by chiral HPLC analysis (entries 2 and 3). Nevertheless, an approximate two fold decrease in the regioselectivity of the cycloaddition was noted for these receptors compared to the same reaction in the absence of the host. On the other hand, with the more flexible receptor **3c**, the cycloadduct **18a** could be isolated possessing a low but measurable enantiomeric excess of 17%, whereas its regioisomer **19a** proved to be racemic (entry 4). The choice of solvent proved critical as no asymmetric induction in **18a** was observed when the cycloaddition reaction was performed in THF (entry 5). Expecting an increase in the enantioselectivity upon use of host **4** possessing both C3,C3′-substitutents on the BINOL unit, it was somewhat surprising to isolate only racemic **18a** upon completion of the cycloaddition (entry 6) considering the ability of the barbiturate conjugate to effectively bind to **4** (Table 1).

Table 2 Results of cycloaddition of nitrile oxides to the host–guest complexes of the cinnamate conjugates **17a**–**17c**[a]



17a R = *i*-Pr
17b R = Me
17c R = Ph

18a	R = *i*-Pr, R' = Ph	**19a**
18b	R = *i*-Pr, R' = 4-*t*-Bu-phenyl	**19b**
18c	R = *i*-Pr, R' = 2-Naphthyl	**19c**
18d	R = Me, R' = 2-Naphthyl	**19d**
18e	R = Ph, R' = 2-Naphthyl	**19e**

Entry	Chiral receptor	R	R′	Yield (%)[b]	Ratio **18** : **19**	Ee of **18** (%)[c]
1	—	*i*-Pr	Ph	95	5.5 : 1	—
2	**3a**	*i*-Pr	Ph	71 (96)	3.3 : 1	<5
3	**3b**	*i*-Pr	Ph	67 (86)	2.7 : 1	<5
4	**3c**	*i*-Pr	Ph	66 (94)	4.0 : 1	17
5[d]	**3c**	*i*-Pr	Ph	84	3.7 : 1	<5
6	**4**	*i*-Pr	Ph	61 (82)	3.1 : 1	<5
7	—	*i*-Pr	4-*t*-Bu-phenyl	44 (81)	2.2 : 1	—
8	**3c**	*i*-Pr	4-*t*-Bu-phenyl	65 (86)	3.1 : 1	15
9	—	*i*-Pr	2-Naphthyl	69 (75)	2.7 : 1	—
10	**3c**	*i*-Pr	2-Naphthyl	75 (81)	3.7 : 1	31
11	—	Me	2-Naphthyl	65 (91)	4.5 : 1	—
12	**3c**	Me	2-Naphthyl	80	11 : 1	12
13	—	Ph	2-Naphthyl	~0	—	—
14	**3c**	Ph	2-Naphthyl	57 (91)	3.2 : 1	14
15	**5**	*i*-Pr	2-Naphthyl	54 (70)	2.4 : 1	5
16	**6**	*i*-Pr	2-Naphthyl	—[e]	2.6 : 1[f]	13

[a] Only one of the two enantiomers of the chiral isoxazolines is illustrated. [b] Yields in parantheses are corrected based on recovered starting material **17a**–**c**. [c] Ee of regioisomers **19a**–**e** in all cases low. [d] Reaction run with THF as solvent. [e] Not determined due to problems of separation from host. [f] Ratio determinded by HPLC

The effect on the asymmetric induction in the cycloadditions with the host **3c** and the cinnamate **17a** was also examined employing bulkier 1,3-dipoles, such as the 4-(*t*-Bu)benzo and the 2-naphthonitrile oxides (entries 7 and 9). With the latter, a substantial increase in the enantiomeric excess was observed with the formation of the cycloadduct **18b** possessing a 31% ee (entry 10), whereas no increase was noted in the isoxazoline product **18e** from 4-(*t*-Bu)benzonitrile oxide (entry 8).[28] Subsequent studies were therefore carried out with the 2-naphthonitrile oxide.

It is interesting to note that of the two barbiturate–cinnamate conjugates **17b** and **17c**, the latter displays limited solubility in CH_2Cl_2, resulting in no production of cycloadducts when the reaction was performed in the absence of a receptor (entries 11 and 13). However, in the presence of one equivalent of the macrocycle **3c**, the products **18d**,**e** and **19d**,**e** were isolated in combined yields of 80% and 57% (entries 12 and 14). In these cases, both **18d** and **18e** furnished lower enantiomeric excesses of approx 13% ee suggesting different binding modes for these cinnamate conjugates in the host **3c** compared to **18a**. Surprisingly, with the barbiturate **17b** a profound influence on the regioselectivity (>10 : 1) was observed (entry 12). Nonetheless, these latter results lead to the important conclusion that at least with receptor **3c**, the cycloadditions are indeed taking place with a barbiturate–cinnamate–receptor complex and not only with unbound **17** in equilibrium with the bound complex **17**–**3c**.

Finally, the cycloaddition reactions carried out on the conjugate **17c** and 2-naphthonitrile oxide were also examined in the presence of the deoxycholate based receptors **5** and **6** (entries 15 and 16). Only in the latter case was a notable enantiomeric excess observed for the major regioisomer, the preference of which proved to be the same as that observed for the host **3c**.

As a final remark to the cycloaddition studies, it is interesting to note our ability to directly measure the enantiomeric excesses of the cycloadducts **18** from the ^{1}H-NMR spectra of the crude reaction mixtures due to the diastereomeric interaction of the barbiturate–isoxazoline conjugates with the chiral receptors. In general, both protons at either C4 or C5 of each of the enantiomeric isoxazoline products in the presence of the receptor could be identified on the ^{1}H-NMR spectrum, whereafter the enantiomeric excess was determined by simple integration. This is illustrated in Fig. 4 in the analysis of the reaction between the 2-naphthonitrile oxide and cinnamate **17a**. In the absence of a receptor, both the C4 and C5 of the isoxazoline product **18d** are found as doublets at 5.97 and 4.53 ppm, respectively (Fig. 4a). When the reaction is performed in the presence of receptor **3c** sufficient line separation of the C5-protons is observed and an enantiomeric excess of approx. 30% can be measured, corresponding to the 31% obtained by HPLC. On the other hand, with receptor **5** the C4-protons are separated showing approximately a 5% ee for the cycloadducts **18d**.

A potential explanation for the relatively low enantioselectivities observed in these 1,3-dipolar cycloadditions may be sought from a previous X-ray structure of a host : barbital complex (**2** : **1**).[4d] In this structure, the barbital is not in a coplanar orientation with respect to the macrocycle, but is tilted at an angle of 27° relative to the plane of the pyridine rings. Recently, two other receptor : barbiturate structures have been reported revealing the same tendency.[29] This non-coplanarity was attributed to the narrowness of the binding cavity and unfavorable interactions between the isophthaloyl C2-proton and the barbital C2-carbonyl group. As a consequence of this orientation one of the two ethyl groups of barbital is projected away from, and at an approximate 90° angle to the naphthyl

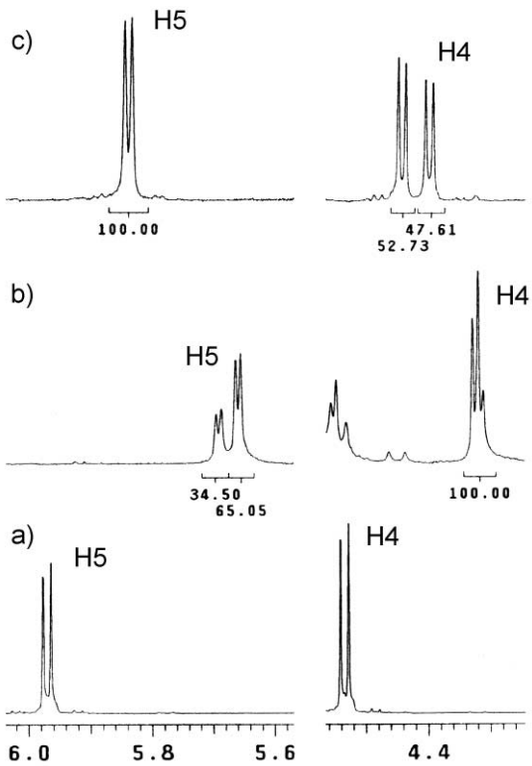


Fig. 4 ^{1}H-NMR spectra (400 MHz) of crude cycloaddition reaction mixtures displaying the H4 and H5 protons of the oxazoline ring of **18d**. a) Reaction between 2-naphthonitrile oxide and **17a** in the absence of receptor (Table 2, entry 9); b) the same reaction with receptor **3c** (Table 2, entry 10); c) the same reaction with receptor **5** (Table 2, entry 15).

ring. It is more than likely that the same non-coplanarity will be observed with the barbiturate–cinnamate conjugates and the chiral macrocyclic hosts synthesized, which may even be amplified by the possibly smaller size of their binding cavity compared to receptor **2** due to both the lengths of the linkers and the smaller distance between the two connecting oxygens in BINOL and deoxycholate compared to 2,7-dihydroxynaphthalene. Unfortunately, we have not been able to obtain suitable crystals of any of these complexes for X-ray structural analysis. However, if the cinnamate moiety is also oriented in an approx. 90° angle to the receptor upon binding of the conjugate to these hosts, the influence of the chiral unit may be small upon reaction with the arylnitrile oxides. Support for this hypothesis may also be sought from the absence of any enantioselectivity observed in the formation of the regioisomeric isoxazolines **19**. It was initially assumed that this regioisomer would reveal the highest ee upon cyclization as the aryl fragment of the nitrile oxide was anticipated to be in close contact with the chiral subunit.[30] However, this cyclization mode would place the aryl fragment even further away from the chiral unit compared to that in the formation of the isoxazolines **18**.

Experimental

General Methods

NMR spectra (^{1}H at 200 MHz and ^{13}C at 50 MHz) were recorded on a Varian Gemini 2000 spectrometer. Chemical shifts (δ in ppm) are given relative to those for Me_4Si; *J*-values are given in Hz. ES mass spectra were recorded with a Micromass LC-TOF instrument. TLC was performed on Kieselgel 60 F_{254} (Merck). Dichloromethane was freshly distilled from calcium hydride, THF from sodium–benzophenone, whereas DMF was distilled under reduced pressure and stored over 4 Å molecular sieves. The diamine **10** was prepared following a previously published procedure.[4d] Enantiomeric excesses were determined by HPLC on a Chiralpak AD column using *n*-hexane–isopropanol mixtures as eluent. The specific optical rotations were measured in units of 10^{-1} deg cm^2 g^{-1}. The ^{1}H-NMR binding studies and the Job plots were performed employing standard methods.[31]

(*R*)-2,2′-Bis(3-hydroxypropoxy)-1,1′-binaphthyl (7)

A mixture of (*R*)-BINOL (573 mg, 2.00 mmol), allyl bromide (968 mg, 8.00 mmol) and K_2CO_3 (829 mg, 6.00 mmol) was refluxed for 2 hours in dry acetone (12 mL). The solvent was removed under vacuum and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried with Mg_2SO_4 and evaporated to give the di-*O*-allylated BINOL as a white powder (724 mg, 99%).

The crude allyl ether was redissolved in dry THF (10 mL), 9-BBN (5.0 mL, 2.5 mmol, 0.5 M in THF) was added and the solution was stirred for 1 hour at 20 °C. After cooling in an ice bath, 33% aqueous NaOH (2.0 mL) and 35% aqueous H_2O_2 (2.0 mL) were carefully added and the mixture was refluxed for 1 h. The solution was partitioned between ether and brine, and the aqueous phase was extracted once more with ether. The combined organic phases were dried (Mg_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2 : acetone, 9 : 1 to 7 : 1) to give **7** as a white powder (703 mg, 88%); δ_H ($CDCl_3$) 1.48–1.74 (4H, m, 2 × –CH_2–), 2.43 (2H, br s, 2 × –OH), 3.18–3.30 (4H, m, 2 × –C*H*$_2$OH), 3.95–4.22 (4H, m, 2 × –CH_2OAr), 7.08–7.34 (6H, m, ArH), 7.41 (2H, d, *J* 8.8, ArH), 7.84 (2H, br d, *J* 8.1, ArH), 7.94 (2H, d, *J* 8.8, ArH); δ_C ($CDCl_3$) 31.8, 59.9, 67.4, 114.7, 119.6, 123.7, 125.0, 126.3, 127.9, 129.2, 129.5, 133.7, 153.7; HR-MS (ES) calc. for $C_{26}H_{26}O_4Na$ (M + Na): 425.1729, found 425.1724.

(*R*)-2,2′-Bis(2-carboxyethoxy)-1,1′-binaphthyl (8a)

Diol **7** (559 mg, 1.39 mmol) was stirred with the Dess–Martin periodinane (1.41 g, 3.33 mmol) in CH_2Cl_2 (10 mL) for 30 minutes. The organic phase was shaken with aqueous $NaHCO_3$ (sat.), containing 5 g of $Na_2S_2O_3$, until both phases became clear. The organic phase was separated and washed with aqueous $NaHCO_3$ (sat.) followed by H_2O, and then dried (Mg_2SO_4) and evaporated to dryness to give the crude dialdehyde.

The dialdehyde was redissolved in *t*-BuOH (50 mL), and isobutylene (*ca.* 10 g) in THF (100 mL) was added together with $NaClO_2$ (1.51 g, 13.8 mmol) and $NaH_2PO_4{\cdot}H_2O$ (0.96 g, 6.94 mmol) in water (20 mL). The mixture was stirred for one hour and the solvent was removed under vacuum. The residue was dissolved in 2 M NaOH, acidified with 1 M HCl, and the precipitate was filtered off and dried giving **8a** as a slightly yellow solid (593 mg, 99%) which was used without further purification for the macrocyclization step; δ_H (acetone-d_6) 2.43 (4H, t, *J* 6.5, 2 × –C*H*$_2$COOH), 4.16–4.36 (4H, m, 2 × –CH_2O–), 7.01–7.32 (6H, m, ArH), 7.54 (2H, d, *J* 9.0, ArH), 7.86 (2H, br d, *J* 7.9, ArH), 7.96 (2H, d, *J* 9.0, ArH), 9.0 (2H, br s, 2 × –COOH); δ_C (acetone-d_6) 35.9, 67.0, 117.5, 121.9, 125.2, 126.9, 127.8, 129.7, 131.1, 131.2, 135.7, 156.0, 174.2; HR-MS (ES) calc. $C_{26}H_{22}O_6Na$ (M + Na): 453.1314, found 453.1309.

(*R*)-2,2′-Bis(3-carboxypropoxy)-1,1-binaphthyl (8b)

A mixture of (*R*)-BINOL (572 mg, 2.00 mmol), ethyl 4-bromobutyrate (1.25 g, 6.0 mmol) and K_2CO_3 (1.12 g, 8.0 mmol) was refluxed in dry acetone (25 mL) for two days. The solvent was removed under vacuum, and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried with Mg_2SO_4 and evaporated to dryness. Purification by flash chromatography (pentane : ethyl acetate, 7 : 1) gave a quantitative yield of the diethyl ester of **8b**.

The diester was redissolved in a 1 : 1 mixture of 2 M NaOH and EtOH (20 mL) and refluxed overnight followed by removal of the solvent under vacuum. The residue was dissolved in

water, which was then acidified with 1 M HCl. The precipitate formed was filtered off and triturated with acetone to give **8b** as an off-white solid (809 mg, 88%); $[\alpha]_D^{25}$ = +55.6 (*c* = 1.0, THF); δ_H (acetone-d_6) 1.59–1.75 (4H, m, 2 × –CH_2–), 1.92–2.04 (4H, m, 2 × –C*H*$_2$COOH), 3.96–4.14 (4H, m, 2 × –CH_2O–), 7.01–7.32 (6H, m, ArH), 7.53 (2H, d, *J* 9.0, ArH), 7.87 (2H, br d, *J* 7.9, ArH), 7.98 (2H, d, *J* 9.0, ArH); δ_C (acetone-d_6) 26.4, 31.1, 69.8, 117.1, 121.8, 125.2, 126.8, 127.9, 129.8, 131.1 (2C), 135.8, 156.0, 175.9; HR-MS (ES) calc. $C_{28}H_{26}O_6Na$ (M + Na): 481.1627, found 481.1622; IR (KBr) 2939, 1706, 1263 cm^{-1}.

(*R*)-2,2′-Bis(4-carboxybutoxy)-1,1′-binaphthyl (8c)

In a procedure similar to that of **8b**, (*R*)-BINOL (1.14 g, 4.00 mmol), ethyl 5-bromovalerate (2.34 g, 12.0 mmol) and K_2CO_3 (2.21 g, 16.0 mmol) gave the diethyl ester of **8c**, which was hydrolyzed and then recrystallized from acetone to give **8c** as colorless crystals (1.63 g, 84%); mp = 156–157 °C; $[\alpha]_D^{25}$ = +47.1 (*c* = 1.0, THF); δ_H (acetone-d_6) 1.24–1.56 (8H, m, 4 × –CH_2–), 2.02 (4H, t, *J* 7.3, 2 × –C*H*$_2$COOH), 3.96–4.14 (4H, m, 2 × –CH_2O–), 7.06 (2H, br d, *J* 8.1, ArH), 7.16–7.35 (4H, m, ArH), 7.55 (2H, d, *J* 8.8, ArH), 7.90 (2H, br d, *J* 7.3, ArH), 8.01 (2H, d, *J* 8.8, ArH), 10.3 (2H, br s, ArH); δ_C (DMSO-d_6) 20.6, 28.1, 32.9, 68.0, 115.3, 119.0, 123.1, 124.4, 126.0, 127.8, 128.6, 129.0, 133.3, 153.7, 174.1; HR-MS (ES) calc. for $C_{30}H_{30}O_6Na$ (M + Na): 509.1940, found 509.1937; IR (KBr) 2927, 1706, 1230 cm^{-1}.

(*R*)-3,3′-Di-2-naphthyl-2,2′-bis(4-carboxybutoxy)-1,1′-binaphthyl (9)

A mixture of (*R*)-3,3′-di-2-naphthyl-BINOL (140 mg, 0.26 mmol), ethyl 5-bromovalerate (209 mg, 1.00 mmol) and K_2CO_3 (138 mg, 1.00 mmol) was refluxed in dry acetone (4 mL) overnight. The mixture was partitioned between CH_2Cl_2 and water, and the organic layer was separated and dried with Mg_2SO_4 followed by evaporation to dryness. Purification by flash chromatography (pentane : ethyl acetate, 10 : 1) gave the functionalized ester of **9** (177 mg, 86%) as a colorless oil, which was hydrolyzed by refluxing overnight in a 1 : 1 mixture of 2 M NaOH and EtOH (8 mL). The solvent was removed under vacuum and the residue was redissolved in water. After acidification with 1 M HCl and extraction with EtOAc (2×), the combined organic layers were dried with Mg_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2 : acetone, 10 : 1) to give **9** as a colorless oil (107 mg, 56% overall); δ_H ($CDCl_3$) 0.80–1.19 (8H, m, 4 × –CH_2–), 1.65 (4H, t, *J* 6.8, 2 × –C*H*$_2$COOH), 3.15–3.29 (2H, m, 2 × –CH*H*′O–), 3.43–3.57 (2H, m, 2 × –C*H*H′O), 7.22–7.53 (10H, m, ArH), 7.83–8.01 (10H, m, ArH), 8.10 (2H, s, ArH), 8.53 (2H, s, ArH), 10.5 (2H, br s, 2 × –COOH); δ_C ($CDCl_3$) 20.5, 28.8, 32.9, 71.9, 124.9, 125.8, 125.9, 126.0, 126.2, 127.4, 127.5, 127.7, 127.8, 128.1, 130.6, 130.8, 132.5, 133.4, 133.6, 135.2, 136.5, 153.4, 179.6; HR-MS (ES) calc. $C_{50}H_{42}O_6Na$ (M + Na): 761.2879, found 761.2891.

General procedure for the macrocyclizations of the BINOL-diacids with diamine 10

The diacid (typically 1 mmol) was converted into the diacid dichloride by stirring with oxalyl dichloride (10 eq.) and DMF (one drop) in CH_2Cl_2 (40 mL) for 1 to 3 hours. The solvent was removed under vacuum, and the diacid dichloride obtained was dried under vacuum for at least 1 h. The crude diacid dichloride, redissolved in THF (20 mL), and the diamine **10** (1.0 eq.) and triethylamine (1.2 eq.) in THF (20 mL) were separately added dropwise simultaneously to a flask with THF (100 mL) over 1–3 h. After stirring overnight, the solvent was removed under vacuum and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried with Mg_2SO_4 and the residue obtained after evaporation to dryness was purified by flash chromatography to give the macrocycles.

Macrocycle 3a. The diacid **8a** (593 mg, 1.38 mmol) subjected to the above macrocyclization procedure gave after flash chromatography (CH_2Cl_2 : acetone, 15 : 1 to 10 : 1) 370 mg (36%) of **3a** as a white solid; $[\alpha]_D^{25}$ = +276 (*c* = 1.0, THF); δ_H ($CDCl_3$) 2.62–3.04 (4H, m, 2 × –CH_2CO–), 4.00–4.32 (4H, m, 2 × –CH_2O–), 6.80–7.25 (6H, m, ArH), 7.40–7.56 (4H, m, ArH), 7.68–8.05 (9H, m, ArH), 8.25–8.38 (4H, m, ArH), 8.49 (2H, br s, 2 × –CONH–), 9.33 (2H, br s, 2 × –CONH–); δ_C ($CDCl_3$) 37.4, 67.3, 110.1, 111.0, 117.3, 121.5, 124.8, 125.0, 125.2, 127.0, 127.8, 130.0, 130.3, 130.8, 132.6, 133.9, 134.0, 140.1, 148.2, 149.9, 153.2, 164.9, 170.5; HR-MS (ES) calc. for $C_{44}H_{34}N_6O_6Na$ (M + Na): 765.2438, found 765.2440; IR (KBr) 3386, 1684, 1534, 1450 cm^{-1}.

Macrocycle 3b. The diacid **8b** (252 mg, 0.55 mmol) subjected to the above macrocyclization procedure gave after flash chromatography (CH_2Cl_2 : acetone, 10 : 1) 216 mg (56%) of **3b** as a white solid; $[\alpha]_D^{25}$ = +259 (*c* = 1.0, THF); δ_H ($CDCl_3$) 3.70–3.84 (2H, m, 2 × –C*H*H′O–), 4.10–3.95 (2H, m, 2 × –CH*H*′O–), 7.09–7.38 (6H, m, ArH), 7.40–7.50 (2H, m, ArH), 7.66–7.86 (9H, m, ArH), 7.91–8.00 (2H, m, ArH), 8.07–8.16 (2H, m, ArH), 8.29–8.36 (3H, m, ArH and 2 × –CONH–), 8.95 (2H, br s, 2 × –CONH–); δ_C 25.3, 33.5, 69.8, 109.6, 110.0, 117.4, 121.6, 123.7, 124.2, 125.2, 126.5, 127.9, 129.6, 129.7, 129.9, 132.8, 133.7, 133.9, 140.8, 149.3, 149.7, 154.3, 164.4, 171.2; HR-MS (ES) calc. for $C_{46}H_{38}N_6O_6Na$ (M + Na): 793.2751, found 793.2750; IR (KBr) 3386, 1686, 1586, 1452 cm^{-1}.

Macrocycle 3c. The diacid **8c** (973 mg, 2.0 mmol) subjected to the above macrocyclization procedure gave after flash chromatography (CH_2Cl_2 : acetone, 10 : 1) 910 mg (57%) of **3c** as a white solid; $[\alpha]_D^{25}$ = +121 (*c* = 1.0, THF); δ_H ($CDCl_3$) 1.18–1.60 (8H, m, 2 × –CH_2–), 1.80–1.94 (4H, m, 2 × –CH_2CO–), 3.91–4.02 (4H, m, 2 × –CH_2O–), 7.12–7.37 (6H, m, ArH), 7.43–7.52 (2H, m, ArH), 7.67–7.85 (9H, m, ArH), 7.91–7.99 (2H, m, ArH), 8.06–8.13 (2H, m, ArH), 8.22–8.37 (3H, m, ArH and 2 × –CONH–), 8.78 (2H, br s, 2 × –CONH–); δ_C ($CDCl_3$) 22.5, 28.9, 37.3, 70.6, 110.3, 110.3, 110.7, 117.1, 123.4, 124.7, 124.9, 126.0, 127.1, 128.5, 130.2, 130.3, 130.9, 133.6, 134.8, 134.8, 150.3, 150.3, 155.0, 164.9, 172.1; HR-MS (ES) calc. for $C_{48}H_{42}N_6O_6Na$ (M + Na): 821.3064, found 821.3065; IR (KBr) 3390, 1686, 1585, 1451 cm^{-1}.

Macrocycle 4. The diacid **9** (177 mg, 0.22 mmol) subjected to the above macrocyclization procedure gave after flash chromatography (CH_2Cl_2 : acetone, 25 : 1) 115 mg (50%) of **4** as a white solid; $[\alpha]_D^{25}$ = −248 (*c* = 0.5, THF); δ_H ($CDCl_3$) 0.83–1.18 (8H, m, 2 × –CH_2–), 1.67–1.88 (4H, m, 2 × –CH_2CO–), 3.16–3.33 (2H, m, 2 × –C*H*H′O–), 3.41–3.54 (2H, m, 2 × –CH*H*′O–), 7.12–8.26 (36H, m, ArH and 2 × –CONH–), 8.68 (2H, br s, 2 × –CONH–); δ_C ($CDCl_3$) 22.0, 28.9, 37.2, 72.2, 109.3, 109.9, 125.2, 128.3–125.7 (multiple peaks), 128.9, 130.2, 130.7, 130.8, 132.4, 132.8, 133.3, 133.6, 134.0, 134.7, 136.3, 140.7, 149.2, 149.4, 153.3, 164.2, 171.1; HR-MS (ES) calc. for $C_{68}H_{54}N_6O_6Na$ (M + Na): 1073.4003, found 1073.3994.

(3α,12α-Dihydroxy-5β-cholan-24-yloxy)triphenylmethane (11)

$LiAlH_4$ (150 mg, 3.87 mmol) was added with caution to a solution of methyl deoxycholate (1.05 g, 2.58 mmol) in THF (25 mL). The reaction mixture was refluxed for 40 h and then carefully quenched with saturated Na_2SO_4 (10 mL). The resulting precipitate was filtered off and washed with hot THF and MeOH. The combined filtrate was dried over $MgSO_4$ and the solvent was removed under vacuum affording 5β-cholan-3α,12α,24-triol as colorless crystals (0.935 g, 96%); mp = 115 °C (lit. 122–124 °C);[32] δ_H ($CDCl_3$) 0.68 (3H, s, –CH_3), 0.91 (3H, s,

–CH_3), 0.98 (3H, d, *J* 6.6, –CHCH_3), 1.01–1.95 (28H, m, cholan–CH and CH_2's), 3.52–3.70 (3H, m, –CH_2OH and cholan–CH), 3.99 (1H, m, cholan–CH); δ_C (DMSO-d_6) 12.5, 14.2, 17.4, 23.1, 23.6, 25.2, 26.2, 27.1, 27.4, 28.7, 29.4, 30.3, 32.0, 33.9, 35.4, 35.8, 36.3, 41.7, 46.0, 46.4, 47.5, 67.1, 70.0, 71.1; HR-MS (ES) calc. for $C_{24}H_{42}O_3Na$ (M + Na): 401.3032, found 401.3026; IR (KBr) 3363, 2938, 1044 cm^{-1}.

The above triol (0.88 g, 2.33 mmol) was subjected to trityl chloride (0.91 g, 3.26 mmol), DMAP (5 mg), and triethylamine (0.7 mL, 5.0 mmol) in DMF (12 mL) and then stirred for 3 days at 50 °C. Water and ethyl acetate were added to the reaction mixture, and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with water and brine. After drying with $MgSO_4$ and evaporation to dryness, flash chromatography (pentane : ethyl acetate, 2 : 1) afforded **11** as a white solid (1.02 g, 70%); δ_H ($CDCl_3$) 0.66 (3H, s, –CH_3), 0.91 (3H, s, CH_3), 0.95 (3H, d, *J* 6.3, –CHCH_3), 0.98–1.94 (28H, m, cholan–CH and CH_2's), 2.97–3.07 (2H, m, –CH_2OTr), 3.60 (1H, m, cholan–CH), 3.98 (1H, m, cholan–CH), 7.16–7.34 (9H, m, 9 × trityl-H), 7.40–7.48 (6H, m, 6 × trityl-H); δ_C ($CDCl_3$) 13.0, 14.2, 17.9, 23.4, 23.9, 26.4, 26.8, 27.3, 27.7, 28.7, 30.7, 32.4, 33.9, 34.3, 35.5, 36.3, 36.6, 42.3, 46.7, 47.8, 48.5, 64.3, 72.0, 73.5, 86.5, 127.9 (3C), 128 (6C), 128.9 (6C), 144.7 (3C); HR-MS (ES) calc. for $C_{43}H_{56}O_3Na$ (M + Na): 643.4127, found 643.4214; IR (KBr) 3410, 2936, 1448, 705 cm^{-1}.

3α,12α-Bis(3′-hydroxypropoxy)-5β-cholan-24-oxytriphenylmethane (12)

NaH (60% in mineral oil, 0.20 g, 5.0 mmol) was carefully added to a solution of **11** (1.01 g, 1.63 mmol) in THF (20 mL), whereafter the reaction mixture was refluxed for 30 minutes. Allyl bromide (2.0 mL, 16 mmol) was then added and refluxing was continued for another 48 h. As TLC analysis revealed that the reaction was not complete, an additional portion of NaH (0.33 g, 8.2 mmol) and allyl bromide (2.0 mL, 16 mmol) was added. After refluxing for 40 h, the reaction mixture was cooled to 20 °C, and the excess NaH was destroyed with H_2O. After neutralization with 1 M HCl, the mixture was extracted with ether, and the organic phase was washed with water and brine, and then dried over $MgSO_4$. The residue obtained after evaporation under vacuum was purified by flash chromatography (pentane : ethyl acetate, 125 : 1) yielding a yellow solid (0.92 g, 80%); δ_H ($CDCl_3$) 0.64 (3H, s, –CH_3), 0.82–2.03 (32H, m, cholan–CH, –CH_2 and –CH_3's), 3.01 (2H, m, –CH_2OTr), 3.29 (1H, m, cholan–OCH), 3.54 (1H, m, cholan–OCH), 3.75 (1H, ddt, *J* 12.6, 5.4, 1.5, –C*H*H′O–), 4.00 (2H, dt, *J* 5.5, 1.4, –CH_2O–), 4.05 (1H, ddt, *J* 12.6, 5.4, 1.3, –CH*H*′O–), 5.07–5.18 (2H, m, 2 × allyl-H), 5.20–5.35 (2H, m, 2 × allyl-H), 5.82–6.04 (2H, m, 2 × allyl-H), 7.16–7.33 (9H, m, 9 × trityl-H), 7.40–7.48 (6H, m, 6 × trityl-H); δ_C ($CDCl_3$) 13.0, 18.0, 23.4, 23.6, 23.9, 26.3, 26.8, 27.6, 27.7, 27.8, 32.5, 33.3, 33.9, 34.8, 35.7, 36.3, 42.5, 46.6, 46.8, 49.0, 64.4, 69.0, 69.6, 78.9, 81.3, 86.4, 116.0, 116.6, 127.0, 127.9, 128.9, 135.8, 136.0, 144.8 (3C); HR-MS (ES) calc. for $C_{49}H_{64}O_3Na$ (M + Na): 723.4753, found 723.4749; IR (KBr) 2938, 1449, 1075, 706 cm^{-1}.

9-BBN (17 mL, 8.5 mmol, 0.5 M in THF) was added dropwise to the above diallylated compound (1.87 g, 2.67 mmol) in THF (30 mL) at 0 °C, under N_2 and the solution was stirred for 2 h at 20 °C. After cooling down to 0 °C, 35% aqueous H_2O_2 (3.8 mL) and 33% aqueous NaOH (4.1 mL) were carefully added. The reaction mixture was stirred overnight and then diluted with 100 mL of brine. The aqueous phase was extracted twice with ethyl acetate, whereafter the combined organic phases were dried over Na_2SO_4. After evaporation to dryness, the residue obtained was purified by flash chromatography (pentane : ethyl acetate, 1 : 1) affording the diol **12** as a white solid (1.48 g, 75%); δ_H ($CDCl_3$) 0.64 (3H, s, –CH_3), 0.82–1.95 (36H, m, cholan–CH, –CH_2 and –CH_3's and 2 × propoxy–CH_2–), 2.95–3.07 (4H, m, –CH_2OTr and 2 × OH), 3.18–3.37 (2H, m, cholan–OCH and –C*H*H′O–), 3.50 (1H, m, cholan–OCH), 3.62–3.84 (7H, m, 2 × CH_2OH, –CH_2O– and –CH*H*′O–), 7.16–7.34 (9H, m, 9 × trityl–H), 7.40–7.47 (6H, m, 6 × trityl–H); δ_C ($CDCl_3$) 13.0, 18.2, 22.7, 23.4, 23.9, 26.3, 26.8, 27.2, 27.4, 27.7, 32.2, 32.5, 32.7, 33.3, 33.8, 34.6, 35.4, 35.5, 36.1, 42.2, 46.4, 47.1, 49.2, 62.0, 62.8, 64.3, 66.7, 67.6, 79.5, 81.4, 86.4, 126.9, 127.8, 128.9, 144.7; HR-MS (ES) calc. for $C_{49}H_{68}O_5Na$ (M + Na): 759.4965, found 759.4968.

Macrocycle 5

Phosgene (1.1 mL, 1.54 mmol, 1.4 M in toluene) was added to a solution of **10** (211 mg, 0.61 mmol) in THF (10 mL) at 0 °C. After stirring for 15 min at 20 °C, Et_3N (0.38 mL, 2.8 mmol) was added to the suspension. Stirring was continued at this temperature for an additional 15 min, afterwhich the reaction mixture was heated to reflux. Methyl deoxycholate (0.25 g, 0.61 mmol) in THF (10 mL) was added over a period of 30 hours. After completed addition, the reaction mixture was refluxed for an additional 48 hours. The solvent was removed under vacuum and the residue was redissolved in CH_2Cl_2 and H_2O, and filtered through Celite. The organic phase was washed with water and dried over $MgSO_4$. The pure product (57 mg, 12%) was obtained as a colorless solid by flash chromatography (CH_2Cl_2 : acetone, 50 : 1); $[\alpha]_D^{25} = +66$ (*c* = 0.8, THF); δ_H ($CDCl_3$) 0.76 (3H, s, –CH_3), 0.89 (3H, d, *J* 5.4, –CHCH_3), 0.94 (3H, s, –CH_3), 0.98–2.53 (26H, m, cholan–CH and CH_2's), 3.67 (3H, s, –OCH_3), 4.63 (1H, m, cholan–OCH), 5.26 (1H, m, cholan–OCH), 7.07–7.37 (3H, m, ArH), 7.57–7.87 (5H, m, ArH), 7.96 (1H, d, *J* 8.0, ArH), 8.13 (1H, d, *J* 8.0, ArH), 8.20–8.29 (2H, m, 2 × –OCONH–), 8.90 (1H, br s, –CONH–), 9.10 (1H, br s, –CONH–); HR-MS (ES) calc. for $C_{45}H_{54}N_6O_8Na$ (M + Na) 829.3901, found 829.3903; IR (KBr) 3409, 2948, 1740, 1585, 1455, 1210 cm^{-1}.

Macrocycle 6

Phosgene (0.72 mL, 1.0 mmol, 1.4 M in toluene) was added to a solution of **10** (150 mg, 0.43 mmol) in THF (15 mL) at 0 °C. The colorless suspension obtained was stirred for 15 min at 20 °C, followed by the addition of Et_3N (0.26 mL, 1.9 mmol). The reaction mixture was stirred at 20 °C for an additional 15 min, and then a solution of **12** (317 mg, 0.43 mmol) in THF (15 mL) was added over a period of 2 hours. After stirring for 1 h, the solvent was removed under vacuum, and the residue was redissolved in CH_2Cl_2 and washed with H_2O and dried with $MgSO_4$. After evaporation to dryness, the pure macrocycle **6** (72 mg, 15%) was obtained as a colorless solid by flash chromatography (CH_2Cl_2 : acetone, 30 : 1); $[\alpha]_D^{25} = +5.0$ (*c* = 0.5, THF); δ_H (acetone-d_6) 0.69 (3H, m, –CH_3), 0.88–2.05 (36H, m, cholan–CH, CH_2 and CH_3's and 2 × propoxy–CH_2), 3.06 (2H, m, –CH_2OTr), 3.23–3.40 (2H, m, cholan–OCH and –C*H*H′O–), 3.49–3.79 (4H, m, cholan–OCH–, –CH*H*′O– and –CH_2O–), 4.19–4.37 (4H, m, 4 × –CH_2OCONH–), 7.18–7.28 (9H, m, 9 × trityl-H), 7.42–7.51 (6H, m, 6 × trityl-H), 7.60–7.87 (7H, m, ArH and 2 × –OCONH–), 8.04–8.11 (2H, m, ArH), 8.19–8.27 (2H, m, ArH), 8.56 (1H, d, *J* 8.7, ArH), 8.75 (1H, br s, –CONH–), 9.99 (1H, br s, –CONH–); HR-MS (ES) calc. for $C_{69}H_{80}N_6O_9Na$ (M + Na) 1159.5885, found 1159.5804; IR (KBr) 3406, 2938, 1740, 1687, 1583, 1453, 1304, 1210 cm^{-1}.

5-Hydroxymethyl-5-isopropylbarbituric acid (16a)[20]

5-Isopropylbarbituric acid (3.40 g, 20 mmol), formaldehyde (1.7 mL, 23 mmol, 35% in H_2O) and 2 drops of conc. HCl were mixed in water (10 mL) and refluxed until the barbiturate had completely dissolved (approx. 1 h). After cooling in an ice bath for several hours, the colorless crystals of **16a** were filtered off (3.80 g, 95%); mp = 185–187 °C; δ_H (DMSO-d_6) 0.88 (6H, d, *J* 6.9, 2 × isopropyl–CH_3), 2.19 (1H, sept, *J* 6.9, isopropyl–CH),

3.82 (2H, s, $-CH_2-$), 11.41 (2H, br s, 2 × NH); HR-MS (ES) calc. for $C_8H_{12}N_2O_4Na$ (M + Na) 223.0695, found 223.0650; IR (KBr) 3481, 3259, 1762, 1716, 1690 cm^{-1}.

5-Hydroxymethyl-5-methylbarbituric acid (16b)

Employing a similar procedure as described for the preparation of **16a**, 5-methylbarbituric acid (1.15 g, 8.1 mmol) was converted into **16b** (299 mg, 22%); δ_H (DMSO-d_6) 1.20 (3H, s, $-CH_3$), 3.63 (2H, d, *J* 5.0, $-CH_2-$), 5.51 (1H, t, *J* 5.0, –OH), 11.2 (2H, br s, 2 × NH); IR (KBr) 3240, 1717, 1168 cm^{-1}.

5-Hydroxymethyl-5-phenylbarbituric acid (16c)

Employing a similar procedure as described for the preparation of **16a**, 5-phenylbarbituric acid (2.04 g, 10 mmol) was converted into **16c** (1.90 g, 81%); mp = 181–182 °C; δ_H (acetone-d_6) 4.46 (2H, d, *J* 5.0, $-CH_2-$), 4.72 (1H, t, *J* 5.0, –OH), 7.36–7.42 (5H, m, 5 × phenyl-H), 10.45 (2H, br s); HR-MS (ES) calc. for $C_{11}H_{10}N_2O_4Na$ (M + Na) 257.0539, found 257.0538; IR (KBr) 3255, 1760, 1714 cm^{-1}.

5-Cinnamoyloxymethyl-5-isopropylbarbituric acid (17a)

Barbiturate **16a** (0.80 g, 4.0 mmol) was refluxed in THF (20 mL) with cinnamoyl chloride (2.67 g, 16.0 mmol) for 2 days. After evaporation to dryness, the residue was purified by flash chromatography (pentane : ethyl acetate, 4 : 1) followed by recrystallization in ethyl acetate–pentane to give **17a** as colorless crystals (1.08 g, 82%); mp = 201–202 °C; δ_H (acetone-d_6) 1.06 (6H, d, *J* 7.0, 2 × isopropyl–CH_3), 2.42 (1H, sept, *J* 7.0, isopropyl–CH), 4.62 (2H, s, $-CH_2-$), 6.38 (1H, d, *J* 16.0, alkene-H), 7.31–7.40 (3H, m, 3 × phenyl-H), 7.49–7.62 (3H, m, 2 × phenyl-H and alkene-H), 10.39 (2H, br s, 2 × NH); HR-MS (ES) calc. for $C_{17}H_{18}N_2O_5Na$ (M + Na) 353.1114, found 353.1112; IR (KBr) 3094, 1764, 1717, 1686, 1643 cm^{-1}.

5-Cinnamoyloxymethyl-5-methylbarbituric acid (17b)

Employing a similar procedure as described for the synthesis of **17a**, **16b** (290 mg, 1.64 mmol) was converted into **17b** (447 mg, 90%); mp = 186–187 °C; δ_H ($CDCl_3$) 1.61 (3H, s, $-CH_3$), 4.59 (2H, s, $-CH_2-$), 6.33 (1H, d, *J* 16.0, alkene-H), 7.36–7.42 (3H, m, 3 × phenyl-H), 7.47–7.54 (2H, m, 2 × phenyl-H), 7.64 (1H, d, *J* 16.0, alkene-H), 7.98 (2H, br s); HR-MS (ES) calc. for $C_{15}H_{14}N_2O_5Na$ (M + Na) 325.0801, found 325.0801; IR (KBr) 3243, 1710, 1640 cm^{-1}.

5-Cinnamoyloxymethyl-5-phenylbarbituric acid (17c)

Employing a similar procedure as described for the synthesis of **17a**, **16c** (234 mg, 1.0 mmol) was converted into **17c** (317 mg, 87%); mp = 198–199 °C; δ_H ($CDCl_3$) 4.98 (2H, s, $-CH_2-$), 6.38 (1H, d, *J* 16.0, alkene-H), 7.36–7.44 (8H, m, 8 × phenyl-H), 7.48–7.55 (2H, m, 2 × phenyl-H), 7.68 (1H, d, *J* 16.0, alkene-H), 8.07 (2H, br s, NH); HR-MS (ES) calc. for $C_{20}H_{16}N_2O_5Na$ (M + Na) 387.0957, found 387.0962; IR (KBr) 3095, 1764, 1718, 1687, 1642 cm^{-1}.

General procedure for the nitrile oxide cycloadditions

The cinnamoyl derivative (0.1 mmol) and the chiral host (0.12–0.14 mmol) were dissolved in CH_2Cl_2 (1 mL). A solution of the chlorooxime (0.12 mmol) in CH_2Cl_2 (1 mL) was added followed by triethylamine (0.12 mmol), and the reaction mixture was stirred overnight at 20 °C. The solvent was removed under vacuum and the residue was purified by flash chromatography (CH_2Cl_2 : acetone, 40 : 1 to 6 : 1) affording a mixture of the regioisomeric cycloaddition adducts **18** and **19** as white solids, the unreacted cinnamate **17**, and the recovered chiral host.

Cycloaddition adducts 18a and 19a. Mixture of regioisomers; δ_H ($CDCl_3$) 1.00 ($6H_{18a}$, d, *J* 6.9, 2 × isopropyl–CH_3), 1.06 ($3H_{19a}$, d, *J* 6.9, isopropyl–CH_3), 1.07 ($3H_{19a}$, d, *J* 6.9, isopropyl–CH_3), 2.33 ($1H_{18a}$ + $1H_{19a}$, sept, *J* 6.9, 2 × isopropyl–CH), 4.39 ($1H_{18a}$, d, *J* 5.4, 4-H), 4.59 ($1H_{18a}$, d, *J* 10.1, –C*H*H′–), 4.66 ($1H_{19a}$, d, *J* 10.0, –C*H*H′–), 4.71 ($1H_{18a}$, d, *J* 10.1, –CH*H*′–), 4.76 ($1H_{19a}$, d, *J* 10.0, –CH*H*′–), 4.87 ($1H_{19a}$, d, *J* 4.1, isoxazoline-H), 4.90 ($1H_{19a}$, d, *J* 4.1, isoxazoline-H), 5.90 ($1H_{18a}$, d, *J* 5.4, 5-H), 7.15–7.63 ($10H_{18a}$ + $10H_{19a}$, m, 20 × ArH), 8.15 ($2H_{18a}$ + $2H_{19a}$, br s, 4 × NH); HR-MS (ES) calc. for $C_{24}H_{23}N_3O_6Na$ (M + Na) 472.1486, found 472.1491; IR (KBr) 3238, 3111, 1714, 1420, 1318, 1221 cm^{-1}.

Cycloaddition adducts 18b and 19b

Mixture of regioisomers; δ_H ($CDCl_3$) 0.97–1.15 ($6H_{18b}$ + $6H_{19b}$, m, 4 × isopropyl–CH_3), 1.32 ($9H_{18b}$ + $9H_{19b}$, s, 6 × tertbutyl–CH_3), 2.29–2.64 ($1H_{18b}$ + $1H_{18b}$, m, isopropyl–CH), 4.36 ($1H_{18b}$, d, *J* 5.4, 4-H), 4.54–4.79 ($2H_{18b}$ + $2H_{19b}$, m, 2 × $-CH_2-$), 4.85 ($1H_{19b}$, d, *J* 4.0, isoxazoline-H), 4.88 ($1H_{19b}$, d, *J* 4.0, isozazoline-H), 5.84 ($1H_{18b}$, d, *J* 5.4, 5-H), 7.14–7.90 ($9H_{18b}$ + $9H_{19b}$, m, 18 × ArH), 8.90 ($2H_{18b}$ + $2H_{19b}$, br s, 4 × NH); HR-MS (ES) calc. for $C_{28}H_{31}N_3O_6Na$ (M + Na) 528.2111, found 528.2110; IR (KBr) 3240, 2967, 1706, 1635, 1317 cm^{-1}.

Cycloaddition adducts 18c and 19c. Mixture of regioisomers; δ_H ($CDCl_3$) 0.90 ($6H_{18c}$, d, *J* 6.6, 2 × isopropyl–CH_3), 1.01–1.13 ($6H_{19c}$, m, 2 × isopropyl–CH_3), 2.16–2.45 ($1H_{18c}$ + $1H_{19c}$, m, 2 × isopropyl–CH), 4.52 ($1H_{18c}$, d, *J* 5.2, 4-H), 4.56–4.77 ($2H_{18c}$ + $2H_{19c}$, m, 2 × $-CH_2-$), 4.93 ($1H_{19c}$, d, *J* 4.0, isoxazoline-H), 5.05 ($1H_{19c}$, d, *J* 4.0, isoxazoline-H), 5.96 ($1H_{18c}$, d, *J* 5.2, 5-H), 7.14–7.95 ($12H_{18c}$ + $12H_{19c}$, m, 24 ArH), 8.41 ($2H_{18c}$ + $2H_{19c}$, br s, 4 × NH); HR-MS (ES) calc. for $C_{28}H_{25}N_30_6Na$ (M + Na) 522.1641, found 522.1644; IR (KBr) 3340, 3216, 1762, 1718, 1448, 1313 cm^{-1}.

Cycloaddition adducts 18d and 19d. Mixture of regioisomers; δ_H ($CDCl_3$) 1.42 ($3H_{18d}$, s, $-CH_3$), 1.55 ($3H_{19d}$, s, $-CH_3$), 4.48–4.64 ($3H_{18d}$ + $2H_{19d}$, m, 2 × $-CH_2-$ and 4-H), 4.94 ($1H_{19d}$, d, *J* 4.0, isoxazoline-H), 5.08 ($1H_{19d}$, d, *J* 4.0, isozazoline-H), 5.97 ($1H_{18d}$, d, *J* 5.0, 5-H), 7.18–7.94 ($12H_{18d}$ + $12H_{19d}$, m, 12 × ArH), 8.71 ($2H_{18d}$ + $2H_{19d}$, br s, 4 × NH); HR-MS (ES) calc. for $C_{26}H_{21}N_3O_6Na$ (M + Na) 494.1329, found 494.1323; IR (KBr) 3441, 3232, 3108, 1719, 1456, 1392, 1342 cm^{-1}.

Cycloaddition adducts 18e and 19e. Mixture of regioisomers; δ_H ($CDCl_3$) 4.58 ($1H_{18e}$, d, *J* 5.0, 4-H), 4.79–5.13 ($2H_{18e}$ + $4H_{19e}$, m, 2 × $-CH_2-$ and 2 × isoxazoline-H), 6.10 ($1H_{18e}$, d, *J* 5.0, 5-H), 7.10–8.03 ($17H_{18e}$ + $17H_{19e}$, m, 34 × ArH), 8.73 ($2H_{18e}$ + $2H_{19e}$, br s, 4 × NH); HR-MS (ES) calc. for $C_{31}H_{23}N_3O_6Na$ (M + Na) 556.1485, found 556.1496; IR (KBr) 3238, 3111, 1714, 1420, 1318, 1221 cm^{-1}.

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