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# Chiral Macrocyclic Bis(oxazoline) $Cu^{I}$ Complexes – Structure/Stereoselectivity Relationships in Catalytic Cyclopropanations

**Tomislav Portada,[a] Marin Roje,[a] Zlata Raza,[a] Vesna Čaplar,[a] Mladen Žinić,*[a] and Vitomir Šunjić[a][‡]**

**Keywords:** Bis(oxazolines) / Catalytic cyclopropanation / Copper(I) complexes / Diastereoselectivity / Macrocyclic ligands

The design and synthesis of 18 chiral macrocycles with built in $C_2$-symmetric bis(oxazoline) units is described and the catalytic properties of their copper(I) complexes in cyclopropanations of styrene with ethyl diazoacetate are assessed. The bridging of two homochiral centers in the bis(oxazoline) unit gives a macrocyclic ligand, which upon binding of $Cu^{I}$ is transformed into a macrocyclic catalytic complex containing a chiral cavity. Such a complex represents a conceptually new type of supramolecular organometallic catalyst, possessing a chiral reaction cavity. A clear relationship between catalyst structures and the stereoselectivity outcome in the catalytic cyclopropanations has been established and it is demonstrated that both the enantioselectivity and the diastereoselectivity can be independently modified by variation of the ligand structural parameters. The $Cu^{I}$ complex of the ligand **3b** gave a *trans*/*cis* diastereomeric ratio of 94:6 (*de* = 88 %), representing the highest diastereoselectivity obtained to date for cyclopropanations catalyzed by the bis(oxazoline) class of complexes. An explanation of the observed relationship between stereochemical outcome and ligand structure is proposed.



## Introduction

Many naturally occurring and synthetic biologically important compounds contain chiral substituted cyclopropane ring systems,[1] and considerably different biological activities of the stereoisomers are often observed.[2] The need for the efficient synthesis of stereochemically pure cyclopropanes has prompted extensive investigation of carbene additions to alkene double bonds catalyzed by metal complexes of different chiral ligands.[3] Ligands with diverse structures have been tested, and some of them have given very good enantioselectivity but as a rule only low or medium diastereoselectivity [rarely higher than 60% *de* (80:20 *trans*/*cis* ratio)].[4–13] Pfaltz et al.[4,14] introduced $C_2$-symmetric semicorrin and 5-aza-semicorrin[10] ligands for the preparation of $Cu^{I}$ catalytic complexes used in catalytic cyclopropanations, while Evans,[7,8] Masamune,[5] and Pfaltz[9] later developed synthetically more accessible bis(oxazoline) ligands while Katsuki[11] and Kanemasa[12] introduced new ligands of the bipyridine and diamine type, respectively. Cobalt(II) and cobalt(III) complexes of chiral salen and tetradentate Schiff-base ligands[15,16] have achieved *trans*- and *cis*-selective cyclopropanations in a highly enantioselective manner, while ruthenium(II) complexes of bidentate Schiff-base ligands[17] have provided excellent levels of diastereo- and enantioselectivity in catalytic alkene cyclopropanations. Chiral ruthenium porphyrin complexes have also been used[18,19] in asymmetric inter- and intramolecular cyclopropanations of alkenes, while chiral iminophosphoranes possessing stereogenic phosphorus centers have been successfully used as ligands in asymmetric copper-catalyzed cyclopropanations of olefins with ethyl diazoacetate.[20]

However, the $C_2$-symmetric bis(oxazoline) ligands appear to be of the highest importance, since they are synthetically readily available and in some cases also afford very high enantioselectivities.[5–9] A range of chiral bis(oxazoline)–metal complexes have also received a great deal of attention in various other catalytic processes such as Diels–Alder and hetero-Diels–Alder reactions, 1,3-dipolar cycloadditions, [2 + 2] photochemical cycloadditions, Mukaiyama aldol reactions and Mukaiyama–Michael addition reactions,[21–24] and allylic substitution reactions,[24,25] while $Pd^{II}$ complexes of chiral bis(oxazolines) have been applied in catalytic allylic alkylations.[25] A comprehensive review of $C_2$-symmetric chiral bis(oxazoline) ligands in asymmetric catalysis has appeared recently.[26]

Many investigations have shown that ligand structure has a strong influence on the stereoselectivity of cyclopropanation. Even very small structural changes often have drastic and sometimes unpredictable effects on the enantioselectivity, but examples in which the *trans*/*cis* diastereoselectivity is higher than the most commonly observed ra-

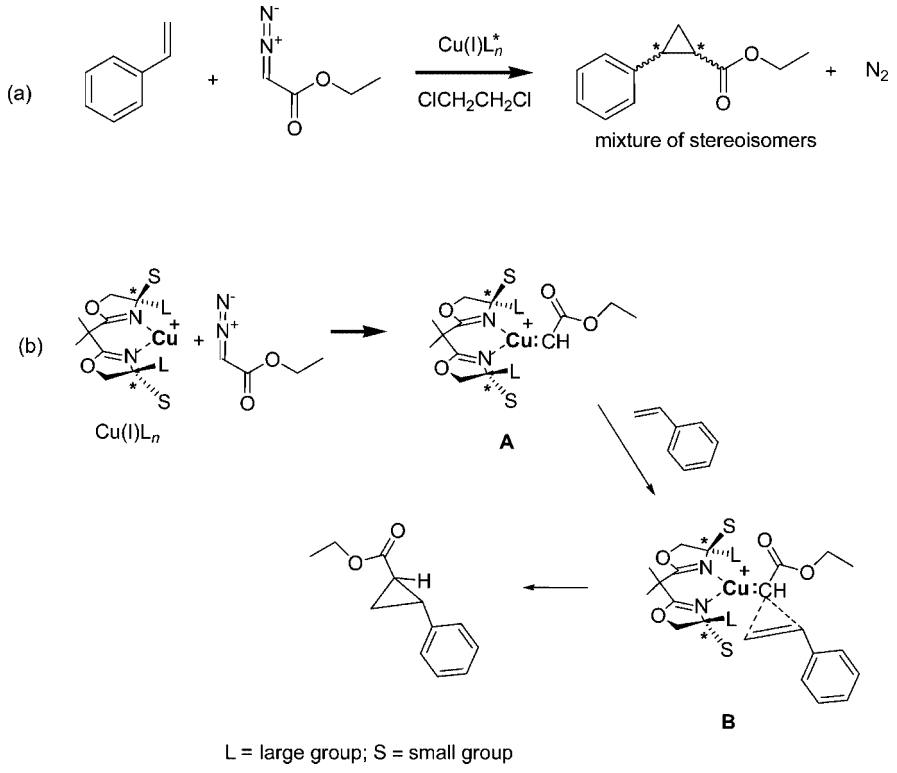
[a] Department of Organic Chemistry and Biochemistry, Rudjer Bošković Institute,
P. O. Box 180, 10002 Zagreb, Croatia
Fax: +385-1-4680195
E-mail: zinic@irb.hr
[‡] Current address: Glaxo, Smith and Kline, Research Institute, Zagreb, Croatia

tios of 60:40 to 70:30 are exceptionally rare. It should be also noted that in the vast majority of studies the diastereoselectivity outcome was simply neglected and only the enantioselectivity was considered. It appears that the search for more efficient catalysts for cyclopropanations should be directed towards those capable of giving both high enantioselectivity and also high diastereoselectivity (i.e., high *total* or cumulative stereoselectivity) and that such investigations might bring about a new generation of superior stereoselective catalysts for cyclopropanations. In a wider context, the results of such studies could also be of importance for other types of stereoselective transformations that use $C_2$ chiral organometallic catalysts or give stereoisomeric products.

It is well known that the mechanism of asymmetric cyclopropanation catalyzed by metal complexes of chiral bis(oxazoline) ligands (Scheme 1, a) involves the formation of a metal–carbene complex A (Scheme 1, b).[24] In the subsequent step, styrene reacts with the electrophilic α-carbon of the ester to give the cyclopropane product as the mixture of diastereomers. The stereochemical outcome is determined by the repulsive and/or attractive interactions in transition state B. As proposed by Pfaltz,[4] enantioselectivity in catalytic cyclopropanations is determined by the difference in accessibility of the two enantiotopic faces of the metal-carbene bond and is influenced by the presence of large substituents on adjacent chiral centers in the bis(oxazoline) ligand, so enantioselectivity will depend on the positions and bulkiness of substituents on stereogenic centers. On the other hand, diastereoselectivity will be determined by mutual orientation of phenyl and carbethoxy groups (*cis* or *trans* with respect to the plane of the forming cyclopropane ring) in the transition state B (Scheme 1).

In the search for a catalyst capable of giving higher total (enantio- and dia-) stereoselectivity we considered structures containing topologically more constrained catalytic cavities than found in the common acyclic $C_2$-symmetric bis(oxazoline)–$Cu^{I}$ catalysts, which prompted us to consider macrocyclic structures incorporating $C_2$-symmetric bis(oxazoline) units (Figure 1). Conceptually, the bridging of two homochiral centers in a planar, $C_2$-symmetric bis(oxazoline) $Cu^{I}$ complex by a bridge of sufficient rigidity should result in the induction of a certain degree of helicity in the bridge (Figure 2). In this way, the $C_2$-chirality around the metallic center would be extended to a larger space, determined by the size of the macrocycle. Since the catalytic transformation takes place through the transition state B (Scheme 1, b), in a macrocyclic system of sufficient size the process would occur inside the chiral cavity of the catalyst. Hence, the macrocyclic analogue of the transition state B should be stereochemically more constrained, so many more noncovalent interactions may be expected to occur than in the acyclic transition state B. Consequently, with the macrocyclic catalysts higher total stereoselectivity may be obtained through improvement of enantioselectivity and/or diastereoselectivity. In addition, such catalysts offer the unique potential for substrate discrimination through variation of the size of a macrocyclic ring; the latter property of substrate recognition would resemble one of the basic functions of enzymes or synthetic supramolecular catalysts.[27]




Scheme 1.

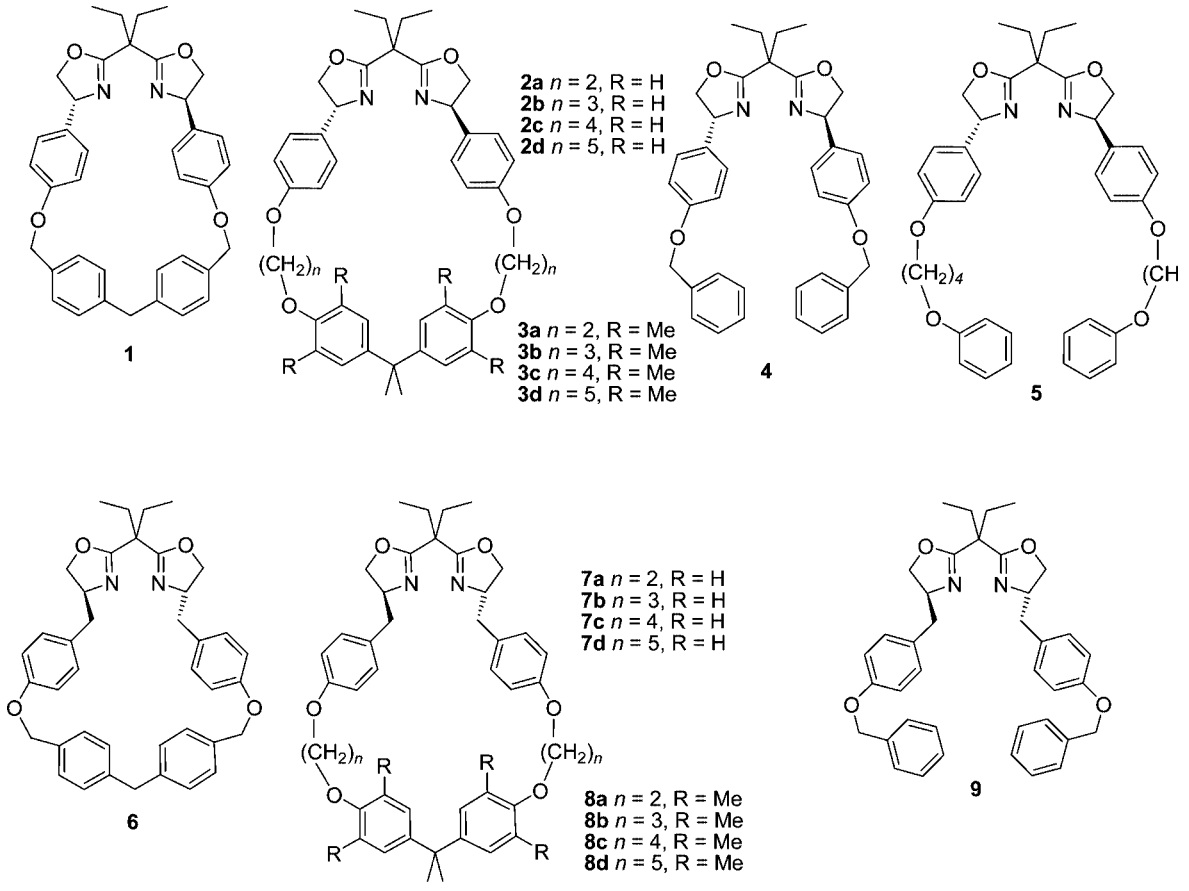



Figure 1. Chiral macrocyclic and acyclic bis(oxazoline) ligands derived from (*R*)-*p*-hydroxyphenylglycinol (**1**, **2a**–**d**, **3a**–**d**, and **4**, **5**) and (*S*)-tyrosinol (**6**, **7a**–**d**, **8a**–**d**, and **9**).

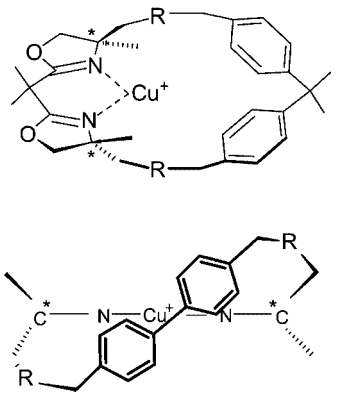


Figure 2. Structures of macrocyclic bis(oxazoline)s with chiral reaction cavities.

To test this hypothesis, two series of macrocyclic ligands – **2/3** and **7/8**, derived from D-hydroxyphenylglycinol and L-tyrosinol, respectively – and *p*,*p*′-oligomethylenediphenylmethane bridges were prepared (Figure 1) and the catalytic properties of their $Cu^{I}$ complexes were tested in the cyclopropanation of styrene with ethyl diazoacetate. For purposes of comparison the acyclic analogues **4**, **5**, and **9**, as well as two cyclic derivatives **1** and **6**, possessing the smallest rings, were prepared and their $Cu^{I}$ catalytic complexes were also tested. It is well known that the best bis(oxazoline) ligands prepared to date, such as those of bis(*tert*-butyl) derivatives **A**[7] and **B**[28] (Figure 3), giving enantioselectivities of up to 99.9% *ee*, do not exhibit diastereoselectivities higher than 46% for ligand **A** or 68% *de* (84:16 *trans*/*cis* ratio) for ligand **B**. Here we report diastereoselectivities of 86 and 88% *de* for **2a** and **3b**, respectively, these being the highest values obtained to date for bis(oxazoline) ligands.

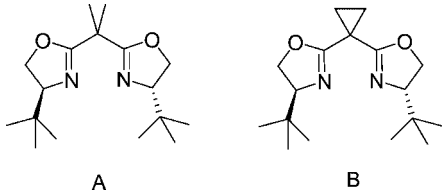


Figure 3. The two best bis(oxazoline) ligands prepared to date for copper(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate.

## Results and Discussion

### Synthesis

Here we describe the syntheses of the macrocyclic ligands **1**, **2a**–**d**,[29] **3a**–**d**, **6**, **7a**–**d**, and **8a**–**d** (Figure 1), containing macrocyclic cavities of various sizes, as well as that of the closely related acyclic analogue **5** prepared for purposes of comparison, while acyclic **4** and **9** had been prepared earlier.[30] The macrocyclic bis(oxazolines) of the series **2/3** and **7/8** were prepared from D-hydroxyphenylglycinol and L-tyrosinol, respectively, and differ in the absolute configurations at their stereogenic centers. The bis(oxazoline) fragments were prepared by the treatment of the activated malonic acid derivatives with L-tyrosinol or D-hydroxyphenylglycinol. Both optically active amino alcohols were prepared by reduction of the corresponding α-amino acids.[30]

Our earlier findings with acyclic bis(oxazolines) had shown that the acidic hydrogen atoms on the methylene bridge undergo tautomeric exchange (Figure 4)[31] and that because of such tautomerism the yields of bis(oxazoline)s are generally low due to subsequent oxidative transformations. To enhance the stabilities of the bis(oxazolines) their derivatives with two ethyl substituents on the bridging carbon were prepared (Figure 4).

The spacers with variable numbers of methylene groups were introduced in the form of α,ω-disubstituted alkanes in order to vary the sizes and flexibilities of the macrocycles (Figure 1). In addition to the short and flexible polymethylene fragments, however, a more rigid unit, based on bisphenol A, was also introduced to ensure the induction of a certain degree of helicity in the macrocycle. The bisphenol A derivative with four methyl substituents on its phenol rings was used for the preparation of **3a**–**d** and **8a**–**d**, in which the methyl groups might increase the level of steric discrimination during the catalytic transformation occurring in the macrocyclic cavity.

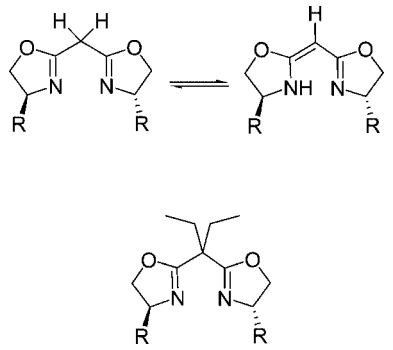
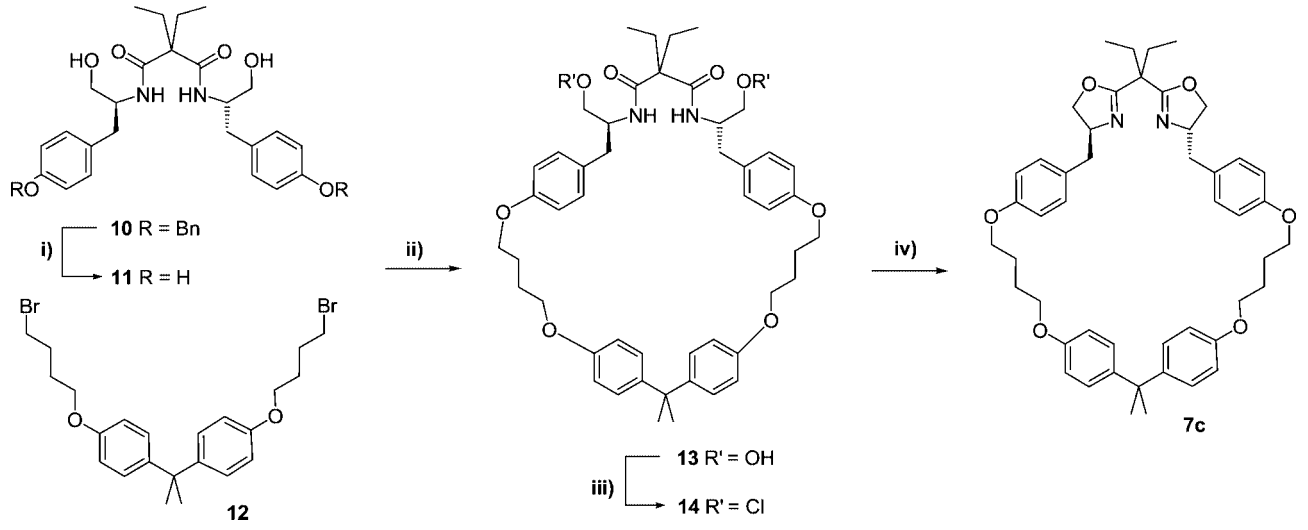


Figure 4. Tautomeric equilibrium of methylene-bridged bis(oxazoline) and stable diethylmethylene-bridged bis(oxazoline).

The syntheses of the macrocyclic bis(oxazoline)s were initially approached through the key 1:1 macrocyclization step between **11** and **12** under high-dilution conditions as outlined in Scheme 2 for the preparation of **7c**. The diamide **10**, previously prepared from L-tyrosinol in our group,[30] served as one component of the macrocyclization. Hydrogenolytic cleavage of the benzylic protection groups in **10** in the presence of palladium on carbon gave **11** in quantitative yield. The second component for macrocyclization, compound **12**, was prepared by treatment of bisphenol A with a large excess of 1,4-dibromoethane (yield 42%). Macrocyclization under the high-dilution conditions to give **13** (yield 23%) was performed by dropwise addition of acetonitrile solutions of **11** and **12** to a suspension of cesium carbonate at reflux in a large volume of acetonitrile. The dihydroxy compound **13** gave the dichloride **14** (56%) on treatment with triphosgene and triphenylphosphane, and this was subsequently transformed into the target macrocyclic bis(oxazoline) **7c** (76%) under alkaline conditions (NaOH in boiling methanol).




Scheme 2. Reaction conditions: i) $H_2$, 10% Pd/C, MeOH, r.t., 18 h. ii) $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h. iii) Triphosgene, $Ph_3P$, $CH_2Cl_2$, r.t., 1 h. iv) NaOH, MeOH, reflux, 2 h.

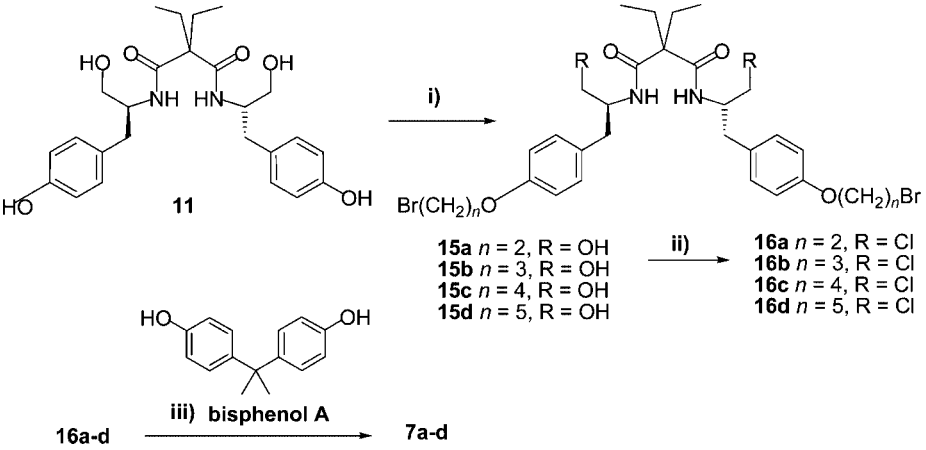
The reaction path outlined in Scheme 3, however, proved to be much more efficient, offering a minimal number of steps and much better overall yields. The alkane spacers were introduced by treatment of selected α,ω-dibromoalkanes with the diamide **11**, and the formed dihydroxy compounds **15a**–**d** (yields 29–59%) were subsequently transformed into dichlorides **16a**–**c** by treatment with triphosgene (yields 66–75%) or thionyl chloride (yields 56–76%). **The key and final step was the simultaneous triple ring closure (two oxazoline and the macrocycle ring) in a single reaction step!** Treatment of compounds **16a**–**d** with bisphenol A in the presence of $Cs_2CO_3$ thus directly afforded the end-products **7a**–**d** (yields 28–50%).

Ligands **2a**–**d** were prepared in the same way, starting from hydroxyphenylglycinol diamide **17**[30] (Scheme 4), with subsequent debenzylation to provide compound **18** (99%) by hydrogenolytic cleavage. Treatment of **18** with α,ω-dibromoalkanes gave the dihydroxy compounds **19a**–**d** (yields 20–64%), which were chlorinated to provide compounds **20a**–**d** (yields 69–88%) and treated in the last step with bisphenol A to give ligands **2a**–**d** (yields 24–48%). It was observed that treatment of diamide **18** with 1,2-dibromoethane gave a lower yield then obtained in the reactions with higher α,ω-dibromoalkanes, while in the reaction between **18** and 1,3-dibromopropane the presence of an elimination product was observed. The same observations also hold for the reactions between tyrosinol derivative **11** and α,ω-dibromoalkanes.

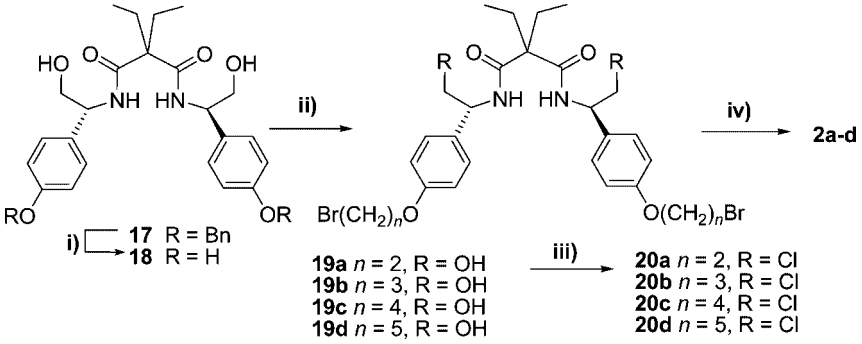
For purposes of wider structure/stereochemical outcome studies, extended beyond the ligands **2a**–**d** and **7a**–**d**, we also designed the new ligands **1** and **6** (Figure 1), incorporating smaller macrocycles. This was initiated by the observation that diastereoselectivity was increased in smaller macrocycle cavities.[29] Instead of bisphenol spacers, **1** and **6** each contain a bis(methylphenyl)methane fragment attached directly to the oxygens of the hydroxyphenyl units; since no methylene group is present between the hydroxyphenyl and the bis(methylphenyl)methane fragments, ligands **1** and **6** could be regarded as the $n = 0$ analogues of the **2** and the **7** series (Figure 1), respectively.

Treatment of the dihydroxy compound **11** with thionyl chloride gave the dichloride **21** (86%), which yielded ligand **6** (46%) in the macrocyclization reaction with bis(4-bromomethylphenyl)methane (**22**)[32] as shown in Scheme 5.

The compounds **3a**–**d** and **8a**–**d**, each bearing four methyl groups on the phenyl rings of the bridge (the tetramethyl analogues of ligands **2a**–**d** and **7a**–**d**), were also synthesized (Figure 1). For this purpose the bisphenol **25**, a tetramethyl analogue of bisphenol A, was prepared by an acid-catalyzed condensation between 2,6-dimethylphenol and acetone in

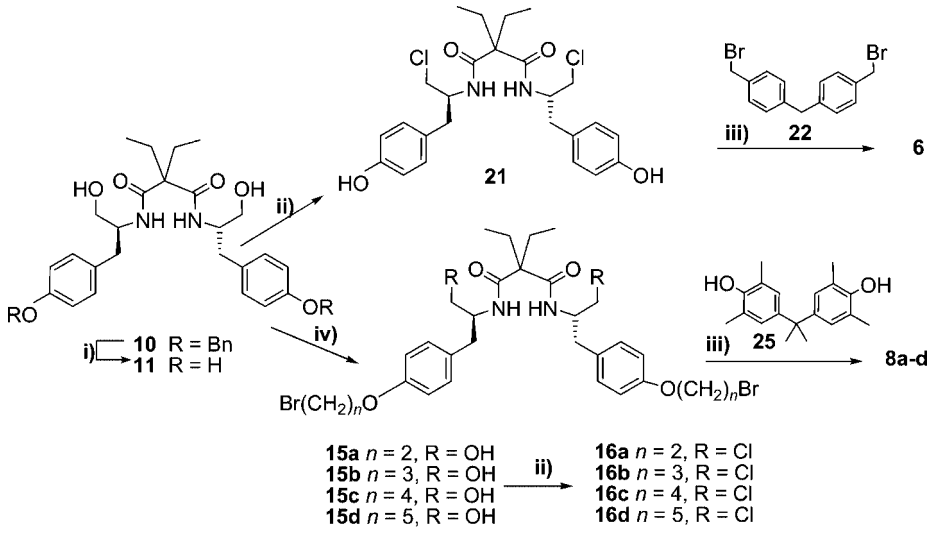



Scheme 3. Reaction conditions: i) $Br(CH_2)_nBr$, $n$ = 2–5, $K_2CO_3$, MeCN, reflux, 18 h. ii) $SOCl_2$, $CH_2Cl_2$, r.t., 18 h or triphosgene, $Ph_3P$, $CH_2Cl_2$, r.t., 1 h. iii) $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h.




Scheme 4. Reaction conditions: i) $H_2$, 10% Pd/C, MeOH, r.t., 18 h. ii) $Br(CH_2)_nBr$, $n$ = 2–5, $K_2CO_3$, MeCN, reflux, 18 h. iii) $SOCl_2$, $CH_2Cl_2$, r.t., 18 h or triphosgene, $Ph_3P$, $CH_2Cl_2$, r.t., 1 h. iv) Bisphenol A, $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h.

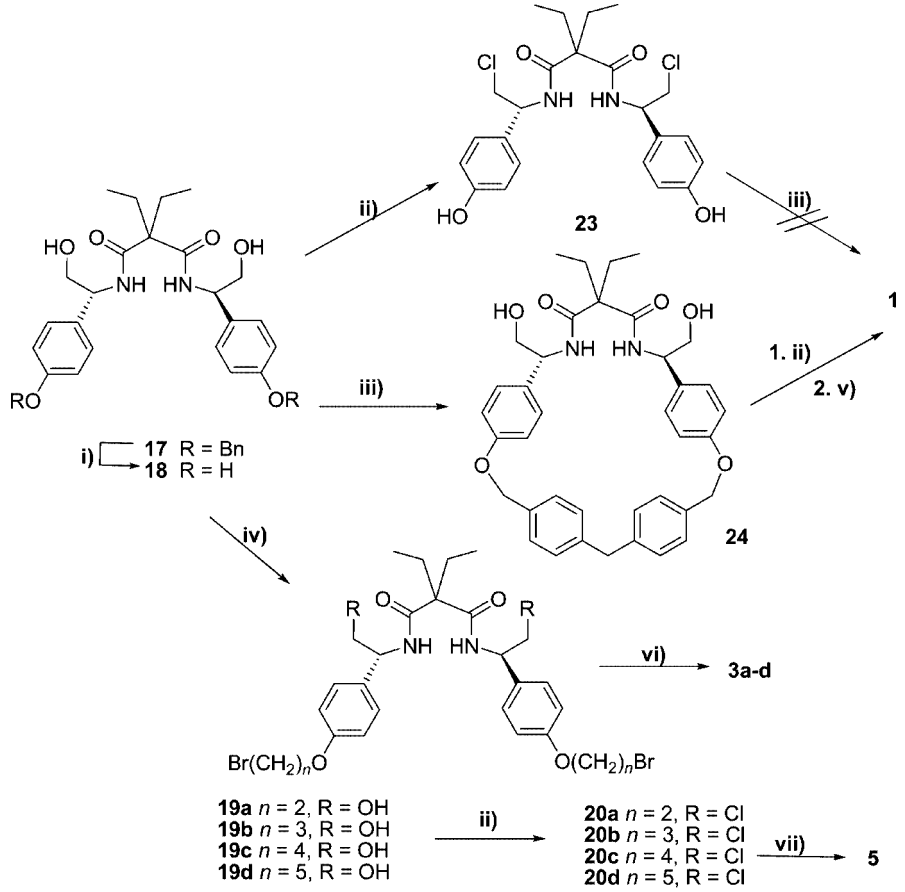
  




Scheme 5. Reaction conditions: i) $H_2$, 10% Pd/C, MeOH, r.t., 18 h. ii) $SOCl_2$, $CH_2Cl_2$, r.t., 18 h. iii) $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h. iv) $Br(CH_2)_nBr$, $n$ = 2–5, $K_2CO_3$, MeCN, reflux, 18 h.

77% yield. The syntheses of ligands **8a**–**d** (yields 28–50%) were performed by starting from diamide **10** (Scheme 5) and those of ligands **3a**–**d** (yields 14–40%) by starting from diamide **17** (Scheme 6), with the same synthetic steps as described for compounds **7a**–**d** and **2a**–**d**, respectively.

We also tried to prepare ligand **1** analogously to the preparation of ligand **6** (Scheme 6). Compound **18**, the hydroxyphenylglycine analogue of compound **11**, was therefore transformed by treatment with thionyl chloride into the dichloride **23** (90%), an analogue of dichloride **21**. Unlike




Scheme 6. Reaction conditions: i) $H_2$, 10% Pd/C, MeOH, r.t., 18 h. ii) $SOCl_2$, $CH_2Cl_2$, r.t., 18 h. iii) **22**, $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h. iv) $Br(CH_2)_nBr$, $n$ = 2–5, $K_2CO_3$, MeCN, reflux, 18 h. v) $K_2CO_3$, MeCN, reflux, 8 h. vi) **25**, $Cs_2CO_3$, MeCN, high dilution, reflux, 18 h. vii) PhOH, $K_2CO_3$, MeCN, reflux, 18 h.

the **21** + **22** macrocyclization, however, the attempted **23** + **22** macrocyclization failed to give the expected product **1**. For this reason we instead started from the macrocyclic dialcohol **24**, prepared by a 1:1 macrocyclization between **18** and **22**. The product **24** was transformed in two reaction steps (substitution of hydroxy group by treatment with thionyl chloride in dichloromethane and oxazoline ring closure by treatment with potassium carbonate in acetonitrile) into the target macrocycle **1**, in an overall yield of 27%, without isolation of the intermediate macrocyclic dichloride. Since **1** can be prepared from the macrocyclic derivative **24** and cannot be prepared by the 1:1 macrocylization of **23** + **22**, it can be concluded that the double intramolecular cyclization of **23** into the bis(oxazoline) derivative is faster and occurs prior to the macrocyclization step. The bis(oxazoline) derivative formed from **23** is rigid, with two *p*-hydroxyphenyls oriented up and down with respect to the best bis(oxazoline) plane, which makes the macrocyclization entropically unfavorable so that the concurrent linear polymerization prevails. However, the analogous bis(oxazoline) formed from **21** is much more flexible, due to the presence of the two methylene groups connecting the *p*-hydroxyphenyl components and the asymmetric carbons, so that the macrocyclization step is not so disfavored in this case.

For purposes of comparison, the corresponding nonmacrocyclic analogues were also prepared. The acyclic ligands **4** and **9** had previously been prepared from the diamides **17** and **10**, respectively,[30] and the synthesis of ligand **5** from **20c** and two equivalents of phenol is also outlined in Scheme 6.

## Catalysis

The catalytic properties of the $Cu^{I}$ complexes of the ligands **2a**–**d** and **7a**–**d** were examined in the cyclopropanation of styrene with ethyl diazoacetate as a model reaction. The reaction yields and the stereochemical outcomes (percentages *ee* and *de*) were determined by gas chromatography of the product mixtures on a Chirasil-DEX CB chiral column.[33]

The chemical yields of the cyclopropane products and the resulting enantio- and diastereoselectivities – expressed as percentages *ee* and *cis*/*trans* ratios and percentages *de*, respectively – obtained in the transformations of the macrocyclic ligands **2a**–**d**, **7a**–**d**, and the acyclic ligands **4**, **5**, and **9** with catalysis by the by $Cu^{I}$ complexes are given in Table 1.

The new macrocyclic bis(oxazolines) **2a**–**d** and **7a**–**d** on average showed slightly better enantioselectivities than their nonmacrocyclic analogues. The best enantioselectivity with the *cis* (73% *ee*) and the *trans* product (81% *ee*) was achieved with ligand **2b**.

However, the most intriguing results are those relating to diastereoselectivity. The majority of ligands described in the literature, as well as the nonmacrocyclic ligands **4**, **5**, and **9**, show diastereoselectivities in a rather narrow range of 20 to 45 *de*% in the case of the *trans*-cyclopropanes. Our macrocyclic ligands exhibited significant aberration from these values and the direction of these deviations depended on the ligand structure. The hydroxyphenylglycinol ligands **2a**–**d** showed enhanced diastereoselectivity in a range from 42 up to 86% *de*, while the diastereoselectivities in cyclopropanations catalyzed by the tyrosinol ligands **7a**–**d** were in a range from –10 (negative sign denotes excess of the *cis* product) to 18% *de*, thus being significantly lower than those observed for the acyclic ligands **4**, **5**, and **9** and the macrocycles **2a**–**d**. For the ligands **2a**–**d** a clear dependence of diastereoselectivity on the macrocyclic ring size was observed, with diastereoselectivity increasing almost linearly with the decreasing number of methylene groups in the alkyl spacers from 5 to 2.[28] It seems plausible that in the catalytic complex of the smallest ring **2a** ($n$ = 2), the $C_2$ to helical chirality transfer is more efficient than in the largest and more flexible **2d** ($n$ = 5; see Figure 1 and Figure 2). Consequently, the orientation and approach of styrene to the more helical carbene complex of **2a** is more restricted than in the case of the less helical complex of **2d**, which results in a much higher diastereoselectivity outcome in the first case.

The macrocyclic effect on diastereoselectivity can be deduced from comparison of *de* values for the macrocyclic **2c** ($n$ = 4; 54% *de*, Table 1) and **1** (56% *de*, Table 2) with those for the acyclic analogues **5** ($n$ = 4) (30% *de*, Table 2) and **4** (32% *de*, Table 1) giving a 24% *de* increase in the case of the macrocyclic ligands.

Table 1. Catalytic properties of ligands **2a**–**d**,[29] **7a**–**d**, **4**, **5**, and **9**.

| Ligand | *cis*/*trans* ratio (% *de*) | *ee* (*cis*) [%] configuration | *ee* (*trans*) [%] configuration | Yield [%][a] |
|---|---|---|---|---|
| **2a** | 7:93 (86) | 59 (1*S*,2*R*) | 65 (1*S*,2*S*) | 55 |
| **2b** | 16:84 (68) | 73 (1*S*,2*R*) | 81 (1*S*,2*S*) | 58 |
| **2c** | 23:77 (54) | 54 (1*S*,2*R*) | 69 (1*S*,2*S*) | 57 |
| **2d** | 29:71 (42) | 62 (1*S*,2*R*) | 68 (1*S*,2*S*) | 63 |
| **7a** | 46:54 (8) | 69 (1*R*,2*S*) | 67 (1*R*,2*R*) | 54 |
| **7b** | 55:45 (–10) | 70 (1*R*,2*S*) | 63 (1*R*,2*R*) | 45 |
| **7c** | 41:59 (18) | 57 (1*R*,2*S*) | 58 (1*R*,2*R*) | 76 |
| **7d** | 43:57 (14) | 64 (1*R*,2*S*) | 61 (1*R*,2*R*) | 63 |
| **4** | 34:66 (32) | 55 (1*S*,2*R*) | 60 (1*S*,2*S*) | 72 |
| **5** | 35:65 (30) | 57 (1*S*,2*R*) | 60 (1*S*,2*S*) | 93 |
| **9** | 40:60 (20) | 62 (1*R*,2*S*) | 56 (1*R*,2*R*) | 53 |

[a] Yields are not optimized.

Table 2. Catalytic properties of ligands **1**, **3a**–**d**, **6**, and **8a**–**d**.

| Ligand | *cis*/*trans* ratio (% *de*) | *ee* (*cis*) [%] configuration | *ee* (*trans*) [%] configuration | Yield [%][a] |
|---|---|---|---|---|
| **1** | 22:78 (56) | 36 (1*R*,2*S*) | 64 (1*S*,2*S*) | 47 |
| **3a** | 11:89 (78) | 20 (1*S*,2*R*) | 73 (1*S*,2*S*) | 62 |
| **3b** | 6:94 (88) | 31 (1*S*,2*R*) | 75 (1*S*,2*S*) | 65 |
| **3c** | 21:79 (58) | 11 (1*S*,2*R*) | 65 (1*S*,2*S*) | 67 |
| **3d** | 26:74 (48) | 37 (1*S*,2*R*) | 60 (1*S*,2*S*) | 78 |
| **6** | 43:57 (14) | 58 (1*R*,2*S*) | 54 (1*R*,2*R*) | 73 |
| **8a** | 51:49 (–2) | 52 (1*R*,2*S*) | 59 (1*R*,2*R*) | 67 |
| **8b** | 46:54 (8) | 67 (1*R*,2*S*) | 63 (1*R*,2*R*) | 52 |
| **8c** | 42:58 (16) | 63 (1*R*,2*S*) | 60 (1*R*,2*R*) | 67 |
| **8d** | 32:68 (36) | 67 (1*R*,2*S*) | 61 (1*R*,2*R*) | 23 |

[a] Yields are not optimized.

With the tyrosinol ligands **7a–d** no linear dependence of diastereoselectivity on the macrocycle ring size was observed. Because of the presence of the phenylmethylene groups in the chiral centers, such macrocycles are more flexible, and $C_2$ to helical chirality transfer must be less efficient. Consequently, the approach of styrene is less restricted, resulting in lower diastereoselectivity. In support of this, we had found earlier that selected ligands with phenyl rings at the stereogenic centers (**2**, **4**, and **5**) displayed stronger Cotton effects (CEs) than the ligands with benzyl groups at the stereogenic centers (**7** and **9**).[33] Larger CEs are attributed to stronger exciton coupling of the two aromatic chromophores at the stereogenic centers in **2**, **4**, and **5**. The differences in the spectra of **7** and **9** with respect to those of **2**, **4**, and **5** were attributed to the difference in geometry and the greater conformational freedom of the *para*-alkoxybenzyl chromophores in the former molecules.[34] These observations are consistent with the differences in helicity of the hydroxyphenylglycinol- and tyrosinol-derived $Cu^{+}$ macrocyclic complexes, which is in turn reflected in their diastereoselectivities.

The macrocyclic effect is absent in the tyrosinol series, as is evident from the *de* values for the macrocyclic ligand **6** (14% *de*, Table 2) and the acyclic ligand **9** (20% *de*, Table 1), the latter even showing a slightly higher diastereoselectivity than the macrocyclic ligand.

The results of the stereochemical outcomes in cyclopropanations catalyzed by $Cu^{I}$ complexes of the smallest ligand **1** and **6** and the ligands **3a–d** and **8a–d** with tetramethylated diphenylmethane bridges are collected in Table 2, while the dependence of diastereoselectivity on the size of the ligand expressed as the number of methylene groups in the spacers is shown in Figure 5.

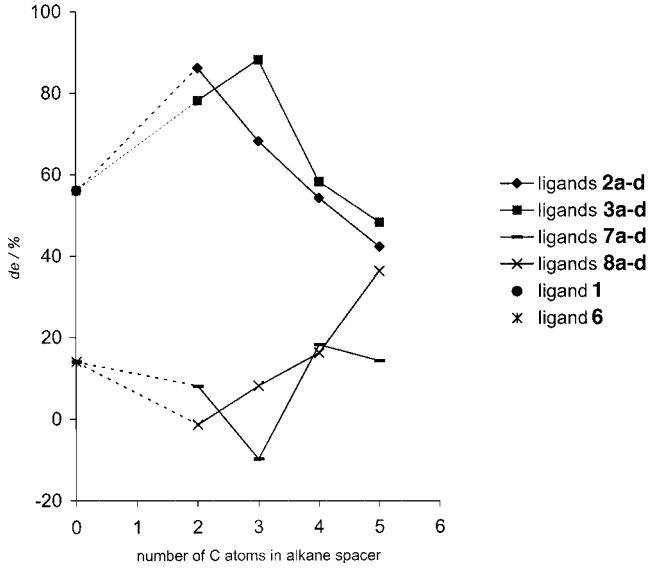



Figure 5. Comparison of the dependence of diastereoselectivity on the macrocycle ring size for the ligands **1**, **2**, **3**, **6**, **7**, and **8**.

The ligands **1** and **6**, with the smallest macrocyclic rings, showed rather low diastereoselectivities of 56% and 14% *de*, respectively, but even with the *p*-hydroxyphenylglycinol derivative **1** the *de* is considerably higher than that obtained with the tyrosinol derivative **6** and those with the acyclic ligands **4**, **5**, and **9** (Table 1).

Ligands **3a–d** showed, on average, slightly higher diastereoselectivities than their non-methylated analogues **2a–d**. *Moreover, ligand **3b**, with three carbon atoms in its alkane spacers, catalyzed cyclopropanation with the highest diastereoselectivity, not only among the ligands investigated in this work, but also among all of the bis(oxazoline) ligands described in the literature until now!*

Reduction of the free space in the reaction cavity through the introduction of additional methyl groups, as in the tetramethylated ligand **3b** ($n$ = 3), resulted in only a slight increase in the diastereoselectivity in relation to the non-methylated **2a** ($n$ = 2) (88% and 86%, resp); both macrocyclic ligands, however, exhibited peak diasteroselectivities within the series, showing that their sizes were close to the optimal size of the macrocycle for achievement of the highest *de*. The decrease in diastereoselectivity in the sequence **3b** to **3a** indicates that ring size reduction and subsequent restriction of conformational freedom of the catalytic complex resulted in a decrease in stereoselectivity.

The diastereoselectivities obtained for the ligands **8a–d** are within the same range as those of their non-methylated analogues **7a–d**, although with **8a–d** the relationship between diastereoselectivity and the macrocyclic ring size is clearly evident, increasing with the number of methylene groups in the spacers (Figure 5). Surprisingly, this relationship contrasts with that observed in the hydroxyphenylglycine series **2a–d** and **3a–d**, in which diastereoselectivity decreases with increasing macrocyclic ring size.

Finally, on comparison of the dependence of diastereoselectivities on ring size for all prepared and examined ligands (Figure 5), it can be concluded that the ligands of both hydroxyphenylglycinol and tyrosinol series show clear dependence of diastereoselectivity on the macrocyclic ring size. For both series of ligands the peak diastereoselectivity is observed for the ligands possessing spacers with 2–3 methylene groups; the configurations of the prevailing diastereomer, however, are opposite, *trans* for **2a** and **3b** and *cis* for **7b** and **8a**.

In terms of enantioselectivity, the tyrosinol derivatives **6** and **8a–d** did not show significant deviation from the values obtained for the corresponding macrocyclic non-methylated (**7a–d**) and acyclic (**9**) analogues. In contrast, the hydroxyphenylglycinol derivatives **3a–d** showed (relative to their non-methylated analogues **2a–d**) a huge drop in the enantioselectivities of the *cis* products (40% *ee* on average), while at the same time there was no significant variation of enantioselectivities for the *trans* products. It is interesting to note that catalysis with the hydroxyphenylglycine ligand **1**, the smallest of all the prepared macrocyclic bis(oxazolines), even resulted in the configurational inversion of the *cis*, but not of the *trans*, product. This unexpected result might be the consequence of the much smaller size and increased rigidity of **1** in relation to ligands of the **2** series, so that the intermediate catalytic states could be different in the two systems.

Significant effects on the diastereoselectivity were also observed in the $Cu^{I}$ complex of one out of five axially chiral macrocyclic phenanthroline and bipyridine ligands described by Benaglia's group.[35] This complex catalyzed cyclopropanation with a diastereoselectivity of –82% *de* (diastereomeric ratio 9:91 in favor of the *cis* product), while all the other ligands exhibited diastereoselectivities of approx. 50% *de*. Furthermore, the diastereoselectivities of $Cu^{I}$ complexes of achiral concave phenanthrolines described by Lüning's group[36] showed that the macrocyclic structure of the catalytic complex also had a strong influence on the diastereoselectivity outcome.

The observed relationship between stereochemical outcome and ligand structure can be explained as follows. As already mentioned in the Introduction, according to Pfaltz[4] the stereochemistry of the predominating *trans* product is determined by the more favorable styrene attack from direction **a**; in the formed transition state **I**, the bulky ethyl ester group faces a "small" hydrogen substituent. In contrast, the attack from direction **b** produces the less stable transition state **II**, due to steric repulsion between the large substituent on the bis(oxazoline) stereogenic center and the ethyl ester group (Figure 6).

The stereochemical outcomes of the reactions catalyzed by macrocyclic bis(oxazoline) complexes **2**- and **3**-$Cu^{I}$ could be interpreted in terms of the transition states **A**–**D** shown in Figure 7.

The formation of the predominant *trans*-(1*S*,2*S*) isomer could be explained by the formation of the transition state **A**. The *trans*-(1*R*,2*R*) enantiomer should be formed by the transition state **B**, with the styrene phenyl ring positioned closer to the bis(oxazoline) ligand, which produces steric repulsion and makes the transition state **B** less stable than that of **A**. The *cis*-(1*S*,2*R*) enantiomer is formed by the transition state **C** being more stable than that of **D**, due to more severe steric hindrance between styrene and bis(oxazoline) phenyls in the latter. The observed high diastereoselectivity in favor of the *trans* products can be explained by much less pronounced steric repulsions between styrene phenyls and the macrocyclic bridge connecting R groups of the bis(oxazoline) stereogenic centers in the transition states **A** and **B** than in the transition states **C** and **D**. In the former pair, the styrene phenyl is located below the bridge segment lying above the bis(oxazoline) plane while in the latter pair the styrene phenyls are located on the same side and close to the same bridge segment so that steric repulsion makes the formation of *cis* diastereomers energetically less favorable. It can be concluded that the extension of local $C_2$ chirality of the bis(oxazoline) unit into a larger volume and its transcription into helical chirality of the bridge increases the energetic discrimination between the transition states **A** and **B** on the one hand and those of **C** and **D** on the other, which results in considerably increased diastereoselectivity. Such discrimination is much less pronounced for the acyclic bis(oxazoline) catalytic complexes, however, so much lower diastereoselectivity is usually observed for acyclic catalysts.

In the ligand series **3a**–**d**, with four additional methyl groups on the phenyls of the 2,2-diphenylpropane bridges, a clear dependence of diastereoselectivity on the macrocycle ring size was again observed (Table 2). In the case of the ligand **3b** the highest *de* reported to date for this type of cyclopropanation (*de* 88%) was obtained. While the *ee* values for the *trans* products obtained by use of ligands **2a**–**d** and **3a**–**d** are comparable, those for the *cis* products are much lower in the case of the **3a**–**d** ligands, which can be explained in terms of the relative stabilities of the **C** and **D**

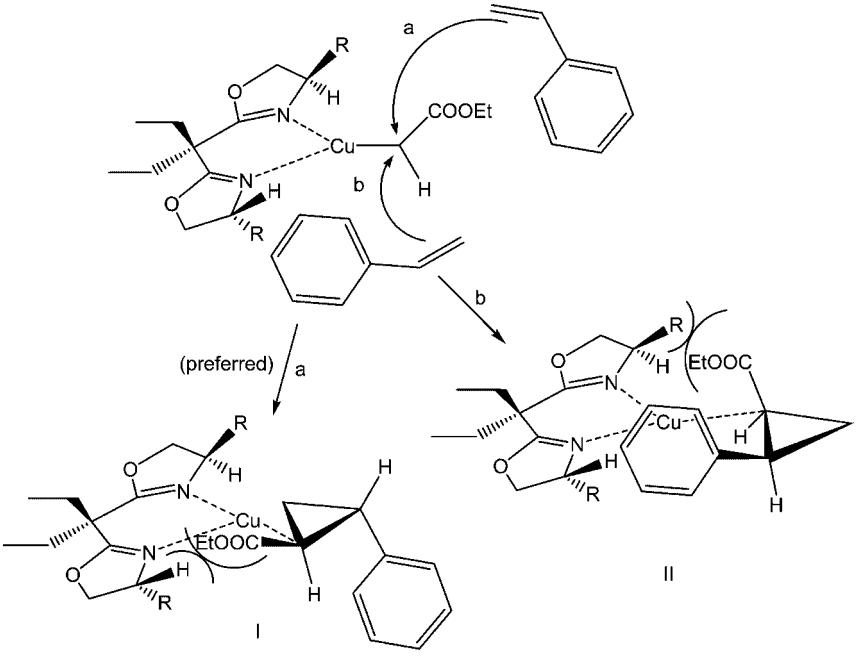



Figure 6. Stereochemical course of cyclopropanation of styrene by ethyl diazoacetate catalyzed by chiral bis(oxazoline)–$Cu^{I}$ complex as proposed by Pfaltz.[4]

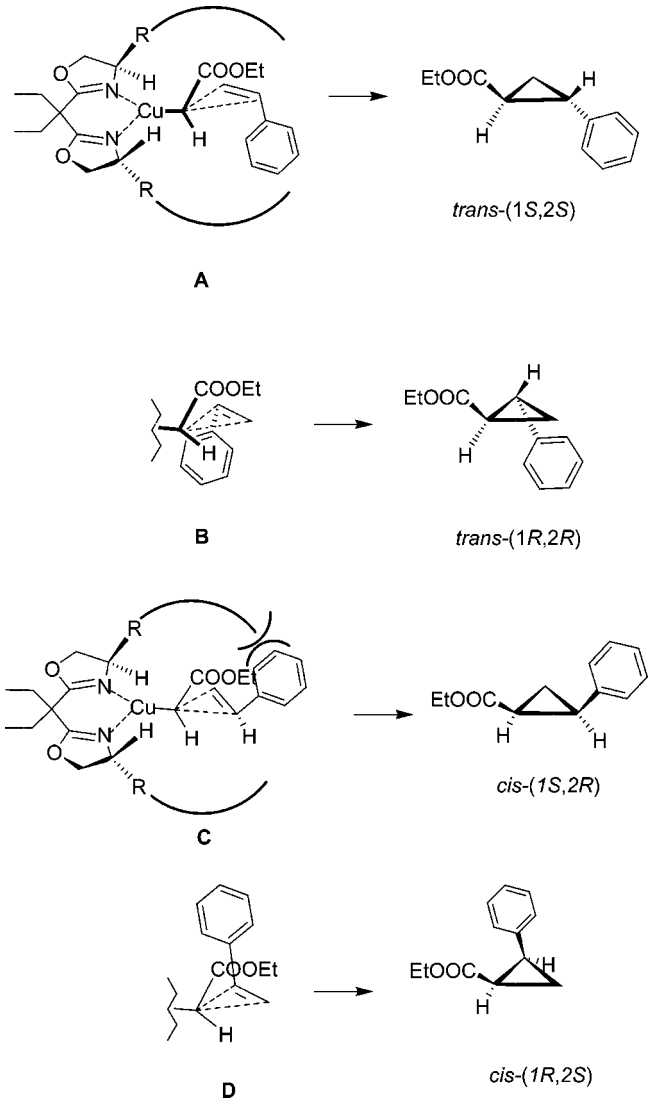



Figure 7. Transition states (**A**, **B**, **C**, **D**) leading to stereoisomeric cyclopropane products. The curves on the bis(oxazoline) R substituents indicate the orientation of the connecting bridge above (thick line) and bellow (dotted line) the bis(oxazoline) plane in the macrocyclic ligands.

transition states for the catalytic complexes **2a**–**d** and **3a**–**d**. The presence of four additional methyl groups in the bridge in the **3a**–**d** series reduces the size of the macrocycle relative to the **2a**–**d** ligands and produces additional steric interactions in the corresponding transition states, and because of these steric interactions the transition states **C** in the **3a**–**d** series should be less stable than those in the **2a**–**d** series. Consequently, less *cis*-(1*S*,2*R*) enantiomer should be formed in the reactions catalyzed by **3a**–**d** catalytic complexes and hence lower *ee* values for *cis* products should be observed.

The main difference between the macrocycles of series **2** and **3** and of the tyrosinol series (**7** and **8**) is the additional methylene groups, which make the macrocyclic bridges significantly more flexible in the ligands of the tyrosinol series. Because of their flexibility, the tyrosinol ligands can easily adopt transition states giving both *cis* and *trans* products, which results in poorer differentiation and hence lower diastereoselectivity.

## Conclusions

The new macrocyclic bis(oxazolines) **1**, **2a**–**d**, **3a**–**d**, **6**, **7a**–**d**, and **8a**–**d** have been synthesized. Their copper(I) complexes are the first representatives of conceptually new supramolecular organometallic catalysts containing chiral reaction spaces. The catalytic properties of such macrocyclic copper(I) complexes were tested in the cyclopropanation of styrene with ethyl diazoacetate as the model reaction, and it was found that the macrocycle structure and its cavity size have profound effects on the diastereoselectivity outcomes of the selected transformation. A clear dependence of diastereoselectivity on the size of the macrocyclic ring was observed (Figure 5) and explained. The more flexible tyrosinol derivatives **7a**–**d** and **8a**–**d** catalyzed cyclopropanations with unusually small diastereoselectivities (–10 to 36% *de*), while in contrast the more rigid hydroxyphenylglycine derivatives **2a**–**d** and **3a**–**d** exhibited surprisingly high diastereoselectivities (42–88% *de*). With the idea of increasing the steric discrimination by constraining the macrocyclic ring, four methyl substituents were added on the bisphenol bridge, giving the ligands **3a**–**d** and **8a**–**d**. *A diastereomeric ratio of 94:6 trans/cis (88% de) was achieved with the ligand **3b**. This result represents the highest diastereoselectivity observed to date in the cyclopropanation of styrene with ethyl diazoacetate catalyzed by the bis(oxazoline) class of $Cu^{I}$ catalytic complexes.* Apparently, the helicity, size, and rigidity of the macrocyclic reaction space guide the approach and orientation of the styrene, resulting, in the cases of the ligands **2a** and **3b**, in the formation of the *trans*-(*S*,*S*)-cyclopropane products with 86 and 88% *de* values and 65 and 75% *ee* values, respectively. It was observed that the introduction of methyl substituents into the bisphenolic bridges of the more rigid hydroxyphenylglycine-derived ligands **2a**–**d**, to give **3a**–**d**, profoundly reduced the enantioselectivity of the *cis* products (40% *ee* on average) without any significant influence on the enantioselectivity of the *trans* products and diastereoselectivity; however, this effect is absent in the more flexible tyrosinol-derived ligands **8a**–**d**.

These results, especially the exceptionally high diastereoselectivities obtained with the catalytic complexes of the rigid hydroxyphenylglycine-derived macrocyclic bis(oxazolines)s **2a** and **3d** and the clearly observed dependence of diastereoselectivity on the macrocycle ring size and its helicity, point the way to a new generation of organometallic catalysts and could be of wide applicability for many other catalytic transformations using $C_2$ chiral organometallic catalysts.[27]

## Experimental Section

**General:** $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini XL 300 spectrometer with tetramethylsilane (TMS) as an

internal standard at 300 MHz, in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All NMR spectra are assigned as shown in Figure 8.

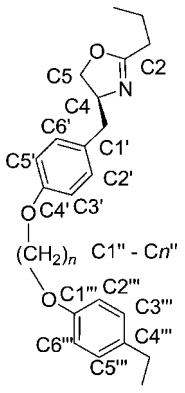



Figure 8. Atom numbering.

Spin multiplicities are abbreviated as s (singlet), d (doublet), t (triplet) pt (pseudotriplet – doublet of doublets), qua (quadruplet), q (quintet) and m (multiplet). IR spectra were recorded on a FT *ABB Bomem MB 102 IR* spectrometer on KBr plates with CsI optics and *DTGS* detector. Wavenumbers ($\tilde{\nu}$) are reported as reciprocal centimeters ($cm^{-1}$). Melting points ($t_m$) were determined on an *Electrothermal Melting Point Apparatus* and are uncorrected. Optical rotations were measured at a temperature of 25 °C on an *Optical Activity AA-10 Automatic Polarimeter* in 1 dm cells at a wavelength of 589 nm. Low-resolution TOF-ESMS were recorded on a *ThermoQuest FT/MS 2001* DD *Fourier Transform Mass Spectrometer* (*Madison*), fitted with a 3 T superconducting magnet. HRMS were measure with *Varian MAT 311* and *MAT 8200* spectrometers. Prepared compounds were purified chromatographically by preparative TLC on *Merck* $HF_{254}$ silica gel. Reagents were purchased from commercial suppliers (*Fluka*, *Sigma–Aldrich*, *Kemika*) and were used without further purification. All solvents were purified and dried by standard laboratory procedures. All reported reaction yields are average values of all reactions performed. Macrocyclic compounds have been named according to phane nomenclature.[37,38]

### Synthesis

The starting dibenzyldiamides **10** and **17** were prepared by the procedures developed in our research group.[30] Compound **22** was prepared by the procedure described in the literature.[32]

**Preparation of 2,2-Bis(4-hydroxy-3,5-dimethylphenyl)propane (25):** Conc. $H_2SO_4$ (14.4 g, 147 mmol) was added slowly to a stirred mixture of 2,6-dimethylphenol (10.0 g; 81.9 mmol), acetone (2.38 g; 40.9 mmol) and water (3.30 g; 183 mmol) cooled to 0 °C, and left overnight at 4 °C. The solid reaction mixture was dissolved in an acetone/methanol mixture (7:3, 80 mL) and neutralized with aq. $Na_2CO_3$ (1 M). The pale brown precipitate was filtered off, washed with water, dried and recrystallized from toluene, in a process that gave product **25** (8.96 g, 77%) as a pale brown, crystalline powder. $t_m$ = 166 °C. $^1$H NMR: δ = 6.87 (s, 4 H, C3 H, C5 H), 4.15 (br s, 2 H, C1OH), 2.34 (s, 12 H, C2$CH_3$, C6$CH_3$), 1.62 (s, 6 H, C4C$CH_3$) ppm. $^{13}$C NMR: δ = 149.7 (C1), 142.6 (C4), 126.8 (C3, C5), 122.0 (C2, C6), 41.2 (*C*$Me_2$), 31.1 (C*Me*$_2$), 16.0 (C2*C*$H_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3351, 3041, 2956, 2923, 2862, 1604, 1487, 1297, 1221, 1179, 1112, 991, 884, 867, 771, 732, 581 $cm^{-1}$. Elemental analysis calcd. (%) for $C_{19}H_{24}O_2$ (284.40): calcd. C 80.24, H 8.51, O 11.25; found: C 80.38, H 8.61.

**General Procedure for Preparation of Diamides 11 and 18 from Diamides 10 and 17:** Pd/C catalyst (10%, 400 mg) was added to a solution of dibenzyldiamide (4.00 g) in methanol (150 mL). The reaction mixture was mixed at room temperature in Parr hydrogenator at 500 kPa overnight and was then filtered off through a celite pad. Products were obtained in almost quantitative yields by evaporation of filtrate without any TLC- or NMR-visible impurities.

**2,2-Diethyl-*N*$^1$,*N*$^3$-bis[(*S*)-1-(hydroxymethyl)-2-(4-hydroxyphenyl)-ethyl]malonamide (11):** This compound was obtained from **10** (4.0 g, 6.28 mmol) in a process that gave product **11** (2.87 g, 99%) as a white/yellow foam. $[\alpha]_D$ = –34.8 (*c* = 0.89 in MeOH). $^1$H NMR ([D$_6$]DMSO): δ = 9.12 (s, 2 H, C4′OH), 8.18 (d, *J* = 8.4 Hz, 2 H, NH), 6.98 (d, *J* = 8.4 Hz, 4 H, C2′H, C6′H), 6.63 (d, *J* = 8.4 Hz, 4 H, C3′H, C5′H), 4.78 (br s, 2 H, C*H), 3.94 (m, 2 H, C$H_a$OH), 3.72 (br s, 2 H, $CH_2O$*H*), 3.28 (m, 2 H, C$H_b$OH), 2.72 (dd, *J* = 5.6 and 13.7 Hz, 2 H, C1′-$CH_a$), 2.53 (m, 2 H, C1′-$CH_b$), 1.68 (m, 4 H, C$H_2CH_3$), 0.40 (t, *J* = 7.2 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR ([D$_6$]DMSO): δ = 172.6 (C=O), 155.7 (C4′), 130.1 (C1′), 129.4 (C2′, C6′), 115.1 (C3′, C5′), 62.7 ($CH_2$OH), 57.3 (C$Et_2$), 52.7 (C*), 35.6 (*C*$H_2$C1′), 29.1 (*C*$H_2CH_3$), 8.9 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3346, 2967, 2939, 2877, 1653, 1614, 1515, 1457, 1361, 1237, 1172, 1108, 1039, 954, 824, 541, 507 $cm^{-1}$. $C_{25}H_{34}N_2O_6$ (458.55): calcd. C 65.48, H 7.47, N 6.11; found: C 65.36, H 7.28, N 6.16. HRMS: $[M]^+$ calculated for $C_{25}H_{34}N_2O_6$: 458.2417; found: 458.2417.

**2,2-Diethyl-*N*$^1$,*N*$^3$-bis[(*R*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]-malonamide (18):** This compound was obtained from **17** (4.00 g, 6.55 mmol) in a process that gave product **18** (2.818 g, 99%) as a pale yellow foam. $[\alpha]_D$ = –82.2 (*c* = 0.85 in MeOH). $^1$H NMR ([D$_6$]-DMSO): δ = 9.23 (s, 2 H, C4′OH), 8.72 (d, *J* = 8.7 Hz, 2 H, NH), 7.04 (d, *J* = 7.6 Hz, 4 H, C2′H, C6′H), 6.64 (d, *J* = 7.6 Hz, 4 H, C3′H, C5′H), 4.80 (m, 4 H, C*H and $CH_2O$*H*), 3.48 (m, 4 H, C$H_2$OH), 1.83 (m, 4 H, C$H_2CH_3$), 0.59 (t, *J* = 6.8 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR ([D$_6$]DMSO): δ = 172.8 (C=O), 156.5 (C4′), 131.7 (C1′), 128.1 (C2′, C6′), 115.0 (C3′, C5′), 64.8 ($CH_2$OH), 57.5 (C$Et_2$), 54.8 (C*), 29.6 (*C*$H_2CH_3$), 9.3 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3327, 2969, 2939, 2877, 1655, 1615, 1515, 1457, 1382, 1235, 1173, 1073, 1035, 832, 584, 543 $cm^{-1}$. $C_{23}H_{30}N_2O_6$ (430.50): calcd. C 64.15, H 7.03, N 6.51; found: C 64.37, H 7.30, N 6.78.

**General Procedure for Preparation of ω-Bromo-Alkylated Compounds 12, 15a–d, and 19a–d from Phenolic Compounds Bisphenol A, 11, and 18:** The phenolic compound (1.00 mmol) was dissolved in acetonitrile (50 mL) and $K_2CO_3$ (553 mg, 4.00 mmol) and the α,ω-dibromoalkane (20.0 mmol) was added. The reaction mixture was stirred and heated to reflux overnight. After the system had cooled to room temperature, inorganic salts were filtered off and the filtrate was evaporated. The oily residue was purified by preparative TLC in a $CH_2Cl_2$/MeOH (10:1) solvent system.

**2,2-Bis[4-(4-bromobutoxy)phenyl]propane (12):** This compound was obtained from bisphenol A (228 mg) and 1,4-dibromobutane (4.32 g); after preparative TLC chromatography in hexanes, product **12** (209 mg, 42%) was obtained as white crystals. $t_m$ = 67 °C. $^1$H NMR: δ = 7.13 (d, *J* = 8.7 Hz, 4 H, C3′′′H, C5′′′H), 6.78 (d, *J* = 9.0 Hz, 4 H, C2′′′H, C6′′′H), 3.96 (t, *J* = 5.9 Hz, 4 H, C4′′$H_2$), 3.48 (t, *J* = 6.5 Hz, 4 H, $CH_2$Br), 2.06 (m, 4 H, C2′′H), 1.94 (m, 4 H, C3′′H), 1.63 (s, 6 H, $CH_3$) ppm. $^{13}$C NMR: δ = 156.6 (C1′′′), 143.1 (C4′′′), 127.6 (C3′′′, C5′′′), 113.6 (C2′′′, C6′′′), 66.9 (C4′′),

41.4 ($CMe_2$), 33.3 (C1′′), 30.8 ($CMe_2$), 29.2 (C2′′), 27.7 (C3′′) ppm. IR (KBr): $\tilde{\nu}$ = 3053, 2946, 2867, 1608, 1513, 1278, 1249, 1182, 1046, 832, 741, 550 $cm^{-1}$. $C_{23}H_{30}Br_2O_2$ (498.32): calcd. C 55.44, H 6.07; found: C 55.20, H 5.97.

**$N^1$,$N^3$-Bis{(*S*)-2-[4-(2-bromoethoxy)phenyl]-1-(hydroxymethyl)-ethyl}-2,2-diethylmalonamide (15a):** This compound was obtained from **11** (459 mg) and 1,2-dibromoethane (3.76 g) in a process that gave product **15a** (195 mg, 29%) as a pale yellow, thick oil. $[\alpha]_D$ = –22.2 (*c* = 1.17 in MeOH). $^1$H NMR: $\delta$ = 7.11 (d, *J* = 8.0 Hz, 4 H, C2′H, C6′H), 6.82 (d, *J* = 7.7 Hz, 4 H, C3′H, C5′H), 6.76 (d, *J* = 8.2 Hz, 2 H, NH), 4.24 (m, 6 H, C*H and C1′′$H_2$), 3.72 (m, 2 H, C$H_a$OH), 3.67, (t, *J* = 6.0 Hz, 4 H, C2′′$H_2$), 3.47 (dd, *J* = 6.0 and 11.3 Hz, 2 H, C$H_b$OH), 2.80 (dd, *J* = 6.2 and 13.9 Hz, 2 H, C1′-$CH_a$), 2.67 (dd, *J* = 8.6 and 13.9 Hz, 2 H, C1′-$CH_b$), 1.71 (m, 4 H, C$H_2$CH$_3$), 0.49 (t, *J* = 7.1 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.2 (C=O), 156.8 (C4′), 130.3 (C1′), 130.0 (C2′, C6′), 114.8 (C3′, C5′), 67.8 (C1′′), 64.3 ($CH_2OH$), 58.1 ($CEt_2$), 52.8 (C*), 36.0 ($CH_2$C1′), 29.0 (C2′′), 26.5 ($CH_2CH_3$), 8.2 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3336, 2970, 2930, 2877, 1655, 1511, 1244, 1178, 1018, 833, 574 $cm^{-1}$. $C_{29}H_{40}Br_2N_2O_6$ (672.48): calcd. C 51.80, H 6.00, N 4.17; found: C 51.70, H 6.10, N 4.30.

**$N^1$,$N^3$-Bis{(*S*)-2-[4-(3-bromopropoxy)phenyl]-1-(hydroxymethyl)-ethyl}-2,2-diethylmalonamide (15b):** This compound was obtained from **11** (459 mg) and 1,3-dibromopropane (4.04 g) in a process that gave product **15b** (406 mg, 58%) as a pale yellow, thick oil. $[\alpha]_D$ = –26.3 (*c* = 2.13 in MeOH). $^1$H NMR: $\delta$ = 7.10 (d, *J* = 8.2 Hz, 4 H, C2′H, C6′H), 6.82 (m, 6 H, C3′H, C5′H and NH), 4.23 (brs, 2 H, C*H), 4.04 (t, *J* = 5.8 Hz, 4 H, C1′′$H_2$), 3.72 (dd, *J* = 3.3 and 8.0 Hz, 2 H, C$H_a$OH), 3.58 (m, 8 H, C$H_b$OH and C3′′$H_2$ and $CH_2OH$), 2.80 (dd, *J* = 6.0 and 11.3 Hz, 2 H, C$H_b$OH), 2.68 (m, 2 H, C1′-$CH_b$), 2.28 (q, *J* = 6.0 Hz, 4 H, C2′′$H_2$), 1.72 (m, 4 H, C$H_2$CH$_3$), 0.50 (t, *J* = 7.1 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.2 (C=O), 157.3 (C4′), 129.9 (C2′, C6′), 129.7 (C1′), 114.5 (C3′, C5′), 65.1 (C1′′), 64.2 ($CH_2OH$), 58.1 ($CEt_2$), 52.8 (C*), 35.9 ($CH_2$C1′), 32.1 (C3′′), 29.9 (C2′′), 26.4 ($CH_2CH_3$), 8.1 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2970, 2934, 2877, 1638, 1509, 1455, 1244, 1034, 816 $cm^{-1}$.

**$N^1$,$N^3$-Bis{(*S*)-2-[4-(4-bromobutoxy)phenyl]-1-(hydroxymethyl)-ethyl}-2,2-diethylmalonamide (15c):** This compound was obtained from **11** (459 mg) and 1,4-dibromobutane (4.32 g) in a process that gave product **15c** (408 mg, 56%) as a pale yellow, thick oil. $[\alpha]_D$ = –23.9 (*c* = 6.99 in MeOH). $^1$H NMR: $\delta$ = 7.08 (d, *J* = 8.5 Hz, 4 H, C2′H, C6′H), 6.77 (m, 6 H, C3′H, C5′H and NH), 4.21 (brs, 2 H, C*H), 3.93 (t, *J* = 5.9 Hz, 4 H, C1′′$H_2$), 3.70 (m, 2 H, C$H_a$OH), 3.46 (m, 6 H, C$H_b$OH and C4′′$H_2$), 2.78 (dd, *J* = 6.3 and 14.0 Hz, 2 H, C1′-$CH_a$), 2.66 (dd, *J* = 8.4 and 14.0 Hz, 2 H, C1′-$CH_b$), 2.03 (m, 4 H, C3′′$H_2$), 1.90 (m, 4 H, C2′′$H_2$), 1.71 (m, 4 H, C$H_2$CH$_3$), 0.50 (t, *J* = 7.2 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.3 (C=O), 157.6 (C4′), 130.0 (C2′, C6′), 129.6 (C1′), 114.5 (C3′, C5′), 66.7 (C1′′), 64.2 ($CH_2OH$), 58.0 ($CEt_2$), 52.7 (C*), 35.9 ($CH_2$C1′), 33.2 (C4′′), 29.2 (C3′′), 27.6 (C2′′), 26.3 ($CH_2CH_3$), 8.0 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3411, 3325, 2958, 2877, 1635, 1508, 1246, 1176, 1042, 945, 825 $cm^{-1}$. HRMS: $[M]^+$ calculated for $C_{33}H_{48}Br_2N_2O_6$: 728.18585; found: 728.18590.

**$N^1$,$N^3$-Bis{(*S*)-2-[4-(5-bromopentyloxy)phenyl]-1-(hydroxymethyl)-ethyl}-2,2-diethylmalonamide (15d):** This compound was obtained from **11** (459 mg) and 1,5-dibromopentane (4.60 g) in a process that gave product **15d** (446 mg, 59%) as a pale yellow, thick oil. $[\alpha]_D$ = –22.1 (*c* = 3.53 in MeOH). $^1$H NMR: $\delta$ = 7.09 (d, *J* = 8.4 Hz, 4 H, C2′H, C6′H), 6.80 (d, *J* = 8.5 Hz, 4 H, C3′H, C5′H), 6.72 (d, *J* = 8.1 Hz, 2 H, NH), 4.21 (m, 2 H, C*H), 3.91 (t, *J* = 6.3 Hz, 4 H, C1′′$H_2$), 3.72 (m, 4 H, C$H_a$O$H$), 3.43 (m, 6 H, C$H_b$OH and C5′′$H_2$), 2.79 (dd, *J* = 6.4 and 13.9 Hz, 2 H, C1′-$CH_a$), 2.66 (dd, *J* = 8.5 and 13.9 Hz, 2 H, C1′-$CH_b$), 1.92 (m, 4 H, C4′′$H_2$), 1.76 (m, 8 H, C$H_2$CH$_3$ and C2′′$H_2$), 1.60 (m, 4 H, C$H_2$CH$_3$), 0.51 (t, *J* = 7.3 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.4 (C=O), 157.8 (C4′), 130.0 (C2′, C6′), 129.4 (C1′), 114.6 (C3′, C5′), 67.4 (C1′′), 64.4 ($CH_2OH$), 58.1 ($CEt_2$), 52.7 (C*), 35.9 ($CH_2$C1′), 33.4 (C5′′), 32.2 (C4′′), 28.2 (C2′′), 26.5 ($CH_2CH_3$), 26.5 (C3′′), 8.1 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3402, 3340, 2936, 2873, 1636, 1512, 1245, 1177, 1044, 816, 636, 553 $cm^{-1}$. $C_{35}H_{52}Br_2N_2O_6$ (756.64): calcd. C 55.56, H 6.93, N 3.70; found: C 55.45, H 7.14, N 3.91.

**$N^1$,$N^3$-Bis{(*R*)-1-[4-(2-bromoethoxy)phenyl]-2-hydroxyethyl}-2,2-diethylmalonamide (19a):** This compound was obtained from **18** (430 mg) and 1,2-dibromoethane (3.76 g) in a process that gave product **19a** (129 mg, 20%) as a pale yellow, thick oil. $[\alpha]_D$ = –66.1 (*c* = 1.05 in MeOH). $^1$H NMR: $\delta$ = 7.55 (d, *J* = 7.4 Hz, 2 H, NH), 7.21 (d, *J* = 8.8 Hz, 4 H, C2′H, C6′H), 6.87 (d, *J* = 8.5 Hz, 4 H, C3′H, C5′H), 5.12 (m, 2 H, C*H), 4.27 (t, *J* = 6.2 Hz, 4 H, C1′′$H_2$), 3.82 (m, 4 H, C$H_2$OH), 3.64, (t, *J* = 6.2 Hz, 4 H, C2′′$H_2$), 3.31 (brs, 2 H, OH), 1.95 (m, 4 H, C$H_2$CH$_3$), 0.81 (t, *J* = 6.5 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.2 (C=O), 157.5 (C4′), 131.5 (C1′), 127.8 (C2′, C6′), 114.9 (C3′, C5′), 67.7 (C1′′), 66.2 ($CH_2OH$), 58.2 ($CEt_2$), 55.0 (C*), 29.0 (C2′′), 28.2 ($CH_2CH_3$), 8.8 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3334, 3036, 2967, 2933, 2876, 1654, 1613, 1511, 1457, 1385, 1244, 1178, 1074, 1031, 877, 829, 573, 542 $cm^{-1}$. $C_{27}H_{36}Br_2N_2O_6$ (644.42): calcd. C 50.33, H 5.63, N 4.35; found: C 50.44, H 5.38, N 4.37.

**$N^1$,$N^3$-Bis{(*R*)-1-[4-(3-bromopropoxy)phenyl]-2-hydroxyethyl}-2,2-diethylmalonamide (19b):** This compound was obtained from **18** (430 mg) and 1,3-dibromopropane (4.04 g) in a process that gave product **19b** (316 mg, 47%) as a pale yellow, thick oil. $[\alpha]_D$ = –66.9 (*c* = 0.51 in MeOH). $^1$H NMR: $\delta$ = 7.55 (d, *J* = 7.4 Hz, 2 H, NH), 7.20 (d, *J* = 8.7 Hz, 4 H, C2′H, C6′H), 6.87 (d, *J* = 8.5 Hz, 4 H, C3′H, C5′H), 5.11 (m, 2 H, C*H), 4.08 (t, *J* = 5.8 Hz, 4 H, C1′′$H_2$), 3.88 (dd, *J* = 3.8 and 11.3 Hz, 2 H, C$H_a$OH), 3.78 (dd, *J* = 6.9 and 11.3 Hz, 2 H, C$H_b$OH), 3.60 (t, *J* = 6.4 Hz, 4 H, C3′′$H_2$), 2.96 (brs, 2 H, OH), 2.31 (q, *J* = 6.1 Hz, 4 H, C2′′$H_2$), 1.95 (q, *J* = 7.3 Hz, 4 H, C$H_2$CH$_3$), 0.82 (t, *J* = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.2 (C=O), 157.9 (C4′), 131.2 (C1′), 127.7 (C2′, C6′), 114.4 (C3′, C5′), 65.6 ($CH_2OH$), 65.0 (C1′′), 58.1 ($CEt_2$), 55.0 (C*), 32.1 (C3′′), 29.9 (C2′′), 27.0 ($CH_2CH_3$), 8.4 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3396, 3326, 3062, 2970, 2933, 2877, 1654, 1614, 1512, 1454, 1234, 1177, 1072, 1031, 929, 828, 727, 609, 541 $cm^{-1}$. $C_{29}H_{40}Br_2N_2O_6$ (672.48): calcd. C 51.80, H 6.00, N 4.17; found: C 51.92, H 6.20, N 4.28.

**$N^1$,$N^3$-Bis{(*R*)-1-[4-(4-bromobutoxy)phenyl]-2-hydroxyethyl}-2,2-diethylmalonamide (19c):** This compound was obtained from **18** (430 mg) and 1,4-dibromobutane (4.32 g) in a process that gave product **19c** (448 mg, 64%) as a pale yellow, thick oil. $[\alpha]_D$ = –61.1 ($\gamma$ = 85.4 g dm$^{-3}$, MeOH). $^1$H NMR: $\delta$ = 7.64 (d, *J* = 8.0 Hz, 2 H, NH), 7.21 (d, *J* = 8.2 Hz, 4 H, C2′H, C6′H), 6.79 (d, *J* = 8.2 Hz, 4 H, C3′H, C5′H), 5.16 (m, 2 H, C*H), 4.43 (brs, 2 H, OH), 3.93 (t, *J* = 5.9 Hz, 4 H, C1′′$H_2$), 3.83 (brs, 4 H, C$H_2$OH), 3.47 (t, *J* = 6.4 Hz, 4 H, C4′′$H_2$), 2.56–1.86 (m, 12 H, C$H_2$CH$_3$ and C2′′$H_2$ and C3′′$H_2$), 0.74 (t, *J* = 6.9 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.4 (C=O), 158.3 (C4′), 131.1 (C1′), 127.9 (C2′, C6′), 114.5 (C3′, C5′), 66.7 (C1′′), 65.9 ($CH_2OH$), 58.2 ($CEt_2$), 55.1 (C*), 33.3 (C4′′), 29.2 (C3′′), 27.7 (C2′′), 26.7 ($CH_2CH_3$), 8.3 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 3337, 2963, 2876, 1655, 1513, 1246, 1178, 1038, 830, 555 $cm^{-1}$.

**$N^1$,$N^3$-Bis{(*R*)-1-[4-(5-bromopentyloxy)phenyl]-2-hydroxyethyl}-2,2-diethylmalonamide (19d):** This compound was obtained from **18** (430 mg) and 1,5-dibromopentane (4.60 g) in a process that gave

product **19d** (342 mg, 47%) as a pale yellow, thick oil. $[\alpha]_D$ = –56.8 ($c$ = 5.74 in MeOH). $^1$H NMR: $\delta$ = 7.67 (d, $J$ = 8.0 Hz, 2 H, NH), 7.20 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.80 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 5.13 (m, 2 H, C*H), 4.48 (brs, 2 H, OH), 3.91 (t, $J$ = 6.2 Hz, 4 H, C1′′$H_2$), 3.81 (m, 4 H, C$H_2$OH), 3.43 (m, 4 H, C5′′$H_2$), 1.92 (m, 8 H, C$H_2$CH$_3$ and C4′′$H_2$), 1.78 (m, 4 H, C2′′$H_2$), 1.60 (m, 4 H, C3′′$H_2$), 0.74 (t, $J$ = 7.1 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 173.4 (C=O), 158.4 (C4′), 131.0 (C1′), 127.8 (C2′, C6′), 114.5 (C3′, C5′), 67.4 (C1′′), 65.7 (CH$_2$OH), 58.2 (CEt$_2$), 55.0 (C*), 33.5 (C5′′), 32.2 (C4′′), 28.2 (C2′′), 26.8 (*C*H$_2$CH$_3$), 24.6 (C3′′), 8.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3423, 3334, 2943, 2877, 1645, 1508, 1243, 1177, 1037, 829, 727, 541 cm$^{-1}$. $C_{33}H_{38}Br_2N_2O_6$ (718.51): calcd. C 55.16, H 5.33, N 3.90; found: C 55.11, H 5.75, N 4.15.

**General Procedures for the Preparation of Dichlorides 14, 16a–d, 20a–d, 21, and 23 from Dihydroxy Compounds 13, 15a–d, 19a–d, 12, and 18. Method *a*:** Thionyl chloride (1.19 g, 10.0 mmol) was added to a solution of the dihydroxy compound (1.00 mmol) in dichloromethane (20 mL) and the reaction mixture was mixed at room temperature overnight. Solvent was then evaporated and the dry residue was purified by preparative TLC in $CH_2Cl_2$/MeOH (20:1) to give the product.

**Method *b*:** Triphosgene (252 mg, 0.844 mmol) was added with stirring to a solution of triphenylphosphane (608 mg, 2.32 mmol) in dichloromethane (15 mL), cooled down to 0 °C. After gas evolution had subsided, a dichloromethane solution of the dihydroxy compound (1.00 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, and then treated as in Method *a*.

**(12*S*,18*S*)-12,18-Bis(chloromethyl)-15,15-diethyl-2,2-dimethyl-4,9,21,26-tetraoxa-13,17-diaza-1,3,10,20(1,4)-tetrabenzenacyclohexacosaphane-14,16-dione (14):** This compound was obtained from **13** (795 mg) by Method *b* in a process that gave product **14** (466 mg, 56%) as a white foam. $[\alpha]_D$ = –8.6 ($c$ = 1.34 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.29 (d, $J$ = 8.0 Hz, 2 H, NH), 7.11 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H or C3′′′H, C5′′′H), 7.10 (d, $J$ = 8.7 Hz, 4 H, C3′′′H, C5′′′H or C2′H, C6′H), 6.80 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H or C2′′′H, C6′′′H), 6.74 (d, $J$ = 8.7 Hz, 4 H, C2′′′H, C6′′′H, C6′′′H or C3′H, C5′H), 4.43 (m, 2 H, C*H), 4.00 (brs, 8 H, C1′′$H_2$ and C4′′$H_2$), 3.64 (dd, $J$ = 4.6 Hz, $J$ = 11.3 Hz, 2 H, C$H_a$Cl), 3.55 (dd, $J$ = 3.6 and 11.0 Hz, 2 H, C$H_b$Cl), 2.84 (m, 4 H, C1′-CH$_2$), 1.93 (brs, 8 H, C2′′$H_2$ and C3′′$H_2$), 1.72 (m, 4 H, C$H_2$CH$_3$), 1.63 (s, 6 H, C4′′′CCH$_3$), 0.57 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.5 (C=O), 157.8 (C4′), 156.5 (C1′′′), 143.1 (C4′′′), 130.1 (C2′, C6′), 128.6 (C1′), 127.6 (C3′′′, C5′′′), 114.7 (C3′, C5′), 113.8 (C2′′′, C6′′′), 67.1 (C1′′ or C4′′), 67.0 (C4′′ or C1′′), 57.9 (CEt$_2$), 50.7 (C*), 46.6 (CH$_2$Cl), 41.3 (*C*Me$_2$), 36.5 (*C*H$_2$C1′), 30.6 (C*Me*$_2$), 30.0 (*C*H$_2$CH$_3$), 25.4 (C2′′ or C3′′), 25.3 (C3′′ and C2′′), 8.7 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3319, 3036, 2963, 2874, 1638, 1511, 1248, 1180, 1025, 829, 786, 554 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*S*)-2-[4-(2-bromoethoxy)phenyl]-1-(chloromethyl)ethyl}-2,2-diethylmalonamide (16a):** This compound was obtained from **15a** (672 mg) by Method *a* in a process that gave product **16a** (539 mg, 76%) as a white solid. $t_m$ = 102 °C. $[\alpha]_D$ = –22.4 ($c$ = 1.07 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.39 (d, $J$ = 8.0 Hz, 2 H, NH), 7.10 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.78 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 4.38 (m, 2 H, C*H), 4.18 (t, $J$ = 6.2 Hz, 4 H, C1′′$H_2$), 3.55 (m, 8 H, CH$_2$Cl and C2′′$H_2$), 2.81 (d, $J$ = 2.5 Hz, 2 H, C1′-CH$_a$), 2.78 (d, $J$ = 2.2 Hz, 2 H, C1′-CH$_b$), 1.71 (m, 4 H, C$H_2$CH$_3$), 0.60 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 173.3 (C=O), 156.7 (C4′), 129.9 (C2′, C6′), 129.4 (C1′), 114.6 (C3′, C5′), 67.6 (C1′′), 57.7 (CEt$_2$), 50.7 (C*), 46.3 (CH$_2$Cl), 36.3 (*C*H$_2$C1′), 30.3 (*C*H$_2$CH$_3$), 29.0 (C2′′), 8.8 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 3320, 3035, 2966, 2927, 1637, 1512, 1246, 1017, 1246, 1178, 1017, 839, 811 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*S*)-2-[4-(3-bromopropoxy)phenyl]-1-(chloromethyl)-ethyl}-2,2-diethylmalonamide (16b):** This compound was obtained from **15b** (700 mg), by Method *a* in a process that gave product **16b** (413 mg, 56%) as a white solid. $t_m$ = 112 °C. $[\alpha]_D$ = –20.4 ($c$ = 1.42 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.42 (d, $J$ = 8.1 Hz, 2 H, NH), 7.16 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.85 (d, $J$ = 8.4 Hz, 4 H, C3′H, C5′H), 4.53 (m, 2 H, C*H), 4.06 (t, $J$ = 5.7 Hz, 4 H, C1′′$H_2$), 3.65 (dd, $J$ = 4.1 and 11.3 Hz, 2 H, C$H_a$Cl), 3.59 (t, $J$ = 6.4 Hz, 4 H, C3′′$H_2$), 3.52 (dd, $J$ = 3.4 and 11.2 Hz, 2 H, C$H_b$Cl), 2.86 (d, $J$ = 7.4 Hz, 4 H, C1′-CH$_2$), 2.29 (q, $J$ = 6.0 Hz, 4 H, C2′′$H_2$), 1.78 (m, 4 H, C$H_2$CH$_3$), 0.69 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.4 (C=O), 157.5 (C4′), 130.2 (C1′), 130.1 (C2′, C6′), 114.6 (C3′, C5′), 65.2 (C1′′), 57.9 (CEt$_2$), 50.9 (C*), 46.5 (CH$_2$Cl), 36.5 (*C*H$_2$C1′), 32.2 (C3′′), 30.4 (*C*H$_2$CH$_3$), 29.9 (C2′′), 9.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2961, 2925, 2877, 1635, 1512, 1242, 1033, 823, 528 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*S*)-3-[4-(4-bromobutoxy)phenyl]-1-(chloromethyl)ethyl}-2,2-diethylmalonamide (16c):** This compound was obtained from **15c** (729 mg) by both Method *a* and Method *b*. Method *a* yielded 582 mg (76%) and Method *b* yielded 505 mg (66%) of product **16c** as a white solid. $t_m$ = 99 °C. $[\alpha]_D$ = –21.0 ($c$ = 6.15 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.41 (d, $J$ = 8.0 Hz, 2 H, NH), 7.14 (d, $J$ = 8.2 Hz, 4 H, C2′H, C6′H), 6.81 (d, $J$ = 8.0 Hz, 4 H, C3′H, C5′H), 4.41 (m, 2 H, C*H), 3.94 (t, $J$ = 5.8 Hz, 4 H, C1′′$H_2$), 3.64 (dd, $J$ = 4.0 and 11.1 Hz, 2 H, C$H_a$Cl), 3.47 (m, 6 H, C$H_b$Cl and C4′′$H_2$), 2.84 (d, $J$ = 7.2 Hz, 4 H, C1′-CH$_2$), 2.04 (m, 4 H, C3′′$H_2$), 1.90 (m, 4 H, C2′′$H_2$), 1.77 (m, 4 H, C$H_2$CH$_3$), 0.67 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.6 (C=O), 157.9 (C4′), 130.2 (C2′, C6′), 128.9 (C1′), 114.6 (C3′, C5′), 66.7 (C1′′), 57.9 (CEt$_2$), 50.9 (C*), 46.4 (CH$_2$Cl), 36.4 (*C*H$_2$C1′), 33.3 (C4′′), 30.3 (*C*H$_2$CH$_3$), 29.2 (C3′′), 27.7 (C2′′), 8.9 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3316, 3035, 2962, 2871, 1636, 1583, 1512, 1473, 1442, 1386, 1245, 1177, 1108, 1042, 940, 838, 737, 655, 532 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*S*)-3-[4-(5-bromopentyloxy)phenyl]-1-(chloromethyl)-ethyl}-2,2-diethylmalonamide (16d):** This compound was obtained from **15d** (757 mg) by both Method *a* and Method *b*. Method *a* yielded 579 mg (73%) and Method *b* yielded 595 mg (75%) of product **16d** as a white solid. $t_m$ = 92 °C. $[\alpha]_D$ = –18.9 ($c$ = 2.59 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.41 (d, $J$ = 8.0 Hz, 2 H, NH), 7.15 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.83 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 4.43 (m, 2 H, C*H), 3.93 (t, $J$ = 6.3 Hz, 4 H, C1′′$H_2$), 3.65 (dd, $J$ = 4.1 and 11.3 Hz, 2 H, C$H_a$Cl), 3.52 (dd, $J$ = 3.3 and 11.3 Hz, 2 H, C$H_b$Cl), 3.43 (t, $J$ = 6.7 Hz, 4 H, C5′′$H_2$), 2.85 (d, $J$ = 7.4 Hz, 4 H, C1′-CH$_2$), 1.93 (m, 4 H, C4′′$H_2$), 1.79 (m, 8 H, C$H_2$CH$_3$ and C2′′$H_2$), 1.63 (m, 4 H, C3′′$H_2$), 0.69 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.4 (C=O), 157.7 (C4′), 130.0 (C2′, C6′), 128.6 (C1′), 114.5 (C3′, C5′), 67.4 (C1′′), 57.9 (CEt$_2$), 50.8 (C*), 46.4 (CH$_2$Cl), 36.4 (*C*H$_2$C1′), 33.4 (C5′′), 32.3 (C4′′), 30.3 (*C*H$_2$CH$_3$), 28.2 (C2′′), 24.6 (C3′′), 8.9 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3316, 2941, 2866, 1636, 1512, 1471, 1300, 1246, 1177, 1046, 839, 737, 651, 539 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*R*)-1-[4-(2-bromoethoxy)phenyl]-2-chloroethyl}-2,2-diethylmalonamide (20a):** This compound was obtained from **19a** (644 mg) by Method *a* in a process that gave product **20a** (538 mg, 79%) as a white solid. $t_m$ = 135 °C. $[\alpha]_D$ = –69.0 ($c$ = 1.46 in $CHCl_3$). $^1$H NMR: $\delta$ = 7.89 (d, $J$ = 7.7 Hz, 2 H, NH), 7.21 (d, $J$ = 8.8 Hz, 4 H, C2′H, C6′H), 6.87 (d, $J$ = 8.8 Hz, 4 H, C3′H, C5′H), 5.31 (q, $J$ = 6.3 Hz, 2 H, C*H), 4.27 (t, $J$ = 6.3 Hz, 4 H, C1′′$H_2$), 3.84 (dd, $J$ = 4.9 and 11.5 Hz, 2 H, CH$_a$Cl), 3.77 (dd, $J$

= 6.3 and 11.3 Hz, 2 H, $CH_bCl$), 3.63 (t, $J$ = 6.2 Hz, 4 H, C2′′$H_2$), 1.95 (q, $J$ = 7.3 Hz, 4 H, C$H_2$CH$_3$), 0.84 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.5 (C=O), 157.7 (C4′), 131.2 (C1′), 127.7 (C2′, C6′), 114.8 (C3′, C5′), 67.7 (C1′′), 58.1 (CEt$_2$), 53.4 (C*), 47.5 (CH$_2$Cl), 30.6 (*C*H$_2$CH$_3$), 28.9 (C2′′), 9.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3301, 3047, 2967, 2933, 2877, 1635, 1512, 1457, 1385, 1292, 1245, 1179, 1075, 1015, 879, 831, 743, 669, 572, 541 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis{(*R*)-1-[4-(3-bromopropoxy)phenyl]-2-chloroethyl}-2,2-diethylmalonamide (20b):** This compound was obtained from **19b** (672 mg) by Method *a* in a process that gave product **20b** (589 mg, 83%) as a white solid. $t_m$ = 141 °C. $[\alpha]_D$ = –62.7 ($c$ = 0.93 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.85 (d, $J$ = 7.5 Hz, 2 H, NH), 7.21 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.87 (d, $J$ = 8.6 Hz, 4 H, C3′H, C5′H), 5.31 (m, 2 H, C*H), 4.09 (t, $J$ = 5.8 Hz, 4 H, C1′′$H_2$), 3.85 (dd, $J$ = 5.1 and 11.3 Hz, 2 H, $CH_aCl$), 3.78 (dd, $J$ = 6.3 and 11.3 Hz, 2 H, $CH_bCl$), 3.60 (t, $J$ = 6.3 Hz, 4 H, C3′′$H_2$), 2.31 (q, $J$ = 6.1 Hz, 4 H, C2′′$H_2$), 1.94 (q, $J$ = 7.3 Hz, 4 H, C$H_2$CH$_3$), 0.85 (t, $J$ = 7.4 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.5 (C=O), 158.3 (C4′), 130.7 (C1′), 127.7 (C2′, C6′), 114.6 (C3′, C5′), 65.1 (C1′′), 58.2 (CEt$_2$), 53.4 (C*), 47.5 (CH$_2$Cl), 32.1 (C3′′), 30.7 (*C*H$_2$CH$_3$), 29.8 (C2′′), 9.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3301, 2967, 2933, 2877, 1635, 1612, 1513, 1246, 1179, 1030, 929, 831, 748 cm$^{-1}$. $C_{29}H_{38}Br_2Cl_2N_2O_4$ (709.38): calcd. C 49.10, H 5.40, N 3.95; found: C 49.36, H 5.31, N 4.03.

***N*$^1$,*N*$^3$-Bis{(*R*)-1-[4-(4-bromobutoxy)phenyl]-2-chloroethyl}-2,2-diethylmalonamide (20c):** This compound was obtained from **19c** (700 mg) by both Method *a* and Method *b*. Method *a* yielded 509 mg (69%) and Method *b* yielded 538 mg (73%) of product **20c** as a white solid. $t_m$ = 117 °C. $[\alpha]_D$ = –65.4 ($c$ = 6.87 in $CH_2Cl_2$/MeOH). $^1$H NMR: $\delta$ = 7.85 (d, $J$ = 7.7 Hz, 2 H, NH), 7.20 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.84 (d, $J$ = 8.7 Hz, 4 H, C3′H, C5′H), 5.30 (m, 2 H, C*H), 3.97 (t, $J$ = 5.9 Hz, 4 H, C1′′$H_2$), 3.80 (m, 4 H, CH$_2$Cl), 3.48 (t, $J$ = 6.4 Hz, 4 H, C4′′$H_2$), 2.06 (m, 4 H, C3′′$H_2$), 1.94 (m, 8 H, C$H_2$CH$_3$ and C2′′$H_2$), 0.84 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.7 (C=O), 158.6 (C4′), 130.6 (C1′), 127.7 (C2′, C6′), 114.6 (C3′, C5′), 66.7 (C1′′), 58.1 (CEt$_2$), 53.4 (C*), 47.3 (CH$_2$Cl), 33.2 (C4′′), 30.5 (*C*H$_2$CH$_3$), 29.2 (C3′′), 27.6 (C2′′), 9.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3301, 3035, 2963, 2877, 1635, 1513, 1294, 1249, 1179, 1040, 939, 831, 747, 541 cm$^{-1}$. $C_{31}H_{42}Br_2Cl_2N_2O_4$ (737.43): calcd. C 50.42, H 5.74, N 3.80; found: C 50.72, H 5.75, N 3.66.

***N*$^1$,*N*$^3$-Bis{(*R*)-1-[4-(5-bromopentyloxy)phenyl]-2-chloroethyl}-2,2-diethylmalonamide (20d):** This compound was obtained from **19d** (729 mg) by both Method *a* and Method *b*. Method *a* yielded 643 mg (84%) and Method *b* yielded 673 mg (88%) of product **20d** as a white solid. $t_m$ = 117 °C. $[\alpha]_D$ = –57.1 ($c$ = 0.96 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.97 (d, $J$ = 7.8 Hz, 2 H, NH), 7.20 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.84 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 5.30 (m, 2 H, C*H), 3.94 (t, $J$ = 6.3 Hz, 4 H, C1′′$H_2$), 3.80 (m, 4 H, CH$_2$Cl), 3.43 (t, $J$ = 6.7 Hz, 4 H, C5′′$H_2$), 1.93 (m, 8 H, C$H_2$CH$_3$ and C4′′$H_2$), 1.80 (m, 4 H, C2′′$H_2$), 1.61 (m, 4 H, C3′′$H_2$), 0.84 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.6 (C=O), 158.5 (C4′), 130.3 (C1′), 127.6 (C2′, C6′), 114.5 (C3′, C5′), 67.4 (C1′′), 58.1 (CEt$_2$), 53.5 (C*), 47.4 (CH$_2$Cl), 33.5 (C5′′), 32.3 (C4′′), 30.7 (*C*H$_2$CH$_3$), 28.2 (C2′′), 24.6 (C3′′), 9.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3297, 3035, 2938, 2871, 1634, 1513, 1469, 1386, 1294, 1246, 1179, 1041, 939, 830, 744, 640, 547 cm$^{-1}$. $C_{33}H_{46}Br_2Cl_2N_2O_4$ (765.49): calcd. C 51.78, H 6.06, N 3.66; found: C 51.71, H 6.01, N 3.63.

***N*$^1$,*N*$^3$-Bis[(*S*)-1-(chloromethyl)-2-(4-hydroxyphenyl)ethyl]-2,2-diethylmalonamide (21):** This compound was obtained from **11** (459 mg) by Method *a* in a process that gave product **21** (426 mg, 86%) as a white foam. $[\alpha]_D$ = –29.1 ($c$ = 1.99 in MeOH). $^1$H NMR: $\delta$ = 7.63 (d, $J$ = 8.0 Hz, 2 H, NH), 7.38 (brs, 2 H, C4′OH), 7.03 (d, $J$ = 8.3 Hz, 4 H, C2′H, C6′H), 6.75 (d, $J$ = 8.2 Hz, 4 H, C3′H, C5′H), 4.46 (m, 2 H, C*H), 3.67 (dd, $J$ = 4.2 and 11.2 Hz, 2 H, $CH_aCl$), 3.56 (dd, $J$ = 3.3 and 11.0 Hz, 2 H, $CH_bCl$), 2.89 (dd, $J$ = 6.2 and 14.0 Hz, 2 H, C1′-$CH_a$), 2.77 (dd, $J$ = 8.6 and 13.8 Hz, 2 H, C1′-$CH_b$), 1.70 (m, 4 H, C$H_2$CH$_3$), 0.49 (t, $J$ = 7.1 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 173.0 (C=O), 154.9 (C4′), 130.1 (C1′), 128.2 (C2′, C6′), 115.5 (C3′, C5′), 57.9 (CEt$_2$), 51.1 (C*), 46.9 (CH$_2$Cl), 36.7 (*C*H$_2$C1′), 31.0 (*C*H$_2$CH$_3$), 8.9 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3255, 2969, 1655, 1614, 1515, 1444, 1355, 1232, 1172, 1107, 825 cm$^{-1}$.

***N*$^1$,*N*$^3$-Bis[(*R*)-1-(chloromethyl)-2-(4-hydroxyphenyl)ethyl]-2,2-diethylmalonamide (23):** This compound was obtained from **18** (430 mg) by Method *a* in a process that gave product **23** (421 mg, 90%) as a white foam. $[\alpha]_D$ = –82.4 ($c$ = 1.20 in MeOH). $^1$H ([D$_6$]DMSO): $\delta$ = 9.43 (brs, 2 H, C4′OH), 9.15 (d, $J$ = 8.0 Hz, 2 H, NH), 7.12 (d, $J$ = 7.6 Hz, 4 H, C2′H, C6′H), 6.68 (d, $J$ = 7.7 Hz, 4 H, C3′H, C5′H), 5.05 (m, 2 H, C*H), 3.80 (m, 4 H, CH$_2$Cl), 1.86 (m, 4 H, C$H_2$CH$_3$), 0.60 (t, $J$ = 6.5 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 172.6 (C=O), 156.9 (C4′), 130.1 (C1′), 128.1 (C2′, C6′), 115.5 (C3′, C5′), 57.6 (CEt$_2$), 54.0 (C*), 47.5 (CH$_2$Cl), 29.9 (*C*H$_2$CH$_3$), 9.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3256, 2970, 1655, 1615, 1517, 1457, 1364, 1230, 1175, 836, 538 cm$^{-1}$.

**Preparation of (1$^4$*S*,3$^4$*S*)-2,2-Diethyl-13,13-dimethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,11,15,20-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,12,14,21(1,4)-tetrabenzenacyclododecosaphane (7c):** A solution of compound **14** (46 mg, 0.061 mmol) in NaOH/MeOH (0.5 M, 2 mL) was heated at reflux for 2 h. After it had cooled to room temperature, product **7c** (32 mg, 76%) precipitated; it was filtered off, washed with water and dried. $[\alpha]_D$ = –50.8 ($c$ = 1.093 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.10 (pt, $J$ = 8.8 Hz, 8 H, C2′H, C6′H and C3′′′H, C5′′′H), 6.78 (m, 8 H, C3′H, C5′H and C2′′′H, C6′′′H, C6′′′H), 4.37 (m, 2 H, C4 H), 4.15 (pt, $J$ = 8.8 Hz, 8 H, C5Ha), 4.01 (m, 8 H, C1′′$H_2$ and C4′′$H_2$), 3.93 (pt, $J$ = 7.7 Hz, 2 H, C5Hb), 2.93 (dd, $J$ = 5.2 Hz, $J$ = 13.7 Hz, 2 H, C1′-$CH_a$), 2.68 (dd, $J$ = 7.3 and 13.6 Hz, 2 H, C1′-$CH_b$), 1.94 (m, 12 H, C2′′$H_2$ and C3′′$H_2$ and C$H_2$CH$_3$), 1.64 (s, 6 H, C4′′′CCH$_3$), 0.77 (t, $J$ = 7.4 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}$C NMR: $\delta$ = 167.9 (C2), 157.5 (C4′), 156.6 (C1′′′), 143.2 (C4′′′), 130.6 (C2′, C6′), 129.6 (C1′), 127.6 (C3′′′, C5′′′), 114.5 (C3′, C5′), 113.6 (C2′′′, C6′′′), 71.0 (C5), 67.1, 67.0 (C1′′ and C4′′), 66.8 (C4), 46.6 (CEt$_2$), 41.4 (*C*Me$_2$), 40.1 (C4*C*H2), 30.7 (C*Me$_2$*), 25.4 (C2′′ and C3′′ and *C*H$_2$CH$_3$), 8.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 3031, 2963, 2933, 2871, 1651, 1610, 1580, 1510, 1471, 1383, 1300, 1245, 1179, 1113, 980, 926, 832, 573 cm$^{-1}$. $C_{48}H_{58}N_2O_6$ (759.00): calcd. C 75.96, H 7.70, N 3.69; found: C 75.72, H 7.58, N 3.85.

**General Procedure for the Preparation of Compounds 13, 2a–d, 3a–d, 7a–d, 8a–d, 6, and 24 by Macrocyclization:** A solution of both reactants (0.40 mmol of each) in acetonitrile (150 mL) was added dropwise to a stirred suspension of $Cs_2CO_3$ (977 mg, 3.00 mmol) in acetonitrile (150 mL) with heating at reflux for 3–4 h. The boiling reaction mixture was stirred overnight, and cooled to room temperature. Inorganic salts were removed, the filtrate was concentrated, and the oily residue was purified by preparative TLC in a $CH_2Cl_2$/EtOAc (7:3) solvent system.

**(12*S*,18*S*)-15,15-Diethyl-2,2-dimethyl-12,18-bis(hydroxymethyl)-4,9,21,26-tetraoxa-13,17-diaza-1,3,10,20(1,4)-tetrabenzenacyclohexacosaphane-14,16-dione (13):** This compound was obtained from **11** (183 mg) and **12** (199 mg) in a process that gave product **13** (73 mg, 23%) as a white foam. $[\alpha]_D$ = 14.4 ($c$ = 0.90 in $CH_2Cl_2$). $^1$H NMR:

$\delta$ = 7.07 (pt, $J$ = 8.8 Hz, 8 H, C2′H, C6′H and C3′′′H, C5′′′H), 6.75 (m, 8 H, C2′′′H, C6′′′H and C3′H, C5′H), 6.44 (d, $J$ = 8.0 Hz, NH), 4.23 (br s, 2 H, C*H), 3.97 (m, 8 H, C1′′$H_2$ and C4′′$H_2$), 3.79 (dd, $J$ = 2.8 Hz, $J$ = 11.0 Hz, 2 H, C$H_a$OH), 3.49 (m, 4 H, C$H_b$OH and $CH_2OH$), 2.83 (dd, $J$ = 4.6 and 14.1 Hz, 2 H, C1′-$CH_a$), 2.60 (dd, $J$ = 10.4 and 11.3 Hz, 2 H, C1′-$CH_b$), 1.91 (br s, 8 H, C2′′$H_2$ and C3′′$H_2$), 1.62 (m, 10 H, C$H_2CH_3$ and C4′′′$CCH_3$), 0.26 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 173.4 (C=O), 157.6 (C4′), 156.6 (C1′′′), 143.1 (C4′′′), 129.9 (C2′, C6′), 129.4 (C1′), 127.6 (C3′′′, C5′′′), 114.8 (C3′, C5′), 113.8 (C2′′′, C6′′′), 67.0 (C1′′ or C4′′), 66.9 (C4′′ or C1′′), 65.4 ($CH_2OH$), 58.0 ($CEt_2$), 52.7 (C*), 41.4 ($C$Me$_2$), 35.7 ($CH_2$C1′), 30.7 (C$Me_2$), 25.9 ($CH_2CH_3$), 25.4 (C2′′ or C3′′), 25.3 (C3′′ and C2′′), 7.7 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3407, 3328, 2962, 2927, 2877, 1637, 1611, 1511, 1469, 1247, 1180, 1026, 829, 568 cm$^{-1}$.

**(1$^4$*R*,15$^4$*R*)-16,16-Diethyl-8,8-dimethyl-1$^4$,1$^5$,15$^4$,15$^5$-tetrahydro-3,6,10,13-tetraoxa-1,15(2,4)-bis(1,3-oxazola)-2,7,9,14(1,4)-tetrabenzenacyclohexadecaphane (2a):** This compound was obtained from **20a** (273 mg) and bisphenol A (91 mg) in a process that gave product **2a** (86 mg, 32%) as a white foam. $[\alpha]_D$ = +141.3 ($c$ = 2.00 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.13 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H or C3′′′H, C5′′′H), 7.10 (d, $J$ = 9.1 Hz, 4 H, C3′′′H, C5′′′H or C2′H, C6′H), 6.85 (d, $J$ = 8.2 Hz, 4 H, C3′H, C5′H or C2′′′H, C6′′′H), 6.78 (d, $J$ = 8.8 Hz, 4 H, C2′′′H, C6′′′H or C3′H, C5′H), 5.22 (dd, $J$ = 6.9 and 9.3 Hz, 2 H, C4 H), 4.58 (pt, $J$ = 9.2 Hz, 2 H, C5$H_a$), 4.31 (m, 8 H, C1′′$H_2$ and C2′′$H_2$), 4.02 (pt, $J$ = 7.6 Hz, 2 H, C5$H_b$), 2.29 (m, 2 H, C$H_a$CH$_3$), 2.06 (m, 2 H, C$H_b$CH$_3$), 1.65 (s, 6 H, C4′′′$CCH_3$), 0.92 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.7 (C2), 157.3 (C4′), 155.7 (C1′′′), 143.5 (C4′′′), 135.2 (C1′), 127.4 (C2′, C6′ and C3′′′, C5′′′), 115.0 (C3′, C5′), 114.3 (C2′′′, C6′′′), 75.2 (C5), 68.7 (C4), 65.8 (C1′′ or C2′′), 65.6 (C2′′ or C1′′), 46.9 ($CEt_2$), 41.2 ($C$Me$_2$), 30.2 (C$Me_2$), 24.6 ($CH_2CH_3$), 8.2 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2967, 2927, 2877, 1650, 1608, 1509, 1305, 1241, 1222, 1179, 1108, 1058, 923, 830, 553 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{42}H_{46}N_2O_6$: 674.33557; found: 674.33530.

**(1$^4$*R*,17$^4$*R*)-18,18-Diethyl-9,9-dimethyl-1$^4$,1$^5$,17$^4$,17$^5$-tetrahydro-3,7,11,15-tetraoxa-1,17(2,4)-bis(1,3-oxazola)-2,8,11,16(1,4)-tetrabenzenacyclooctadecaphane (2b):** This compound was obtained from **20b** (284 mg) and bisphenol A (91 mg) in a process that gave product **2b** (70 mg, 25%) as a white foam. $[\alpha]_D$ = +166.7 ($c$ = 0.92 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.16 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H or C3′′′H, C5′′′H), 7.11 (d, $J$ = 8.5 Hz, 4 H, C3′′′H, C5′′′H or C2′H, C6′H), 6.84 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H or C2′′′H, C6′′′H), 6.78 (d, $J$ = 8.8 Hz, 4 H, C2′′′H, C6′′′H or C3′H, C5′H), 5.24 (dd, $J$ = 6.3 and 9.9 Hz, 2 H, C4 H), 4.60 (pt, $J$ = 9.1 Hz, 2 H, C5$H_a$), 4.22–4.01 (m, 10 H, C5$H_a$ and C1′′$H_2$ and C3′′$H_2$), 2.33 (m, 2 H, C$H_a$CH$_3$), 2.23 (m, 4 H, C2′′H), 2.12 (m, 2 H, C$H_b$CH$_3$), 1.68 (s, 6 H, C4′′′$CCH_3$), 0.96 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.7 (C2), 158.2 (C4′), 156.5 (C1′′′), 143.0 (C4′′′), 134.7 (C1′), 127.2 (C2′, C6′ and C3′′′, C5′′′), 114.2 (C3′, C5′), 113.7 (C2′′′, C6′′′), 75.3 (C5), 68.7 (C4), 63.6, 63.4 (C1′′ and C3′′), 46.8 ($CEt_2$), 41.1 ($C$Me$_2$), 30.1 (C$Me_2$), 29.1 (C2′′), 24.3 ($CH_2CH_3$), 8.2 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 2965, 2933, 2877, 1654, 1610, 1583, 1512, 1469, 1382, 1245, 1180, 1111, 1058, 987, 829, 547 cm$^{-1}$. $C_{44}H_{50}N_2O_6$ (702.89): calcd. C 75.19, H 7.17, N 3.99; found: C 75.39, H 6.88, N 4.04.

**(1$^4$*R*,19$^4$*R*)-20,20-Diethyl-10,10-dimethyl-1$^4$,1$^5$,19$^4$,19$^5$-tetrahydro-3,8,12,17-tetraoxa-1,19(2,4)-bis(1,3-oxazola)-2,9,13,18(1,4)-tetrabenzenacycloicosaphane (2c):** This compound was obtained from **20c** (295 mg) and bisphenol A (91 mg) in a process that gave product **2c** (140 mg, 48%) as a white foam. $[\alpha]_D$ = +171.8 ($c$ = 1.00 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.15 (d, $J$ = 8.7 Hz, 4 H, C2′H, C6′H or C3′′′H, C5′′′H), 7.07 (d, $J$ = 8.5 Hz, 4 H, C3′′′H, C5′′′H or C2′H, C6′H), 6.82 (d, $J$ = 8.7 Hz, 4 H, C3′H, C5′H or C2′′′H, C6′′′H), 6.73 (d, $J$ = 8.7 Hz, 4 H, C2′′′H, C6′′′H or C3′H, C5′H), 5.17 (dd, $J$ = 6.9 and 9.7 Hz, 2 H, C4 H), 4.58 (dd, $J$ = 8.5 and 9.8 Hz, 2 H, C5$H_a$), 4.06 (pt, $J$ = 8.2 Hz, 2 H, C5$H_b$), 4.03–3.97 (m, 8 H, C1′′$H_2$ and C4′′$H_2$), 2.23 (m, 2 H, C$H_a$CH$_3$), 2.06 (m, 2 H, C$H_b$CH$_3$), 1.94 (m, 8 H, C2′′H and C3′′H), 1.61 (s, 6 H, C4′′′$CCH_3$), 0.96 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.7 (C2), 158.3 (C4′), 156.6 (C1′′′), 143.2 (C4′′′), 134.8 (C1′), 127.7, 127.6 (C2′, C6′ and C3′′′, C5′′′), 114.7 (C3′, C5′), 113.8 (C2′′′, C6′′′), 75.1 (C5), 68.8 (C4), 66.9 (C1′′ and C4′′), 46.7 ($CEt_2$), 41.4 ($C$Me$_2$), 30.7 (C$Me_2$), 25.3, 25.2 (C2′′ and C3′′), 24.6 ($CH_2CH_3$), 8.1 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 3035, 2966, 2877, 1653, 1610, 1511, 1469, 1294, 1246, 1178, 1108, 986, 923, 830, 553 cm$^{-1}$. $C_{46}H_{54}N_2O_6$ (730.94): calcd. C 75.59, H 7.45, N 3.83; found: C 75.55, H 7.20, N 3.75.

**(1$^4$*R*,21$^4$*R*)-22,22-Diethyl-11,11-dimethyl-1$^4$,1$^5$,21$^4$,21$^5$-tetrahydro-3,9,13,19-tetraoxa-1,21(2,4)-bis(1,3-oxazola)-2,10,15,20(1,4)-tetrabenzenacyclodocosaphane (2d):** This compound was obtained from **20d** (306 mg) and bisphenol A (91 mg) in a process that gave product **2d** (73 mg, 24%) as a white foam. $[\alpha]_D$ = +139.8 ($c$ = 1.30 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.16 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H or C3′′′H, C5′′′H), 7.07 (d, $J$ = 8.5 Hz, 4 H, C3′′′H, C5′′′H or C2′H, C6′H), 6.81 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H or C2′′′H, C6′′′H), 6.74 (d, $J$ = 8.5 Hz, 4 H, C2′′′H, C6′′′H or C3′H, C5′H), 5.18 (dd, $J$ = 7.1 and 9.6 Hz, 2 H, C4 H), 4.58 (pt, $J$ = 7.8 Hz, 2 H, C5$H_a$), 4.03 (pt, $J$ = 7.8 Hz, 2 H, C5$H_b$), 3.95 (m, 8 H, C1′′$H_2$ and C5′′$H_2$), 2.22 (m, 2 H, C$H_a$CH$_3$), 2.03 (m, 2 H, C$H_b$CH$_3$), 1.80 (m, 8 H, C2′′H and C4′′H), 1.63 (s, 6 H, C4′′′$CCH_3$), 0.91 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.4 (C2), 158.3 (C4′), 156.5 (C1′′′), 142.9 (C4′′′), 134.5 (C1′), 127.7, (C2′, C6′ and C3′′′, C5′′′), 114.4 (C3′, C5′), 113.6 (C2′′′, C6′′′), 75.0 (C5), 68.8 (C4), 67.5, 67.4 (C1′′ and C5′′), 46.9 ($CEt_2$), 41.3 ($C$Me$_2$), 30.5 (C$Me_2$), 28.6 (C2′′ and C4′′), 25.0 ($CH_2CH_3$), 22.7 (C3′′), 8.1 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2937, 2871, 1654, 1611, 1511, 1469, 1305, 1244, 1179, 1108, 985, 923, 829, 547 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{48}H_{58}N_2O_6$: 758.42950; found: 758.42940.

**(1$^4$*R*,15$^4$*R*)-16,16-Diethyl-7$^2$,7$^6$,8,8,9$^3$,9$^5$-hexamethyl-1$^4$,1$^5$,15$^4$,15$^5$-tetrahydro-3,6,10,13-tetraoxa-1,15(2,4)-bis(1,3-oxazola)-2,7,9,14(1,4)-tetrabenzenacyclohexadecaphane (3a):** This compound was obtained from **20a** (273 mg) and **25** (114 mg) in a process that gave product **3a** (41 mg, 14%) as a white foam. $[\alpha]_D$ = +107.9 ($c$ = 0.72 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.14 (d, $J$ = 8.7 Hz, 4 H, C2′H, C6′H), 6.85 (d, $J$ = 8.7 Hz, 4 H, C3′H, C5′H), 6.75 (s, 4 H, C3′′′H, C5′′′H), 5.21 (dd, $J$ = 6.9 and 9.9 Hz, 2 H, C4 H), 4.57 (dd, $J$ = 8.3 and 9.9 Hz, 2 H, C5$H_a$), 4.26 (t, $J$ = 4.5 Hz, 4 H, C1′′$H_2$ or C2′′$H_2$), 4.13 (m, 4 H, C1′′$H_2$ or C2′′$H_2$), 4.01 (pt, $J$ = 7.7 Hz, 2 H, C5$H_b$), 2.26 (m, 2 H, C$H_a$CH$_3$), 2.12 (s, 12 H, C2′′′$CH_3$), 2.04 (m, 2 H, C$H_b$CH$_3$), 1.57 (s, 6 H, C4′′′$CCH_3$), 0.91 (t, $J$ = 7.5 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.6 (C2), 157.4 (C4′), 152.8 (C1′′′), 145.8 (C4′′′), 135.0 (C1′), 129.6 (C2′′′, C6′′′), 127.5 (C2′, C6′), 126.9 (C3′′′, C5′′′), 114.9 (C3′, C5′), 75.0 (C5), 70.1 (C2′′), 68.6 (C4), 66.4 (C1′′), 47.0 ($CEt_2$), 41.3 ($C$Me$_2$), 30.5 (C$Me_2$), 24.9 ($CH_2CH_3$), 16.5 (C2′′′$CH_3$), 8.2 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3438, 2966, 2925, 2877, 1653, 1611, 1511, 1485, 1454, 1363, 1305, 1246, 1219, 1180, 1109, 1051, 987, 922, 830, 543 cm$^{-1}$. TOF-ESMS: 731 [M + H]$^+$.

**(1$^4$*R*,17$^4$*R*)-18,18-Diethyl-8$^2$,8$^6$,9,9,10$^3$,10$^5$-hexamethyl-1$^4$,1$^5$,17$^4$,17$^5$-tetrahydro-3,7,11,15-tetraoxa-1,17(2,4)-bis(1,3-oxazola)-2,8,11,16(1,4)-tetrabenzenacyclooctadecaphane (3b):** This compound was obtained from **20b** (284 mg) and **25** (114 mg) in a

process that gave product **3b** (97 mg, 32%) as a white foam. $[\alpha]_D$ = +107.8 (*c* = 1.08 in $CHCl_3$). $^1H$ NMR: $\delta$ = 7.13 (d, *J* = 8.7 Hz, 4 H, C2′H, C6′H), 6.81 (d, *J* = 8.7 Hz, 4 H, C3′H, C5′H), 6.74 (s, 4 H, C3′′′H, C5′′′H), 5.19 (dd, *J* = 6.9 and 9.9 Hz, 2 H, C4 H), 4.56 (dd, *J* = 8.4 and 9.9 Hz, 2 H, C5H$_a$), 4.17 (m, 4 H, C1′′H$_2$), 4.02–3.84 (m, 6 H, C3′′H$_2$ and C5H$_b$), 2.29–2.16 (m, 6 H, C2′′H$_2$ and C*H$_a$*CH$_3$), 2.13 (s, 12 H, C2′′′CH$_3$), 2.03 (m, 2 H, C*H$_b$*CH$_3$), 1.58 (s, 6 H, C4′′′CCH$_3$), 0.91 (t, *J* = 7.5 Hz, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 168.6 (C2), 158.2 (C4′), 153.3 (C1′′′), 145.8 (C4′′′), 134.7 (C1′), 129.6 (C2′′′, C6′′′), 127.4, 127.0 (C2′, C6′ and C3′′′, C5′′′), 114.3 (C3′, C5′), 75.2 (C5), 68.7 (C4), 68.4 (C3′′), 63.9 (C1′′), 47.0 (CEt$_2$), 41.4 (*C*Me$_2$), 30.6 (C*Me$_2$*), 29.8 (C2′′), 24.9 (*C*H$_2$CH$_3$), 16.4 (C2′′′*C*H$_3$), 8.2 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2964, 2933, 2877, 1654, 1611, 1512, 1474, 1382, 1305, 1244, 1179, 1111, 1058, 987, 923, 830, 547 cm$^{-1}$. TOF-ESMS: 759 [M + H]$^+$.

**(1$^4$*R*,19$^4$*R*)-20,20-Diethyl-9$^2$,9$^6$,10,10,11$^3$,11$^5$-hexamethyl-1$^4$,1$^5$,19$^4$,19$^5$-tetrahydro-3,8,12,17-tetraoxa-1,19(2,4)-bis(1,3-oxazola)-2,9,13,18(1,4)-tetrabenzenacycloicosaphane (3c):** This compound was obtained from **20c** (295 mg) and **25** (114 mg) in a process that gave product **3c** (126 mg, 40%) as a white foam. $[\alpha]_D$ = +147.3 (*c* = 1.46 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.17 (d, *J* = 8.8 Hz, 4 H, C2′H, C6′H), 6.87 (d, *J* = 8.5 Hz, 4 H, C3′H, C5′H), 6.80 (s, 4 H, C3′′′H, C5′′′H), 5.20 (dd, *J* = 7.4 and 9.6 Hz, 2 H, C4 H), 4.61 (pt, *J* = 9.2 Hz, 2 H, C5H$_a$), 4.09 (m, 6 H, C5H$_a$ and C1′′H$_2$), 3.80 (m, 4 H, C4′′H$_2$), 2.30–2.07 (m, 16 H, C2′′′CH$_3$ and C*H$_2$*CH$_3$), 2.00 (m, 8 H, C2′′H$_2$ and C3′′H$_2$), 1.60 (s, 6 H, C4′′′CCH$_3$), 0.91 (m, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 168.1 (C2), 158.1 (C4′), 153.4 (C1′′′), 145.7 (C4′′′), 134.6 (C1′), 129.5 (C2′′′, C6′′′), 127.6 (C2′, C6′), 126.8 (C3′′′, C5′′′), 114.6 (C3′, C5′), 75.1 (C5), 71.1 (C4′′), 68.8 (C4), 66.9 (C1′′), 46.6 (CEt$_2$), 41.3 (*C*Me$_2$), 30.6 (C*Me$_2$*), 26.1, 25.6 (C2′′ and C3′′), 24.6 (*C*H$_2$CH$_3$), 16.5 (C2′′′*C*H$_3$), 8.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 2963, 2875, 1654, 1612, 1513, 1475, 1245, 1179, 1111, 987, 923, 830, 547 cm$^{-1}$. TOF-ESMS: 787 [M + H]$^+$.

**(1$^4$*R*,21$^4$*R*)-22,22-Diethyl-10$^2$,10$^6$,11,11,12$^3$,12$^5$-hexamethyl-1$^4$,1$^5$,21$^4$,21$^5$-tetrahydro-3,9,13,19-tetraoxa-1,21(2,4)-bis(1,3-oxazola)-2,10,15,20(1,4)-tetrabenzenacyclodocosaphane (3d):** This compound was obtained from **20d** (306 mg) and **25** (114 mg) in a process that gave product **3d** (104 mg, 32%) as a white foam. $[\alpha]_D$ = +128.9 (*c* = 1.29 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.19 (d, *J* = 8.5 Hz, 4 H, C2′H, C6′H), 6.85 (d, *J* = 8.5 Hz, 4 H, C3′H, C5′H), 6.80 (s, 4 H, C3′′′H, C5′′′H), 5.21 (dd, *J* = 7.3 and 9.8 Hz, 2 H, C4 H), 4.62 (dd, *J* = 8.7 and 9.8 Hz, 2 H, C5H$_a$), 4.10 (pt, *J* = 7.8 Hz, 2 H, C5H$_b$), 4.00 (m, 4 H, C1H$_2$), 3.79 (t, *J* = 6.2 Hz, 4 H, C5′′H$_2$), 2.30–1.84 (m, 24 H, C2′′′CH$_3$ and C2′′H$_2$ and C3′′H$_2$ and C*H$_2$*CH$_3$), 1.72–1.66 (m, 4 H, C3′′H$_2$), 1.62 (s, 6 H, C4′′′CCH$_3$), 0.95 (t, *J* = 7.4 Hz, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 168.4 (C2), 158.3 (C4′), 153.4 (C1′′′), 145.7 (C4′′′), 134.4 (C1′), 129.5 (C2′′′, C6′′′), 127.5 (C2′, C6′), 126.9 (C3′′′, C5′′′), 114.4 (C3′, C5′), 74.9 (C5), 71.7 (C5′′), 68.8 (C4), 67.5 (C1′′), 46.9 (CEt$_2$), 41.4 (*C*Me$_2$), 30.5 (C*Me$_2$*), 29.6 (C4′′), 28.7 (C2′′), 25.2 (*C*H$_2$CH$_3$), 22.6 (C3′′), 16.5 (C2′′′*C*H$_3$), 8.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3438, 2938, 2871, 1653, 1611, 1512, 1474, 1384, 1305, 1243, 1178, 1111, 988, 923, 830, 549 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{52}H_{66}N_2O_6$: 814.49207; found: 814.49190.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-11,11-dimethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,9,13,16-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,10,12,17(1,4)-tetrabenzenacyclooctadecaphane (7a):** This compound was obtained from **16a** (284 mg) and bisphenol A (91 mg) in a process that gave product **7a** (79 mg, 28%) as a white foam. $[\alpha]_D$ = –45.1 (*c* = 0.61 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.12 (m, 8 H, C2′H, C6′H and C3′′′H, C5′′′H), 6.82 (pt, *J* = 9.2 Hz, 8 H, C3′H, C5′H and C2′′′H, C6′′′H), 4.40–4.23 (m, 10 H, C4H and C1′′H$_2$ and C2′′H$_2$), 4.20 (pt, *J* = 8.9 Hz, 2 H, C5Ha), 3.94 (pt, *J* = 7.7 Hz, 2 H, C5Hb), 2.89 (dd, *J* = 5.8 and 13.7 Hz, 2 H, C1′-CH$_a$), 2.39 (dd, *J* = 6.6 and 13.7 Hz, 2 H, C1′-CH$_b$), 1.94 (m, 4 H, C*H$_2$*CH$_3$), 1.68 (s, 6 H, C4′′′CCH$_3$), 0.79 (t, *J* = 7.4 Hz, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.9 (C2), 156.9 (C4′), 156.0 (C1′′′), 143.6 (C4′′′), 130.6 (C2′, C6′), 130.0 (C1′), 127.4 (C3′′′, C5′′′), 114.6, 114.4 (C3′, C5′ and C2′′′, C6′′′), 70.9 (C5), 66.6, 66.3 (C4 and C1′′ and C2′′), 46.7 (CEt$_2$), 41.3 (*C*Me$_2$), 40.0 (C4*C*H$_2$), 30.2 (C*Me$_2$*), 25.8 (*C*H$_2$CH$_3$), 8.4 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2967, 2931, 2877, 1654, 1610, 1509, 1242, 1180, 1068, 982, 831, 553 cm$^{-1}$. TOF-ESMS: 703 [M + H]$^+$.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-12,12-dimethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,10,14,18-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,11,13,19(1,4)-tetrabenzenacycloicosaphane (7b):** This compound was obtained from **16b** (295 mg) and bisphenol A (91 mg) in a process that gave product **7b** (114 mg, 39%) as a white foam. $[\alpha]_D$ = –62.8 (*c* = 1.70 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.11 (m, 8 H, C2′H, C6′H and C3′′′H, C5′′′H), 6.80 (m, 8 H, C3′H, C5′H and C2′′′H, C6′′′H), 4.38 (m, 2 H, C4 H), 4.23–4.09 (m, 10 H, C5Ha and C1′′H$_2$ and C3′′H$_2$), 3.97 (pt, *J* = 7.4 Hz, 2 H, C5Hb), 2.88 (dd, *J* = 6.0 Hz, *J* = 13.7 Hz, 2 H, C1′-CH$_a$), 2.74 (dd, *J* = 6.6 and 14.0 Hz, 2 H, C1′-CH$_b$), 2.22 (m, 4 H, C*H$_2$*CH$_3$), 1.67 (s, 6 H, C4′′′CCH$_3$), 0.70 (t, *J* = 7.4 Hz, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.7 (C2), 157.4 (C4′), 156.4 (C1′′′), 141.3 (C4′′′), 130.5 (C2′, C6′′′), 129.6 (C1′), 127.4 (C3′′′, C5′′′), 114.2 (C3′, C5′), 113.7 (C2′′′, C6′′′), 70.9 (C5), 66.8 (C4), 64.0 (C1′′ and C3′′), 46.8 (CEt$_2$), 41.3 (*C*Me$_2$), 40.2 (C4*C*H$_2$), 30.4 (C*Me$_2$*), 29.1 (C2′′), 26.1 (*C*H$_2$CH$_3$), 8.5 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3423, 2964, 2933, 2877, 1653, 1610, 1510, 1472, 1300, 1244, 1180, 1112, 1059, 984, 829, 572 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{46}H_{54}N_2O_6$: 730.3982; found: 730.3981.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-13,13-dimethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,11,15,20-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,12,14,21(1,4)-tetrabenzenacyclodocosaphane (7c):** This compound was obtained from **16c** (306 mg) and bisphenol A (91 mg) in a process that gave product **7c** (152 mg, 50%) as a white foam. $[\alpha]_D$ = –52.1 (*c* = 0.75 in $CH_2Cl_2$). All spectroscopic data were same as already described.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-14,14-dimethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,12,16,22-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,13,15,23(1,4)-tetrabenzenacyclotetracosaphane (7d):** This compound was obtained from **16d** (317 mg) and bisphenol A (91 mg) in a process that gave product **7d** (135 mg, 43%) as a white foam. $[\alpha]_D$ = –58.0 (*c* = 10.0 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.09 (pt, *J* = 7.4 Hz, 8 H, C2′H, C6′H and C3′′′H, C5′′′H), 6.78 (m, 8 H, C3′H, C5′H and C2′′′H, C6′′′H), 4.35 (m, 2 H, C4 H), 4.15 (pt, *J* = 8.9 Hz, 8 H, C5Ha), 3.94 (m, 10 H, C5Hb and C1′′H$_2$ and C5′′H$_2$), 2.91 (dd, *J* = 5.5 Hz, *J* = 14.0 Hz, 2 H, C1′-CH$_a$), 2.68 (dd, *J* = 7.1 and 13.8 Hz, 2 H, C1′-CH$_b$), 1.92 (m, 4 H, C*H$_2$*CH$_3$), 1.81 (m, 8 H, C2′′H$_2$ and C4′′H$_2$), 1.64 (m, 10 H, C4′′H$_2$ and C4′′′CCH$_3$), 0.76 (t, *J* = 7.4 Hz, 6 H, CH$_2$C*H*$_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.7 (C2), 157.6 (C4′), 156.6 (C1′′′), 143.0 (C4′′′), 130.5 (C2′, C6′), 129.4 (C1′), 127.5 (C3′′′, C5′′′), 114.3 (C3′, C5′), 113.7 (C2′′′, C6′′′), 71.0 (C5), 67.7, 67.5 (C1′′ and C5′′), 66.8 (C4), 46.6 (CEt$_2$), 41.4 (*C*Me$_2$), 40.1 (C4*C*H2), 30.6 (C*Me$_2$*), 28.7 (C2′′ and C4′′), 25.5 (*C*H$_2$CH$_3$), 22.7 (C3′′), 8.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 3035, 2937, 2866, 1653, 1610, 1510, 1472, 1300, 1245, 1179, 982, 829 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{50}H_{62}N_2O_6$: 786.46082; found: 786.46090.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-10$^2$,10$^6$,11,11,12$^3$,12$^5$-hexamethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,9,13,16-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,10,12,17(1,4)-tetrabenzenacyclooctadecaphane (8a):** This compound was obtained from **16a** (284 mg) and **25** (114 mg) in a pro-

cess that gave product **8a** (116 mg, 38%) as a white foam. $[\alpha]_D$ = –32.6 ($c$ = 0.89 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.08 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.83 (s, 4 H, C3′′′H, C5′′′H), 6.76 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 4.37 (m, 2 H, C4 H), 4.22 (m, 10 H, C1′′$H_2$ and C2′′$H_2$ and C5$H_a$), 3.92 (pt, $J$ = 7.8 Hz, 2 H, C5$H_b$), 2.90 (dd, $J$ = 5.8 and 13.7 Hz, 2 H, C1′-$CH_a$), 2.78 (dd, $J$ = 6.6 and 13.7 Hz, 2 H, C1′-$CH_b$), 2.23 (s, 12 H, C2′′′$CH_3$), 1.96 (m, 4 H, C$H_2$CH$_3$), 1.64 (s, 6 H, C4′′′C$CH_3$), 0.81 (t, $J$ = 7.2 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.6 (C2), 157.0 (C4′), 153.2 (C1′′′), 145.9 (C4′′′), 130.5 (C2′, C6′), 130.0 (C1′), 129.5 (C2′′′, C6′′′), 126.9 (C3′′′, C5′′′), 114.3 (C3′, C5′), 70.9 (C5), 70.4 (C2′′), 67.1, 66.6 (C4 and C1′′), 46.5 (CEt$_2$), 41.4 (*C*Me$_2$), 39.8 (C4*C*H$_2$), 30.5 (C*Me*$_2$), 25.6 (*C*H$_2$CH$_3$), 16.6 (C2′′′*C*H$_3$), 8.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2965, 2927, 1653, 1611, 1510, 1486, 1457, 1303, 1247, 1219, 1180, 1113, 1069, 982, 926, 837, 516 cm$^{-1}$. TOF-ESMS: 759 [M + H]$^+$.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-11$^2$,11$^6$,12,12,13$^3$,13$^5$-hexamethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,10,14,18-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,11,13,19(1,4)-tetrabenzenacycloicosaphane (8b):** This compound was obtained from **16b** (295 mg) and **25** (114 mg) in a process that gave product **8b** (126 mg, 40%) as a white foam. $[\alpha]_D$ = –56.5 ($c$ = 0.92 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.08 (d, $J$ = 8.0 Hz, 4 H, C2′H, C6′H), 6.80 (m, 8 H, C3′′′H, C5′′′H and C3′H, C5′H), 4.36 (m, 2 H, C4 H), 4.17 (m, 6 H, C1′′$H_2$ and C5$H_a$), 3.93 (m, 6 H, C5$H_b$ and C3′′$H_2$), 2.88 (dd, $J$ = 5.8 and 13.8 Hz, 2 H, C1′-$CH_a$), 2.75 (dd, $J$ = 6.6 and 14.0 Hz, 2 H, C1′-$CH_b$), 2.17 (s, 12 H, C2′′′$CH_3$), 2.00–1.81 (m, 8 H, C2′′$H_2$ and C$H_2$CH$_3$), 1.59 (s, 6 H, C4′′′C$CH_3$), 0.74 (t, $J$ = 7.3 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.7 (C2), 157.3 (C4′), 153.3 (C1′′′), 145.8 (C4′′′), 130.6 (C2′, C6′), 130.1 (C1′), 129.6 (C2′′′, C6′′′), 126.9 (C3′′′, C5′′′), 114.1 (C3′, C5′), 70.9 (C5), 68.2 (C3′′), 66.7 (C4), 64.0 (C1′′), 46.7 (CEt$_2$), 41.1 (*C*Me$_2$), 40.0 (C4*C*H$_2$), 30.6 (C*Me*$_2$), 29.8 (C2′′), 25.8 (*C*H$_2$CH$_3$), 16.4 (C2′′′*C*H$_3$), 8.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2965, 2927, 2877, 1653, 1611, 1511, 1475, 1299, 1245, 1181, 1112, 1059, 985, 831, 526 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{50}H_{62}N_2O_6$: 786.4608; found: 786.4609.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-12$^2$,12$^6$,13,13,14$^3$,14$^5$-hexamethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,11,15,20-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,12,14,21(1,4)-tetrabenzenacyclodocosaphane (8c):** This compound was obtained from **16c** (306 mg) and **25** (114 mg) in a process that gave product **8c** (121 mg, 37%) as a white foam. $[\alpha]_D$ = –43.8 ($c$ = 1.62 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.11 (d, $J$ = 8.0 Hz, 4 H, C2′H, C6′H), 6.83 (m, 8 H, C3′′′H, C5′′′H and C3′H, C5′H), 4.39 (m, 2 H, C4 H), 4.17 (pt, $J$ = 8.9 Hz, 2 H, C5$H_a$), 4.09 (m, 4 H, C1′′$H_2$), 3.95 (m, 2 H, C5$H_b$), 3.85 (m, 4 H, C4′′$H_2$), 2.97 (dd, $J$ = 5.5 and 14.0 Hz, 2 H, C1′-$CH_a$), 2.75 (dd, $J$ = 7.6 and 13.9 Hz, 2 H, C1′-$CH_b$), 2.23 (s, 12 H, C2′′′$CH_3$), 1.98 (m, 12 H, C2′′$H_2$ and C3′′$H_2$ and C$H_2$CH$_3$), 1.62 (s, 6 H, C4′′′C$CH_3$), 0.79 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.7 (C2), 157.3 (C4′), 153.4 (C1′′′), 145.7 (C4′′′), 130.4 (C2′, C6′), 130.1 (C1′), 129.5 (C2′′′, C6′′′), 126.9 (C3′′′, C5′′′), 114.5 (C3′, C5′), 71.4 (C4′′), 71.1 (C5), 67.4 (C1′′), 66.9 (C4), 46.5 (CEt$_2$), 41.4 (*C*Me$_2$), 40.1 (C4*C*H$_2$), 30.7 (C*Me*$_2$), 26.5, 25.7, 25.1 (C3′′, C2′′ and *C*H$_2$CH$_3$), 16.6 (C2′′′*C*H$_3$), 8.2 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3427, 2963, 2927, 2877, 1653, 1510, 1299, 1244, 1180, 1108, 985, 831, 526 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{52}H_{66}N_2O_6$: 814.49207; found: 814.49190.

**(1$^4$*S*,3$^4$*S*)-2,2-Diethyl-13$^2$,13$^6$,14,14,15$^3$,15$^5$-hexamethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,12,16,22-tetraoxa-1,3(2,4)-bis(1,3-oxazola)-5,13,15,23(1,4)-tetrabenzenacyclotetracosaphane (8d):** This compound was obtained from **16d** (317 mg) and **25** (114 mg) in a process that gave product **8d** (138 mg, 41%) as a white foam. $[\alpha]_D$ = –49.0 ($c$ = 2.88 in $CH_2Cl_2$). $^1H$ NMR: $\delta$ = 7.10 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.81 (m, 8 H, C3′′′H, C5′′′H and C3′H, C5′H), 4.37 (m, 2 H, C4 H), 4.17 (pt, $J$ = 8.9 Hz, 2 H, C5$H_a$), 3.98 (m, 6 H, C5$H_b$ and C1′′$H_2$), 3.79 (t, $J$ = 6.3 Hz, 4 H, C5′′$H_2$), 2.94 (dd, $J$ = 5.5 and 13.7 Hz, 2 H, C1′-$CH_a$), 2.70 (dd, $J$ = 7.4 and 13.7 Hz, 2 H, C1′-$CH_b$), 2.22 (s, 12 H, C2′′′$CH_3$), 2.01–1.83 (m, 12 H, C2′′$H_2$ and C4′′$H_2$ and C$H_2$CH$_3$), 1.73–1.66 (m, 4 H, C3′′$H_2$), 1.61 (s, 6 H, C4′′′C$CH_3$), 0.77 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.7 (C2), 157.6 (C4′), 153.5 (C1′′′), 145.8 (C4′′′), 130.4 (C2′, C6′), 130.2 (C1′), 129.6 (C2′′′, C6′′′), 127.0 (C3′′′, C5′′′), 114.4 (C3′, C5′), 71.7 (C4′′), 71.0 (C5), 67.7 (C1′′), 66.9 (C4), 46.6 (CEt$_2$), 41.5 (*C*Me$_2$), 40.2 (C4*C*H$_2$), 30.7 (C*Me*$_2$), 29.8 (C4′′), 28.8 (C2′′), 25.5 (*C*H$_2$CH$_3$), 22.7 (C3′′), 16.5 (C2′′′*C*H$_3$), 8.3 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 2936, 2871, 1653, 1611, 1511, 1474, 1383, 1302, 1243, 1179, 1112, 984, 923, 831, 532 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{54}H_{70}N_2O_6$: 842.52338; found: 842.52330.

**(1$^4$*S*,11$^4$*S*)-2,2-Diethyl-1$^4$,1$^5$,3$^4$,3$^5$-tetrahydro-6,12-dioxa-1,3(2,4)-bis(1,3-oxazola)-5,8,10,13(1,4)-tetrabenzenacyclotetradecaphane (6):** This compound was obtained from **21** (198 mg) and **22** (142 mg) in a process that gave product **6** (113 mg, 46%) as a white foam. $[\alpha]_D$ = –53.0 ($c$ = 19.8 in $ClCH_2CH_2Cl$). $^1H$ NMR: $\delta$ = 7.23 (d, $J$ = 7.7 Hz, 4 H, C2′′′H, C6′′′H or C3′′′H, C5′′′H), 7.14 (d, $J$ = 7.7 Hz, 4 H, C3′′′H, C5′′′H or C2′′′H, C6′′′H), 7.00 (d, $J$ = 8.2 Hz, 4 H, C2′H, C6′H), 6.74 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 5.20–5.08 (m, 4 H, C1′′$H_2$), 4.39 (m, 2 H, C4 H), 4.13 (pt, $J$ = 8.9 Hz, 2 H, C5$H_a$), 3.93–3.86 (m, 4 H, C5$H_b$ and C4′′′$CH_2$), 2.84–2.74 (m, 4 H, C1′-$CH_2$), 1.83 (m, 2 H, C$H_a$CH$_3$), 1.70 (m, 2 H, C$H_b$CH$_3$), 0.51 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR: $\delta$ = 167.6 (C2), 156.9 (C4′), 140.5 (C4′′′), 135.4 (C1′′′), 130.9 (C1′ and C2′, C6′), 128.8, 126.6 (C3′′′, C5′′′ and C2′′′, C6′′′), 114.9 (C3′, C5′), 70.3, 69.5 (C5 and C1′′), 66.0 (C4), 46.4 (CEt$_2$), 41.4 (C4′′′*C*H$_2$), 39.1 (C4*C*H$_2$), 25.3 (*C*H$_2$CH$_3$), 8.2 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 2970, 2918, 1649, 1610, 1509, 1221, 1176, 1113, 984 cm$^{-1}$. HRMS: [M]$^+$ calculated for $C_{40}H_{42}N_2O_4$: 614.3145; found: 614.3148.

**(7*R*,13*R*)-10,10-Diethyl-7,13-bis(hydroxymethyl)-5,15-dioxa-8,12-diaza-1,3,6,14(1,4)-tetrabenzenacyclohexadecaphane-9,11-dione (24):** This compound was obtained from **18** (172 mg) and **22** (142 mg) in a process that gave product **24** (98 mg, 37%) as a white foam. $[\alpha]_D$ = –98.0 ($c$ = 1.65 in MeOH). $^1H$ NMR ([D$_6$]acetone): $\delta$ = 8.82 (d, $J$ = 7.7 Hz, 2 H, NH), 7.25 (d, $J$ = 8.3 Hz, 4 H, C2′′′H, C6′′′H or C3′′′H, C5′′′H), 7.21 (d, $J$ = 8.3 Hz, 4 H, C3′′′H, C5′′′H or C2′′′H, C6′′′H), 7.13 (d, $J$ = 8.7 Hz, 4 H, C2′H, C6′H), 6.80 (d, $J$ = 8.6 Hz, 4 H, C3′H, C5′H), 5.20 (s, 4 H, C1′′$H_2$), 4.93 (m, 2 H, C*H), 3.86 (s, 2 H, C4′′′$CH_2$), 3.67 (d, $J$ = 6.3 Hz, 4 H, C$H_2$OH), 2.93 (br s, 2 H, CH$_2$O*H*), 1.97–1.87 (m, 4 H, C$H_2$CH$_3$), 0.63 (t, $J$ = 7.5 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}C$ NMR ([D$_6$]acetone): $\delta$ = 174.2 (C=O), 158.2 (C4′), 141.7 (C4′′′), 136.7 (C1′′′), 133.8 (C1′); 129.7, 128.9, 127.7 (C2′ C6′, C2′′′, C6′′′ and C3′′′, C5′′′), 115.7 (C3′, C5′), 69.1 (C1′′), 66.5 (CH$_2$OH), 58.6 (CEt$_2$), 56.2 (C*) 42.1 (C4′′′*C*H$_2$), 32.6 (*C*H$_2$CH$_3$), 10.1 (CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3421, 3057, 2966, 2934, 2877, 1661, 1611, 1511, 1459, 1226, 1178, 1038, 829, 545 cm$^{-1}$.

**Preparation of (1$^4$*R*,11$^4$*R*)-12,12-Diethyl-1$^4$,1$^5$,12$^4$,12$^5$-tetrahydro-3,9-dioxa-1,11(2,4)-bis(1,3-oxazola)-2,5,7,10(1,4)-tetrabenzenacyclododecaphane (1):** Thionyl chloride (1.19 g, 10 mmol) was added to a solution of dihydroxy compound **24** (660 mg, 1.00 mmol) in dichloromethane (20 mL) and the reaction mixture was stirred overnight at room temperature. Solvent was evaporated and the dry residue was dissolved in acetonitrile (50 mL). $K_2CO_3$ (553 mg, 4 mmol) was added to this solution and the reaction mixture was

heated at reflux for 8 h, and then allowed to cool to room temperature. Inorganic salts were filtered off, the filtrate was concentrated, and the oily residue was purified by preparative TLC in $CH_2Cl_2$/MeOH (20:1). Product **1** (428 mg, 73%) was obtained as a white foam. $[\alpha]_D$ = +170.7 ($c$ = 1.24 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.22 (s, 8 H, C2′′′H, C6′′′H and C3′′′H, C5′′′H), 7.05 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.77 (d, $J$ = 8.5 Hz, 4 H, C3′H, C5′H), 5.25–5.14 (m, 6 H, C1′′$H_2$ and C4H), 4.58 (pt, $J$ = 9.2 Hz, 2 H, C5$H_a$), 4.00 (pt, $J$ = 8.0 Hz, 2 H, C5$H_b$), 3.86 (s, 2 H, C4′′′$CH_2$), 2.25 (m, 2 H, C$H_a$CH$_3$), 2.00 (m, 2 H, C$H_b$CH$_3$), 0.94 (m, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.0 (C2), 156.8 (C4′), 140.3 (C4′′′), 134.8 (C1′ or C1′′′), 134.2 (C1′′′ or C1′), 128.2 (C2′′′, C6′′′ or C3′′′, C5′′′), 127.1 (C2′, C6′), 126.1 (C3′′′, C5′′′ or C2′′′, C6′′′), 115.2 (C3′, C5′), 74.6 (C5), 68.7 (C4 or C1′′), 68.5 (C1′′ or C4), 46.8 (CEt$_2$), 41.5 (C4′′′$CH_2$), 25.0 ($CH_2$CH$_3$), 8.1 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 2970, 2933, 1652, 1610, 1510, 1221, 1175, 1107, 987, 828 cm$^{-1}$. HRMS: $[M]^+$ calculated for $C_{38}H_{38}N_2O_4$: 586.28316; found: 586.28310.

**Preparation of 3,3-Bis{(4*R*)-4-[4-(4-phenoxybutoxy)phenyl]-4,5-dihydro-1,3-oxazol-2-yl}pentane (5):** $K_2CO_3$ (553 mg, 4.00 mmol) was added to a solution of **20c** (737 mg, 1.00 mmol) and phenol (94 mg, 1.00 mmol) in acetonitrile (50 mL). The reaction mixture was heated at reflux for 8 h and was then allowed to cool to room temperature. The inorganic precipitate was removed and the filtrate was concentrated, leaving an oily residue that was purified by preparative TLC in $CH_2Cl_2$/EtOAc (7:3). Product **5** (323 mg, 55%) was obtained as a white foam. $[\alpha]_D$ = +95.4 ($c$ = 7.4 in $CH_2Cl_2$). $^1$H NMR: $\delta$ = 7.28 (t, $J$ = 7.9 Hz, 4 H, C3′′′H, C5′′′H), 7.19 (d, $J$ = 8.5 Hz, 4 H, C2′H, C6′H), 6.96–6.84 (m, 10 H, C3′H, C5′H and C2′′′H, C6′′′H and C4′′′H), 6.73 (d, $J$ = 8.7 Hz, 4 H, C2′′′H, C6′′′H or C3′H, C5′H), 5.20 (pt, $J$ = 9.0 Hz, 2 H, C4 H), 4.63 (pt, $J$ = 9.2 Hz, 2 H.C5$H_a$), 4.09 (pt, $J$ = 8.1 Hz, 2 H.C5$H_b$), 4.02 (m, 8 H, C1′′$H_2$ and C4′′$H_2$), 2.13 (m, 4 H, $CH_2CH_3$), 1.97 (br s, 6 H, C2′′H and C3′′H), 0.94 (t, $J$ = 7.4 Hz, 6 H, $CH_2CH_3$) ppm. $^{13}$C NMR: $\delta$ = 168.4 (C2), 158.8, 158.3 (C4′ and C1′′′), 134.4 (C1′), 129.3 (C3′′′, C5′′′), 127.7 (C2′, C6′), 120.5 (C4′′′), 114.5, 114.3 (C3′, C5′ and C2′′′, C6′′′), 74.9 (C5), 68.9 (C4), 67.4, 67.2 (C1′′ and C4′′), 46.8 (CEt$_2$), 25.9 (C2′′ and C3′′), 25.4 ($CH_2CH_3$), 8.4 ($CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 3041, 2927, 2877, 1656, 1538, 1512, 1389, 1303, 1250, 1173, 1059, 977, 921, 831, 759, 693, 542 cm$^{-1}$. HRMS: $[M]^+$ calculated for $C_{43}H_{50}N_2O_6$: 690.36688; found: 690.36720.

**Catalytic Cyclopropanation:** The tested catalytic ligand (0.03 mmol) was added to a suspension of styrene (0.57 mL, 52 mg; 5 mmol) and CuOTf·½MePh (3.9 mg, 0.015 mmol) in 1,2-dichloroethane (1 mL). The formed solution was stirred under argon for 1 h, and a solution of ethyl diazoacetate (1.0 mmol) in 1,2-dichloroethane (1.0 mL, as 1 M solution) was then introduced by syringe pump over 4.5 h. After all the ethyl diazoacetate had been added the reaction mixture was stirred at room temperature under argon overnight. It was then concentrated and the crude product was purified on a short silica gel column with EtOAc/petroleum ether (1:10) as eluent.

Chemical yields were determined by gas chromatography on an achiral HP-1 column with biphenyl as standard. Diastereoselectivity and enantioselectivity of catalytic cyclopropanation were determined by gas chromatography of the product on a chiral Chirasil-DEX CB column. The initial temperature was 120 °C, temperature gradient 1.0 °C min$^{-1}$, the end temperature 150 °C, nitrogen pressure 70 kPa and split 1/50. Under these conditions the retention times of ethyl 2-phenylcyclopropanecarboxylates on the column described were 20.5 min for the *cis*-(1*S*,2*R*) isomer, 21.4 min for the *cis*-(1*R*,2*S*) isomer, 22.5 min for the *trans*-(1*R*,2*R*) isomer and 22.9 min for the *trans*-(1*S*,2*S*) isomer of ethyl 2-phenylcyclopropanecarboxylate.

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