Synthesis of Chiral Diaza-18-crown-6 Derivatives from Optically Active Diethanolamines

Erik F. J. de Vries,† Pablo Steenwinkel,† Johannes Brussee,*,† Chris G. Kruse,‡ and Arne van der Gen†

Department of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands, and Solvay Duphar B.V., P.O. Box 900, 1380 DA Weesp, The Netherlands

Received February 19, 1993

Homotopic 1,10-diaza-18-crown-6 derivatives with two, four, and six chiral centers have been prepared in optically active form from diethanolamines via a cyclization reaction with tosylates **39** and **48**. The requisite optically active diethanolamines were prepared from chiral cyanohydrins and chiral ethanolamines by a one-pot Grignard–transimination–reduction or a one-pot reduction–transimination–reduction procedure. Yields were strongly affected by the size of the substituents α to the nitrogen atom. The stereoselectivity of the diethanolamine synthesis was found to depend on the configuration of the ethanolamine used.

Introduction

The last two decades have shown a wide interest in the chemistry of chiral crown ethers. A major incentive for this research has been the discovery that chiral recognition and catalytic activity, two important properties of natural enzymes, can be displayed by these macrocycles.[1] Cram and co-workers[2–4] as well as others[5] have shown that these chiral ligands are able to discriminate between the enantiomers of guest alkylammonium salts. This chiral recognition process has been studied by NMR spectroscopy,[5] solvent extraction[2] and chromatographic[3] techniques, and transport phenomena through liquid membranes.[4] Chiral crown ethers have also been used successfully as chiral catalysts or chiral templates in asymmetric reactions, including Michael additions,[6] reductions,[7] and hydrogen cyanide additions.[8]

Despite these efforts, the intermolecular interactions that affect complexation of chiral crown ethers with guest molecules are still incompletely understood.[9] A large number of chiral macrocycles have been designed and synthesized to provide enhanced structural selectivity. Most of these were based on easily available chiral building blocks like binaphthol[10] or *vic*-cyclohexanediol[11] derivatives or natural products such as carbohydrates,[12] tartaric acid,[13] and amino acids.[14] Homotopic chiral crown ethers are especially advantageous in chiral recognition processes. Because of their C_2-symmetry, they present two identical asymmetric faces in host–guest interactions.

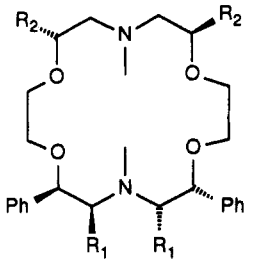
When studying the transformation of optically active cyanohydrins into other classes of chiral compounds,[15–21] it was found that *erythro*-*N*-alkyl-β-ethanolamines could be obtained from O-protected cyanohydrins by a convenient one-pot Grignard–transimination–reduction sequence[19] (Scheme I). We now report how this procedure can be used to prepare di-, tri-, and tetrasubstituted diethanolamines, versatile building blocks for the synthesis of chiral crown ethers in a stereoselective way. Mono- and disubstituted chiral diethanolamines have earlier been studied because of their interesting pharmaceutical properties.[22] Optically active tri- and tetrasubstituted diethanolamines have, to the best of our knowledge, not been synthesized before.

In this report we present the stereoselective synthesis of the novel, homotopic, chiral crown ethers **1–6** (Figure 1), possessing two, four, and six chiral centers. The

† Leiden University.
‡ Solvay Duphar B.V.

(1) Kellogg, R. M. *Pure Appl. Chem.* **1992**, *64*, 413. Newkome, G. R.; Marston, C. R. *J. Org. Chem.* **1985**, *50*, 4238.
(2) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.
(3) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035.
(4) Newcomb, M.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7367.
(5) Zhu, C. Y.; Bradshaw, J. S.; Oscarson, J. L.; Izatt, R. M. *J. Incl. Phenom.* **1992**, *12*, 275. Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1707. Baxter, S. L.; Bradshaw, J. S. *J. Heterocycl. Chem.* **1981**, *18*, 233.
(6) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229. Alonso-López, M.; Jimenez-Barbero, J.; Martín-Lomas, M.; Penadés, S. *Tetrahedron* **1988**, *44*, 1535. Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943. Alonso-López, M.; Martín-Lomas, M.; Penadés, S. *Tetrahedron Lett.* **1986**, *27*, 3551. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625.
(7) De Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.
(8) Dehmlow, E. V.; Knufinke, V. *Liebigs Ann. Chem.* **1992**, 283. Dehmlow, E. V.; Sauerbier, C. *Liebigs Ann. Chem.* **1989**, 181.
(9) Schneider, H.-J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417.
(10) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930. Kyba, E. P.; Gokel, G. W.; De Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.
(11) Hayward, R. C.; Overton, C. H.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2413.
(12) Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1756. Laidler, D. A.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1976**, 979.
(13) Behr, J.-P.; Girodeau, J.-M.; Hayward, R. C.; Lehn, J.-M.; Sauvage, J.-P. *Helv. Chim. Acta* **1980**, *63*, 2096. Girodeau, J.-M.; Lehn, J.-M.; Sauvage, J.-P. *Angew. Chem.* **1975**, *87*, 813.
(14) Žinić, M.; Škarić, V. *J. Org. Chem.* **1988**, *53*, 2582. Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1981**, 992. Wudl, F.; Gaeta, F. *J. Chem. Soc., Chem. Commun.* **1972**, 107.
(15) Brussee, J.; Roos, E. C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485.
(16) Brussee, J.; Loos, W. T.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 979.
(17) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 1653.
(18) Brussee, J.; van Benthem, R. A. T. M.; Kruse, C. G.; Van der Gen *Tetrahedron: Asymm.* **1990**, *1*, 163.
(19) Brussee, J.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 25.
(20) Zandbergen, P.; Van den Nieuwendijk, A. M. C. H.; Brussee, J.; Van der Gen, A.; Kruse, C. G. *Tetrahedron* **1992**, *48*, 3977.
(21) Zandbergen, P.; Brussee, J.; Van der Gen, A.; Kruse, C. G. *Tetrahedron: Asymm.* **1992**, *3*, 769.
(22) Alig, L.; Müller, M. Eur. Pat. Appl. EP 198412, 22 Oct 1986. Hindley, R. M. Eur. Pat. Appl. EP 164700, 18 Dec 1985. Alig, L.; Müller, M. Eur. Pat. Appl. EP 101069, 22 Feb 1984. Lafon, L. Fr. Demande FR 2460668, 30 Jan 1981. Bruce, W. F. U.S. Pat. US 3577462, 4 May 1971.

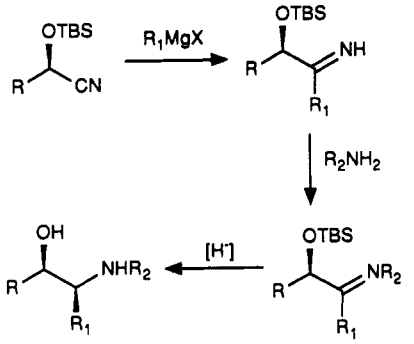
0022-3263/93/1958-4315$04.00/0



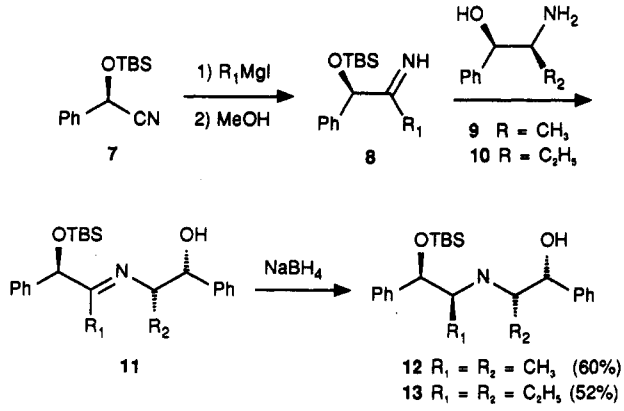
	R_1	R_2
1	H	H
2	CH_3	H
3	C_2H_5	H
4	H	C_6H_5
5	CH_3	C_6H_5
6	C_2H_5	C_6H_5

Figure 1. Chiral 1,10-diaza-18-crown-6 derivatives.

Scheme I. One-Pot Grignard–Transimination–Reduction Sequence



Scheme II. One-Pot Grignard–Transimination–Reduction Synthesis of Chiral Diethanolamines



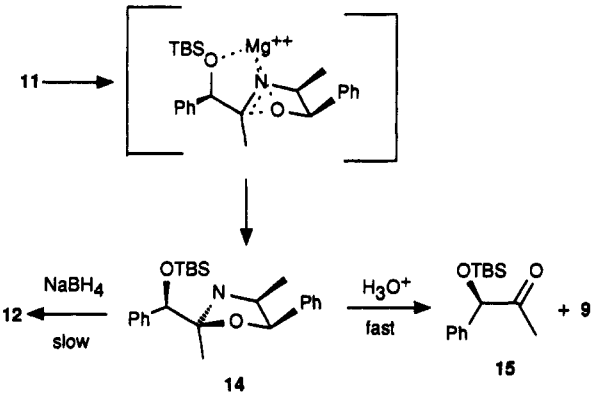
synthetic route followed allows systematic variation of the substituents on the macrocyclic ring.

Results and Discussion

For the synthesis of crown ethers **1–6**, the easily accessible[15] O-protected (*R*)-cyanohydrin **7** was used as the only chiral starting material (Scheme II). First, **7** was converted into optically active *erythro*-ethanolamines **9** and **10** by a one-pot Grignard–reduction sequence, as previously reported.[17]

Chiral diethanolamines **12** and **13** were then obtained from (*R*)-cyanohydrin **7** and *erythro*-ethanolamines **9** and **10** via a four-step one-pot synthesis.[19] Thus, **7** was treated with an excess of methyl- or ethylmagnesium iodide to form the imine–magnesium complex. Dry methanol was added to destroy the excess of Grignard reagent and to protonate the imine anion intermediate. In the third step, the transimination,[19] free primary imine **8** was allowed to react with an excess of **9** or **10**. This led to rapid formation of the more stable secondary imines **11** with loss of NH_3. Finally, the product of the transimination reaction was

Scheme III. Mechanism Describing the Formation of 12 and 15



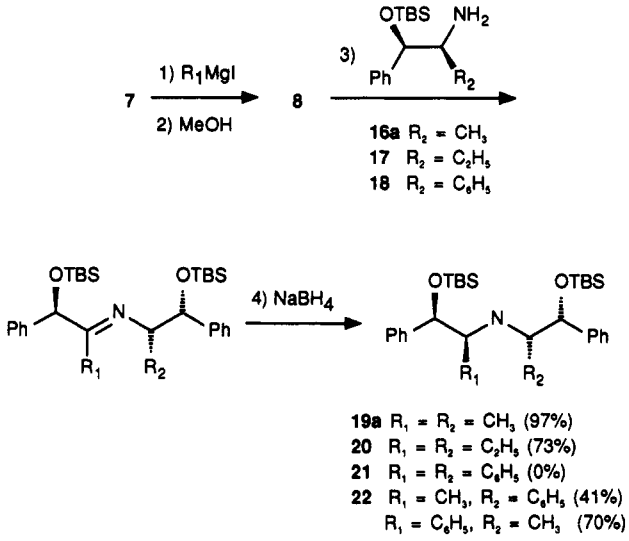
reduced with $NaBH_4$. Upon acidic workup mono, O-protected diethanolamines **12** and **13**, of high diastereomeric purity (de ≥ 96%), were obtained in yields of 60 and 52%, respectively. These yields were considerably lower than those obtained earlier in transiminations with simple alkylamines.[19] Therefore the synthesis of **12** was investigated in more detail.

(*R*)-(+)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenyl-2-propanone (**15**) (Scheme III) was found to be a major side-product in this synthesis (20–30%). An intermediate that was formed during the transimination step was isolated and shown to be the oxazolidine **14**, rather than the expected secondary imine **11**. NOE experiments revealed that the newly formed chiral center of **14** possessed the (*S*)-configuration, as indicated. Oxazolidine **14** is probably formed by a fast intramolecular cyclization of secondary imine **11**. In the transition state, leading to cyclization, the two oxygen atoms and the nitrogen atom are most likely coordinated to magnesium (Scheme III). The incipient five-membered ring will preferentially adopt an envelope conformation with the large α-OTBS-benzyl substituent in a pseudoequatorial position and with the methyl group at C-2 oriented *trans* with respect to the methyl group at C-4 and the phenyl substituent at C-5.

When **14** was treated with $NaBH_4$, a slow reductive ring opening occurred. After 18 h the conversion was still incomplete (60%). Oxazolidine **14** was found to be very sensitive toward acid-catalyzed hydrolysis. Within 5 min, **14** was completely hydrolyzed to ketone **15** and (1*R*,2*S*)-norephedrine (**9**). In the four-step one-pot synthesis of **12** the reduction of intermediate **14** apparently had been incomplete and the remaining oxazolidine was hydrolyzed during workup to form **15**. Longer reaction times for the reduction step indeed led to decreased formation of **15**, but also gave rise to formation of other side-products. Better results were obtained by using O-protected ethanolamines in the transimination step, thereby precluding cyclization (Scheme IV).

Thus, free primary imines **8** were converted into secondary imines via transimination with O-protected ethanolamines **16a**, **17**, and **18**.[17] The secondary imines were stereoselectively reduced *in situ* with $NaBH_4$ to diethanolamines **19a**, **20**, and **22**. The overall yield of this four-step one-pot conversion was found to depend strongly on the size of substituents R_1 and R_2. When R_1 and R_2 both were methyl groups, the yield was almost quantitative (97% isolated). With increasing substituent size the yield rapidly decreased. Compound **21**, with $R_1 = R_2 = Ph$, could not be prepared at all by this method. The

Scheme IV. Synthesis of Di-O-Protected Diethanolamines



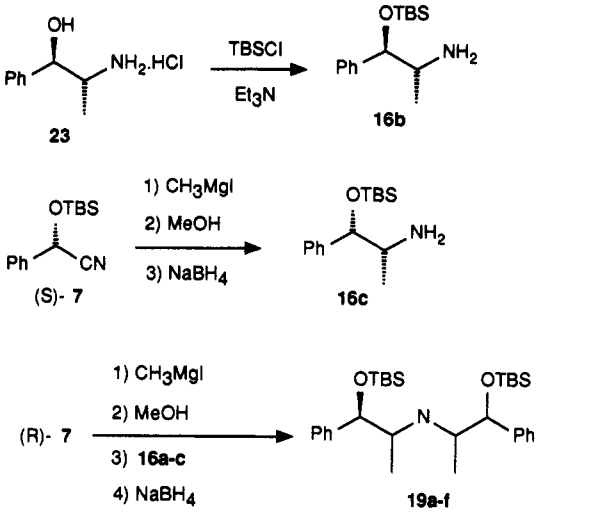
transimination step apparently had not taken place, as the reaction product consisted solely of ethanolamine **18**. At the present time it is not clear whether this results from steric and/or electronic effects of the two α-phenyl substituents.

Asymmetrically substituted diethanolamine **22** was obtained in two different ways. If phenylmagnesium iodide was used in the Grignard reaction and (1*R*,2*S*)-OTBS-norephedrine (**16a**) in the transimination reaction, **22** was obtained in 70% yield. If, on the other hand, methylmagnesium iodide and (1*R*,2*S*)-OTBS-2-amino-1,2-diphenylethan-1-ol (**18**) were used, **22** was isolated in only 41% yield. This difference is ascribed to a decreased nucleophilic reactivity of amine **18**, caused by the α-phenyl substituent. The bis-*erythro*-diethanolamines were formed with high stereoselectivity. The de's of **19a**, **20**, and **22** were determined by ^{1}H NMR to be at least 89%.

To investigate whether the stereoselectivity depends on the configuration of the ethanolamine used in the transimination step, two stereoisomers of **16a** were prepared (Scheme V). (1*S*,2*R*)-OTBS-norephedrine (**16c**) was synthesized from the (*S*)-enantiomer of cyanohydrin **7**[23] in the same manner as **16a** had been prepared from the (*R*)-enantiomer.[17] (1*R*,2*R*)-OTBS-norpseudoephedrine (**16b**) was obtained by silylation of commercially available (1*R*,2*R*)-norpseudoephedrine hydrochloride (**23**). Only O-silylated product was isolated. It is assumed that the kinetically favored N-silylated product is transformed to the more stable O-silyl isomer by a fast *N*,*O*-silyl shift.[24]

When, instead of (1*R*,2*S*)-OTBS-norephedrine (**16a**), (1*R*,2*R*)-OTBS-norpseudoephedrine (**16b**) or (1*S*,2*R*)-OTBS-norephedrine (**16c**) was used in the Grignard–transimination–reduction sequence with (*R*)-cyanohydrin **7**, the prevalence for formation of the *erythro* diastereomer during the reduction step decreased dramatically. The diastereomeric excess, as determined by ^{1}H NMR, was found to be 20 and 28%, respectively. To understand this large difference in stereoselectivity, the conformations that

Scheme V. Synthesis of 19a–f



ethanolanime	major product	minor product	de (%)
(1*R*,2*S*)-**16a**	(1*R*,2*S*,1'*R*,2'*S*)-**19a**	(1*R*,2*R*,1'*R*,2'*S*)-**19d**	92
(1*R*,2*R*)-**16b**	(1*R*,2*S*,1'*R*,2'*R*)-**19b**	(1*R*,2*R*,1'*R*,2'*R*)-**19e**	20
(1*S*,2*R*)-**16c**	(1*R*,2*S*,1'*S*,2'*R*)-**19c**	(1*R*,2*R*,1'*S*,2'*R*)-**19f**	28

the secondary imine intermediates can adopt have to be considered. Under the reaction conditions used, the secondary imine intermediates will be complexed to magnesium.[18] Coordination to magnesium activates the imine toward hydride reduction by polarizing the imine double bond. For each imine intermediate, the two predominant conformers[25] are represented in Scheme VI. Conformer A, formed upon reaction with (1*R*,2*S*)-OTBS-norephedrine (**16a**), is energetically less favorable than conformer B, because of allylic 1,3-strain between the two methyl substituents in A.[26] In conformation A approach of the imine function by $NaBH_4$ is hindered by the α-phenyl group. The predominant conformer B can undergo a fast stereoselective reduction with $NaBH_4$. This explains the formation of **19a** in high diastereomeric excess (de 92%). If, on the other hand, the transimination reaction is performed with **16b** or **16c**, it is the less stable conformer of the secondary imine intermediate (D) that is more prone to reduction. Because of the opposing effects of conformational stability and ease of reduction, a lower stereoselectivity will be observed in these cases.

Next to these diethanolamines with four chiral centers, diethanolamines were prepared with two and three chiral centers (Scheme VII).

O-protected ethanolamine **24** was prepared by reduction of cyanohydrin **7** with DIBALH, followed by $NaBH_4$ reduction of the imine intermediate. **24** was obtained in quantitative yield and used in the subsequent transimination reaction without purification. To synthesize **25** and **26**, cyanohydrin **7** was treated with an excess of DIBALH. Dry methanol was added to destroy the excess of reagent and to protonate the imine–aluminum complex. Upon addition of 2.5 equiv of ethanolamine **16a** or **24**, transimination to the secondary imines occurred rapidly.[20] The latter were reduced *in situ* with $NaBH_4$ to give the desired diethanolamines in good yields.

For the preparation of crown ethers **2**, **3**, **5**, and **6**, the TBS groups in diethanolamines **19a** and **20** were quan-

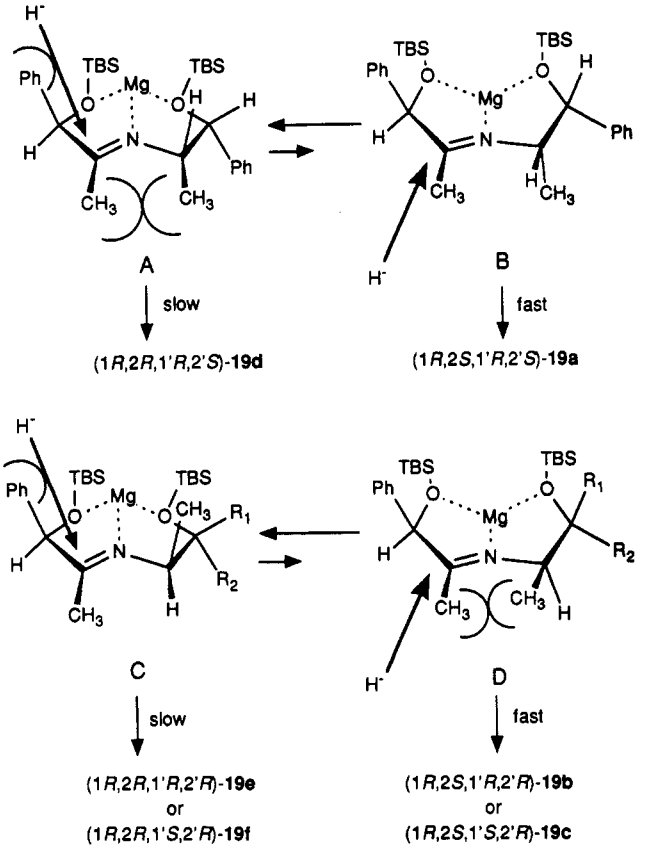
(23) The (*S*)-enantiomer of cyanohydrin **7** can be obtained from its optical antipode by a Mitsunobu esterification reaction, using *p*-nitrophenylacetic acid as the protonated nucleophile, followed by acid-catalyzed hydrolysis. Warmerdam, E. G. J. C.; Brussee, J.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1993**, *49*, 1063.

(24) Silks, III, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495.

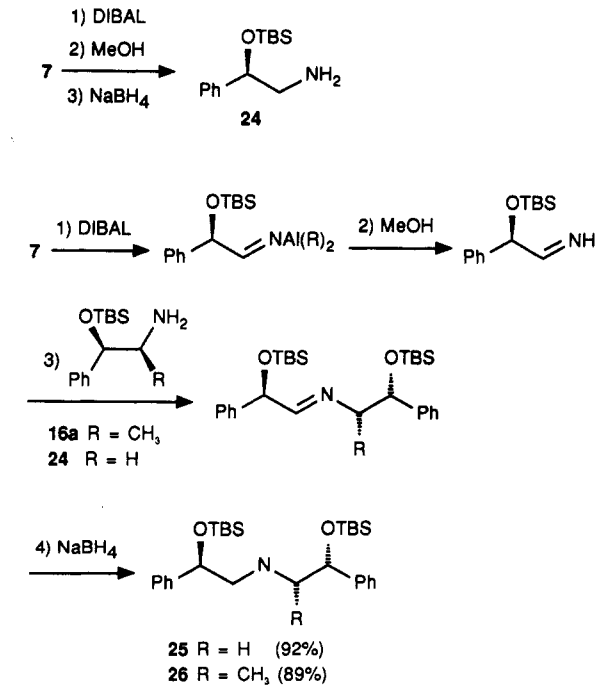
(25) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H.; *J. Am. Chem. Soc.* **1971**, *93*, 1637.

(26) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1124. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

Scheme VI. Conformations of the Secondary Imine Intermediates in the Synthesis of 19a–f

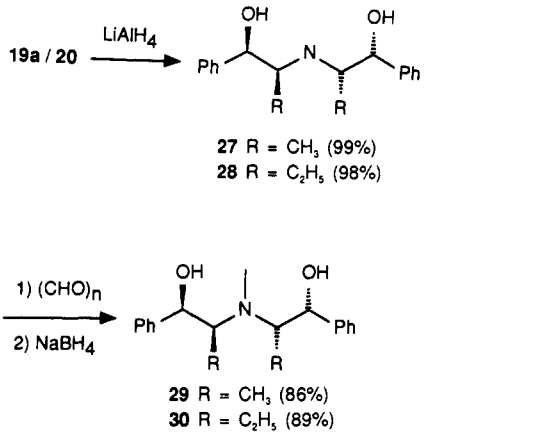


Scheme VII. Synthesis of Di- and Trisubstituted Diethanolamines 25 and 26

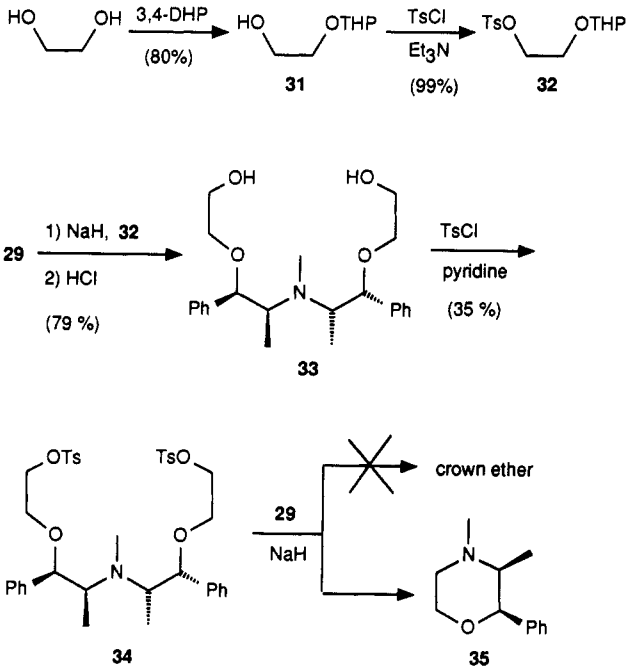


titatively removed with $LiAlH_4$[18] (Scheme VIII). To reduce their nucleophilic reactivity, the unprotected diethanolamines **27** and **28** were then methylated at nitrogen following a modified literature procedure.[27] The N-methylated products **29** and **30** were isolated in good yields.

Scheme VIII. Synthesis of O-Unprotected *N*-Methyl diethanolamines 29 and 30



Scheme IX. Attempted Synthesis of an Octasubstituted Crown Ether



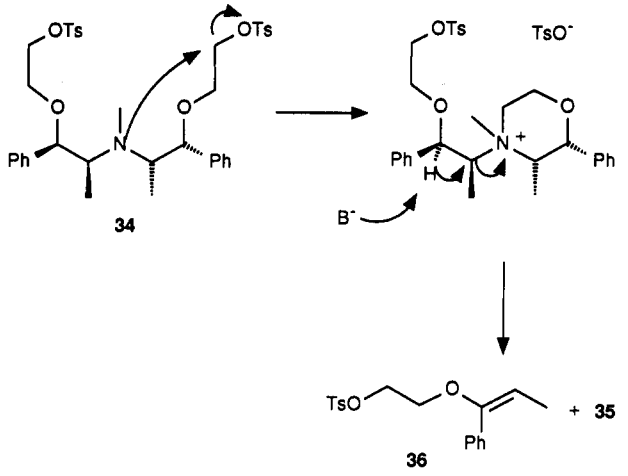
Diethanolamine **29** was extended at both hydroxyl groups by a two-carbon unit, using the THP ether of 2-(tosyloxy)ethanol (**32**). This C_2-building block was synthesized by an improved literature procedure[28] (Scheme IX). First, ethylene glycol was pseudoselectively monoprotected with 3,4-2*H*-dihydropyran to give **31** in 80% yield. The remaining free hydroxyl group in **31** was then tosylated to obtain **32** in nearly quantitative yield. Alkylation of **29** with tosylate **32**, followed by removal of the THP protecting groups, provided diol **33** in 79% yield. In an attempt to synthesize an octasubstituted crown ether, tosylate **34**, obtained from **33**, was allowed to react with the dianion from tetrasubstituted diethanolamine **29**. However, only morpholine derivative **35**, along with unchanged diethanolamine **29** and small quantities of several unidentified products were isolated.

Intramolecular cyclization leading to morpholine derivatives has been reported in literature for secondary

(27) Saavedra, J. E. *J. Org. Chem.* **1985**, *50*, 2271.

(28) Weber, E. *Liebigs Ann. Chem.* **1983**, 770.

Scheme X. Proposed Mechanism for the Formation of Morpholine 35



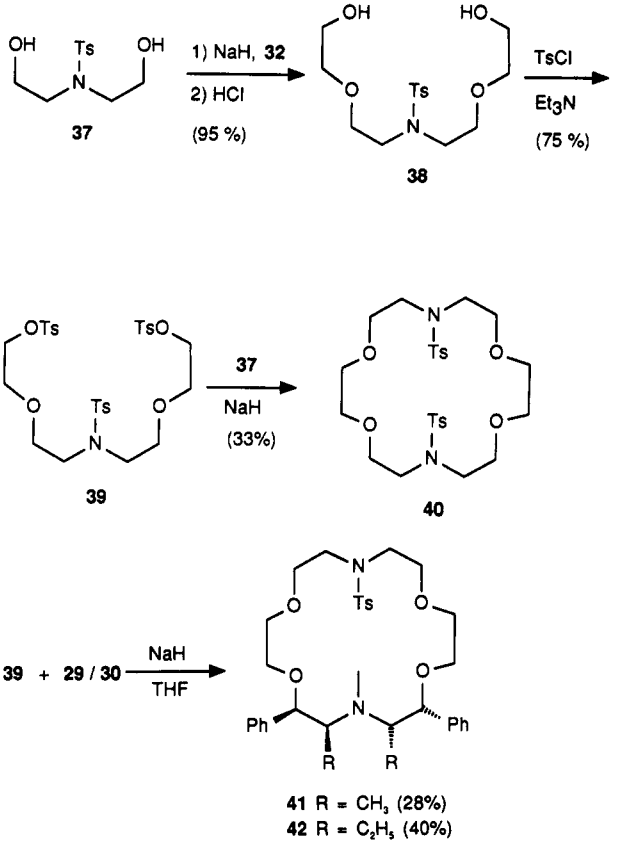
amines,[29] but not for tertiary amines and not accompanied by C–N bond fission. To account for the formation of **35**, the mechanism depicted in Scheme X is proposed. Intramolecular nucleophilic attack by nitrogen at one of the tosylated carbon atoms is followed by a β-elimination, with morpholine **35** acting as the leaving group. The other expected reaction product, enol ether **36**, was not isolated. It is assumed to be unstable under the reaction conditions. If the proposed mechanism is correct, it should be possible to avoid the intramolecular cyclization reaction by further decreasing the nucleophilicity of the nitrogen atom in tosylate **34**.

To test this hypothesis sulfonamide **39** was prepared (Scheme XI). When **39** was allowed to react with the dianion obtained from diol **37**[30] under high dilution conditions, the known[31] crown ether **40** was obtained in 33% yield. In this reaction sequence no formation of morpholine derivatives was observed.

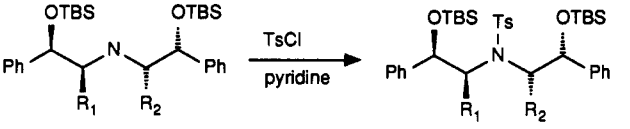
Next, tosylate **39** and optically active diethanolamines **29** and **30** were applied to the synthesis of chiral crown ethers **41** and **42**, possessing four chiral centers. The macrocycles were obtained in satisfactory yields.

To prepare crown ethers with more than four chiral centers, chiral analogues of tosylate **39** were desired. Diethanolamines **19a**, **25**, and **26** were therefore treated with tosylate chloride in pyridine (Scheme XII). Amine **25**, having no α-alkyl substituents, was readily tosylated (reaction time 18 h, yield of sulfonamide **43**, 98%). Tosylation of diethanolamine **26**, carrying one α-methyl substituent, was considerably more difficult. Longer reaction times were needed and the yield of **44** was only 75%. Amine **19a**, with two α-methyl groups, did not react at all under these conditions. Attempts to improve this situation by changing the base from pyridine to triethylamine, butyllithium, or sodium hydride or by substituting tosyl chloride for mesyl chloride, remained without success. Thus, no N-tosylated tetrasubstituted diethanolamine could be made available and, as a consequence, no octasubstituted crown ether could yet be synthesized.

Scheme XI. Synthesis of Crown Ethers 40–42



Scheme XII. Tosylation of Chiral O-Protected Diethanolamines



amine	R_1	R_2	product	time	Yield (%)
25	H	H	**43**	18 h	98
26	CH_3	H	**44**	48 h	75
19a	CH_3	CH_3	**45**	7 d	0

Sulfonamide **43**, containing a C_2 axis of symmetry, was used for the synthesis of four additional homotopic chiral crown ethers. Removal of the TBS groups in **43** with tetrabutylammonium fluoride (TBAF) gave **46** in nearly quantitative yield (Scheme XIII). The dianion of **46** was then bis-alkylated with THP-ether **32** as before. After removal of the THP groups, diol **47**, isolated in 65% yield, was tosylated to give **48**. Under high dilution conditions, tosylate **48** was allowed to react with optically active diethanolamines **29** and **30**. Macrocycles **49** and **50**, containing six chiral centers, were obtained in moderate yields. Finally, chiral crown ethers **51** and **52** were synthesized from optically active disubstituted sulfonamide **46** and tosylates **39** and **48** in over 50% yield.

To improve the complexation properties of the crown ethers obtained so far, the tosylated secondary amino groups were converted into tertiary amines. This was accomplished by reductively removing the tosyl groups with $LiAlH_4$ and methylating the secondary amines by an Eschweiler–Clark reductive amination (Scheme XIV).

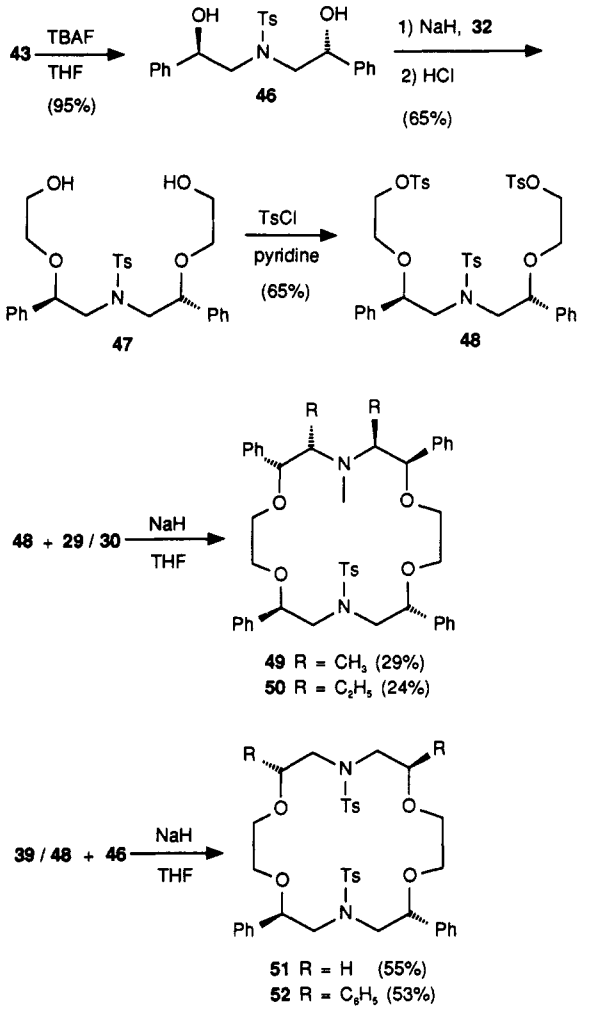
^1H NMR analysis revealed the de's of crown ethers **2**, **3**, **5**, and **6** to be $\geq$94%, which is higher than the de's of

(29) De Jong, F.; Van Zon, A.; Reinhoudt, D. N.; Torny, G. J.; Tomassen, H. P. M. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 164. Maeda, H.; Furuyoshi, S.; Nakatsuji, Y.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3073. King, A. P.; Kespan, C. G. *J. Org. Chem.* **1974**, *39*, 1315.

(30) Eisleb, O. *Chem. Ber.* **1941**, *74*, 1433.

(31) The achiral crown ether **40** has been obtained earlier by different routes. See: Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268. Rasshofer, W.; Vögtle, F. *Liebigs Ann. Chem.* **1978**, 552.

Scheme XIII. Synthesis of Chiral Crown Ethers 49–53



the optically active building blocks from which they had been prepared.[32] This implies that these crown ethers racemize only very slowly, if at all, under the reaction conditions used and also that they had been diastereomerically enriched during purification. To establish the stability of the benzylic chiral centers, crown ether 1 was treated with 4 equiv of NaH in THF. After for 24 h of reflux, the optical rotation had not changed. It must be concluded that crown ethers of this type do not perceptively racemize under these strongly basic conditions.

In conclusion, it can be said that optically active diethanolamines, with two and four chiral centers, have shown to be valuable new building blocks for the synthesis of homotopic chiral crown ethers of high optical purity and with a wide variety in substituent pattern.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. De's were determined by integration of the ^{1}H NMR signals of the benzylic protons or by HPLC analysis using a CHIRALCEL OD column (flow rate: 1 mL/min, eluent: **25**: hexane/2-propanol = 99.75/0.25; **51**: hexane/2-propanol = 90/10).

Chemicals. Commercially available chemicals were used, with the exception of (*R*)-7,[16] (*S*)-7,[23] **37**,[30] **9**, **10**, **16a**, **17**, and **18**,[17] which were synthesized by methods described before. THF was freshly distilled from $LiAlH_4$ prior to use. Diethyl ether was dried on sodium wire. Methanol was dried on molecular sieves (3 Å). All reactions were carried out in a nitrogen atmosphere.

[(1*R*,2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropan-2-yl][(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]amine (12). To a solution of 30 mmol of CH_3MgI in 50 mL of anhydrous ether was added dropwise a solution of 4.95 g (20 mmol) (*R*)-(+)-α-[(*tert*-butyldimethylsilyl)oxy]benzeneacetonitrile (**7**) in 50 mL of ether. After 3 h of reflux, 25 mL of dry methanol and a solution of 6.00 g (40 mmol) (1*R*,2*S*)-norephedrine (**9**) in 25 mL of dry methanol were added successively at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 °C and 1.52 g (40 mmol) $NaBH_4$ was added in small portions. The reaction mixture was stirred overnight at ambient temperature. After addition of 100 mL 1 M HCl, the mixture was extracted with ether (3 × 75 mL). The water layer was basified with solid NaOH and extracted with CH_2Cl_2 to recover the excess of **9**. The combined ethereal layers were washed with 1 M NaOH (100 mL) and with a saturated NaCl solution (brine), dried on K_2CO_3, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: triethylamine/ether/petroleum ether 40–60 = 3/5/92): yield 4.80 g (60%); $[\alpha]^{20}_D$ −21° (*c* = 1, $CHCl_3$); mp 82–83 °C; de 98% (NMR); ^{1}H NMR δ (ppm) 7.30 (m, 10H, Ph), 4.65 (d, 2H, *J* = 4.1 Hz, CHO), 3.07 (dq, 1H, *J* = 4.1 Hz, *J* = 6.7 Hz, CHN), 2.97 (dq, 1H, *J* = 4.1 Hz, *J* = 6.7 Hz, CHN), 0.99 (d, 3H, *J* = 6.7 Hz, CH_3), 0.89 (s, 9H, *t*-Bu), 0.69 (d, 3H, *J* = 6.7 Hz, CH_3), 0.02 (s, 3H, $SiCH_3$), −0.20 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 142.4, 141.5, 128.1, 128.0, 127.4, 127.0, 126.9, 126.3 (Ph), 78.0, 74.0 (CHO), 56.3, 55.0 (CHN), 26.0 ($C(CH_3)_3$), 18.3 ($C(CH_3)_3$), 16.2, 14.7 (CH_3), −4.3, −4.9 ($SiCH_3$); IR ν (cm^{-1}) 3370, 2942, 2922, 2830, 1580, 1450, 1255, 1054, 860, 838, 775, 700.

[(1*R*,2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylbutan-2-yl][(1*R*,2*S*)-1-hydroxy-1-phenylbutan-2-yl]amine (13). Prepared as described for **12**, using C_2H_5MgI as the Grignard reagent and amine **10** in the transimination reaction: yield 52%; $[\alpha]^{20}_D$ −33° (*c* = 1, $CHCl_3$); de 96% (NMR); ^{1}H NMR δ (ppm) 7.28 (m, 10H, Ph), 4.75 (d, 1H, *J* = 4.1 Hz, CHO), 4.72 (d, 1H, *J* = 5.1 Hz, CHO), 2.85 (m, 2H, CHN), 1.52 (m, 4H, CH_2), 1.01 (t, 3H, *J* = 7.2 Hz, CH_3), 0.90 (s, 9H, *t*-Bu), 0.67 (t, 3H, *J* = 7.4 Hz, CH_3), 0.04 (s, 3H, $SiCH_3$), −0.21 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 142.0, 141.2, 127.9, 127.4, 127.1, 126.7, 126.0 (Ph), 76.3, 72.0 (CHO), 62.5, 61.8 (CHN), 25.8 ($C(CH_3)_3$), 23.1, 22.0 (CH_2), 18.2 ($C(CH_3)_3$), 10.9, 10.2 (CH_3), −4.2, −5.0 ($SiCH_3$).

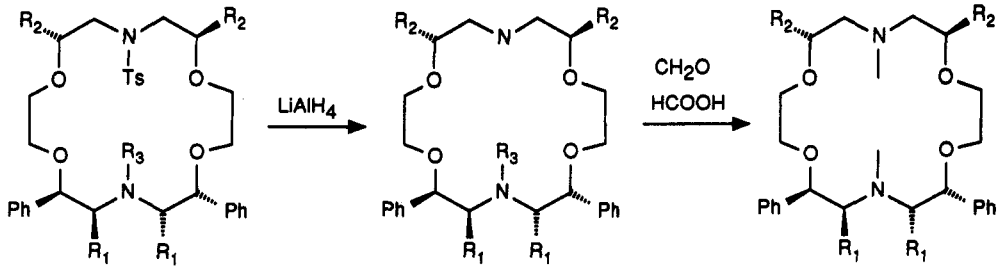
(2*S*,4*S*,5*R*)-2-[(*R*)-α-[(*tert*-Butyldimethylsilyl)oxy]benzyl]-2,4-dimethyl-5-phenyloxazolidine (14). To a solution of 7.5 mmol of CH_3MgI in 15 mL of dry ether was added a solution of 1.20 g (5.0 mmol) **7** in 15 mL of ether. After refluxing for 3 h, the reaction mixture was cooled to 0 °C and 5 mL of dry methanol was added. This was directly followed by the addition of a solution of 1.50 g (10 mmol) **9** in 5 mL of methanol. The reaction mixture was stirred for 1 h at room temperature, poured into 50 mL of water, and extracted three times with 50 mL of ether. The combined organic layers were washed with a saturated $NaHCO_3$ solution and with brine and dried on K_2CO_3, and the solvent was evaporated. After flash column chromatography (eluent: triethylamine/ether/petroleum ether 40–60 = 10/10/80) oxazolidine **14** was obtained as a white paste: yield 1.80 g (71%); $[\alpha]^{20}_D$ −132° (*c* = 1, $CHCl_3$); ^{1}H NMR δ (ppm) 7.30 (m, 10H, Ph), 4.95 (d, 1H, *J* = 8.0 Hz, OCHCH), 4.68 (s, 1H, TBSOCH), 3.82 (dq, 1H, *J* = 8.0 Hz, *J* = 6.7 Hz, CHN), 2.02 (bs, 1H, NH), 1.17 (s, 3H, 2-CH_3), 0.85 (s, 9H, t-Bu), 0.64 (d, 3H, *J* = 6.7 Hz, 4-CH_3), −0.03 (s, 3H, $SiCH_3$), −0.22 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 140.8, 139.9, 128.7, 127.6, 127.5, 126.8, 126.7 (Ph), 96.9 (CON), 80.1, 78.3 (CHO), 55.9 (CHN), 25.6 ($C(CH_3)_3$), 22.0 (CH_3), 18.1 ($C(CH_3)_3$), 16.4 (CH_3), −4.7, −5.5 ($SiCH_3$); IR: ν (cm^{-1}) 3195, 3020, 2930, 1253, 1080, 1055, 1020, 778, 702.

Reduction of Oxazolidine 14. To a solution of 320 mg (0.61 mmol) **14** in 5 mL of dry methanol was added 46 mg (1.2 mmol) of $NaBH_4$. After stirring for 18 h at room temperature, 20 mL of water was added and the mixture was extracted with ether (3 × 25 mL). The combined ethereal layers were washed with brine, dried on K_2CO_3, and concentrated *in vacuo*. A mixture (320 mg, 100%) of product **12** and unreacted oxazolidine **14** was obtained. Conversion 60% (^{1}H NMR).

(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenyl-2-propanone (15). A 1 M HCl solution (3 mL) was added to a solution of 330 mg (0.63 mmol) **14** in 3 mL of methanol. The reaction

(32) The de's of crown ethers **1** and **4** could not be determined by ^{1}H NMR or HPLC analysis.

Scheme XIV. Detosylation and Methylation of Crown Ethers



I II III

I	R_1	R_2	R_3	II	R_3	Y (%)	III	Y (%)
51	H	H	Ts	**53**	H	54	**1**	62
41	Me	H	Me	**54**	Me	67	**2**	83
42	Et	H	Me	**55**	Me	57	**3**	60
52	H	Ph	Ts	**56**	H	46	**4**	89
49	Me	Ph	Me	**57**	Me	46	**5**	68
50	Et	Ph	Me	**58**	Me	49	**6**	63

mixture was stirred for 5 min, after which it was diluted with 10 mL of water and extracted with ether (3 × 10 mL). The combined organic layers were washed with 15 mL of brine and dried on $MgSO_4$, and the solvent was evaporated. Product **15** (160 mg, 96%) was isolated as a colorless oil: $[\alpha]^{20}_D$ +64° (*c* = 1, $CHCl_3$); lit.[15] $[\alpha]^{20}_D$ +61° (*c* = 1, $CHCl_3$); ^1H NMR data were identical to literature data;[15] ^{13}C NMR δ (ppm) 208.5 (C=O), 138.5, 128.4, 127.9, 125.7 (Ph), 81.1 (CHO), 25.6 ($C(CH_3)_3$), 23.8 (CH_3), 18.1 ($C(CH_3)_3$), -5.2 ($SiCH_3$); IR ν (cm^{-1}) 3060, 3025, 2915, 2860, 1713, 1465, 1455, 1350, 1255, 1100, 865, 840, 780, 700.

Bis[(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (19a). To a solution of 15 mmol of CH_3MgI in 25 mL of anhydrous ether was added a solution of 2.50 g (10 mmol) of **7** in 20 mL of ether. After 3 h of reflux, 10 mL of dry methanol and a solution of 8.00 g (30 mmol) **16a** in 10 mL of methanol were added successively at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h. Then at 0 °C 0.76 g (20 mmol) of $NaBH_4$ was added in small portions, after which the reaction mixture was stirred overnight at room temperature. After adding 150 mL of water, the mixture was extracted with ether (3 × 75 mL). The combined organic layers were washed with brine, dried on $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (eluent: triethylamine/petroleum ether 40–60 = 3/97) afforded 5.01 g (97%) of **19a** and 4.50 g of **16a** (85% of the excess): $[\alpha]^{20}_D$ -36° (*c* = 1, $CHCl_3$); mp 45–47 °C; de 92% (NMR); ^1H NMR δ (ppm) 7.25 (m, 10H, Ph), 4.51 (d, 2H, *J* = 4.6 Hz, CHO), 2.83 (dq, 2H, *J* = 4.6 Hz, *J* = 6.2 Hz, CHN), 0.89 (d, 6H, *J* = 6.2 Hz, CH_3), 0.81 (s, 18H, *t*-Bu), -0.05 (s, 6H, $SiCH_3$), -0.29 (s, 6H, $SiCH_3$); ^{13}C NMR: δ (ppm) 143.2, 127.8, 127.0 (Ph), 79.1 (CHO), 56.3 (CHN), 25.8 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), 14.1 (CH_3), -4.6 ($SiCH_3$), -5.0 ($SiCH_3$); IR ν (cm^{-1}) 3400, 3060, 3025, 1252, 1060, 777, 749, 700; MS *m/z* 514 (M + H^+).

Bis[(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylbutan-2-yl]amine (20). Prepared as described for **19a**, using C_2H_5MgI as the Grignard reagent and amine **17** in the transimination reaction: yield 73%; $[\alpha]^{20}_D$ -28° (*c* = 1, $CHCl_3$); de 90% (NMR); ^1H NMR δ (ppm) 7.24 (m, 10H, Ph), 4.48 (d, 2H, *J* = 5.7 Hz, CHO), 2.68 (m, 2H, CHN), 1.35 (m, 5H, CH_2 + NH), 0.83 (s, 18H, t-Bu), 0.64 (t, 6H, CH_3), -0.02 (s, 6H, $SiCH_3$), -0.30 (s, 6H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.4, 127.6, 127.3, 126.9 (Ph), 77.2 (CHO), 61.7 (CHN), 25.9 ($C(CH_3)_3$), 21.3 (CH_2), 18.1 (($C(CH_3)_3$), 8.9 (CH_3), -4.5 ($SiCH_3$); MS *m/z* 542 (M + H^+).

[(1*R*,2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2-diphenylethan-2-yl][(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (22). Prepared as described for **19a**, with PhMgI as the Grignard reagent and amine **16a** in the transimination reaction. Yield: 70%.

Alternatively, **22** was prepared as described for **19a**, using CH_3MgI as the Grignard reagent and amine **18** in the transimination reaction: yield 40%; $[\alpha]^{20}_D$ -41° (*c* = 1, $CHCl_3$); de 89% (NMR); ^1H NMR: δ (ppm) 7.12 (m, 15H, Ph), 4.68 (d, 1H, *J* = 5.1 Hz, CHO), 4.44 (d, 1H, *J* = 5.1 Hz, CHO), 3.83 (d, 1H, *J* = 5.1 Hz, PhC*H*N), 2.48 (m, 1H, CH_3CHN), 1.58 (bs, 1H, NH), 0.81 (d, 3H, *J* = 6.2 Hz, CH_3), 0.80 (s, 9H, t-Bu), 0.69 (s, 9H, t-Bu), -0.03 (s, 3H, $SiCH_3$), -0.26 (s, 3H, $SiCH_3$), -0.27 (s, 3H, $SiCH_3$), -0.41 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.1, 142.4, 140.0, 129.2, 127.7, 127.5, 127.3, 127.2, 127.0, 126.7 (Ph), 79.5 (CHO), 66.6 (PhC*H*N), 55.7 (CH_3CHN), 25.8, 25.7 ($C(CH_3)_3$), 18.1, 17.9 ($C(CH_3)_3$), 13.5 (CH_3), -4.6, -4.9, -5.3 ($SiCH_3$); MS *m/z* 576 (M + H^+).

[(1*R*,2*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (16b). To a suspension of 10.0 g (53 mmol) (1*R*,2*R*)-(-)-Norpseudoephedrine hydrochloride (**23**) in 100 mL of CH_2Cl_2 were added successively 8.00 g (53 mmol) TBSCl and 15.3 mL (110 mmol) triethylamine at 0 °C. After stirring at room temperature for 18 h, the reaction mixture was filtered. The filtrate was concentrated *in vacuo*. The crude product was suspended in ether, filtered, and concentrated again. Purification by flash column chromatography (eluent: triethylamine/ether/petroleum ether 40–60 = 3/10/87) afforded 11.35 g (80%) **16b**: $[\alpha]^{20}_D$ -66° (*c* = 1, $CHCl_3$); de 98% (NMR); ^1H NMR δ (ppm) 7.29 (m, 5H, Ph), 4.30 (d, 1H, *J* = 6.2 Hz, CHO), 2.93 (q, 1H, *J* = 6.2 Hz, CHN), 1.21 (bs, 2H, NH_2), 0.94 (d, 3H, *J* = 6.7 Hz, CH_3), 0.90 (s, 9H, t-Bu), 0.04 (s, 3H, $SiCH_3$), -0.22 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 142.7, 127.7, 127.0, 126.5 (Ph), 80.7 (CHO), 73.7 (CHN), 25.6 ($C(CH_3)_3$), 19.3 (CH_3), 17.9 ($C(CH_3)_3$), -4.8, -5.3 ($SiCH_3$).

[(1*S*,2*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (16c). To a solution of 21 mmol of CH_3MgI in 20 mL of anhydrous ether was added dropwise a solution of 3.01 g (12 mmol) of (*R*)-cyanohydrin **7** in 20 mL of ether. The mixture was refluxed for 4 h and then cooled to 0 °C. Dry methanol (18 mL) was added slowly, followed by 1.05 g (28 mmol) $NaBH_4$. After stirring overnight at room temperature, 100 mL of water was added and the mixture was extracted with ether (3 × 50 mL). The combined ethereal layers were washed twice with brine and dried on $MgSO_4$, and the solvent was evaporated. The crude product was dissolved in absolute ethanol and neutralized with a 0.48 M HCl solution (4 mL of 12 M HCl mixed with 96 mL of absolute ethanol). The solvent was evaporated and the residue was recrystallized from absolute ethanol. To the crystals was added 50 mL 1 M NaOH and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried on $MgSO_4$, and the solvent was evaporated: yield 1.50 g (47%); $[\alpha]^{20}_D$ +49° (*c* = 1, $CHCl_3$); de 99% (NMR); ^1H NMR δ (ppm) 7.27 (m, 5H, Ph), 4.40 (d, 1H, *J* = 5.1 Hz, CHO), 3.01 (dq, 1H, *J* = 5.1 Hz, *J* = 6.7 Hz, CHN), 1.01 (d, 3H, *J* = 6.7 Hz, CH_3), 0.89 (s, 9H, t-Bu), 0.03 (s, 3H, $SiCH_3$), -0.18 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 141.7, 127.6, 127.0, 126.7 (Ph), 79.9 (CHO), 53.2 (CHN), 25.6 ($C(CH_3)_3$), 18.7 (CH_3), 17.9 ($C(CH_3)_3$), -4.8, -5.3 ($SiCH_3$).

[(1*R*,2*S*))-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropan-2-yl][(1*R*,2*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (19b). Prepared as described for **19a**,

using **16b** in the transimination reaction: yield 78%; $[\alpha]^{20}_D$ −51° (c = 1, $CHCl_3$); de 20% (NMR).

Major Isomer (19b): ^1H NMR δ (ppm) 7.23 (m, 10H, Ph), 4.60 (d, 1H, J = 4.1 Hz, CHO), 4.42 (d, 1H, J = 6.2 Hz, CHO), 3.01 (m, 1H, CHN), 2.87 (m, 1H, CHN), 1.04 (d, 3H, J = 6.7 Hz, CH_3), 0.93 (s, 9H, t-Bu), 0.87 (s, 9H, t-Bu), 0.86 (d, 3H, J = 6.6 Hz, CH_3), 0.12 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), −0.16 (s, 3H, $SiCH_3$), −0.20 (s, 3H, $SiCH_3$).

Minor Isomer (19e): ^1H NMR δ (ppm) 7.23 (m, 10H, Ph), 4.49 (d, 2H, J = 6.2 Hz, CHO), 2.87 (m, 2H, CHN), 0.82 (s, 18H, t-Bu), 0.80 (d, 6H, J = 6.7 Hz, CH_3), 0.00 (s, 6H, $SiCH_3$), −0.23 (s, 6H, $SiCH_3$).

[(1*R*,2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropan-2-yl][(1*S*,2*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (19c). Prepared as described for **19a**, using **16c** in the transimination reaction: yield 90%; $[\alpha]^{20}_D$ −7° (c = 1, $CHCl_3$); de 28% (NMR).

Major Isomer (19c): ^1H NMR: δ (ppm) 7.20 (m, 10H, Ph), 4.38 (d, 2H, J = 4.6 Hz, CHO), 2.63 (m, 2H, CHN), 0.97 (d, 6H, J = 6.2 Hz, CH_3), 0.86 (s, 18H, t-Bu), 0.00 (s, 3H, $SiCH_3$), −0.24 (s, 6H, $SiCH_3$).

Minor Isomer (19f): ^1H NMR δ (ppm) 7.20 (m, 10H, Ph), 4.49 (d, 1H, J = 4.5 Hz, CHO), 4.44 (d, 1H, J = 5.4 Hz, CHO), 2.83 (m, 2H, CHN), 0.86 (s, 9H, t-Bu), 0.85 (s, 9H, t-Bu), 0.82 (d, 3H, J = 6.4 Hz, CH_3), 0.64 (d, 3H, J = 6.4 Hz, CH_3), 0.03 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), −0.22 (s, 3H, $SiCH_3$), −0.25 (s, 3H, $SiCH_3$).

(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethan-2-yl]amine (24). To a solution of 24.7 g (100 mmol) **7** in 400 mL of anhydrous ether was added 175 mL 1 M DIBALH in hexane at −80 °C. After stirring at this temperature for 3 h, 200 mL of dry methanol was added at −90 °C. Then 7.60 g (200 mmol) of $NaBH_4$ was added in 3 portions, after which the reaction mixture was allowed to warm to room temperature and stirred for another 18 h. The reaction mixture was poured into 1 L of water and extracted with ether (3 × 300 mL). The combined organic layers were washed with brine and dried on $MgSO_4$, and the solvent was evaporated. Compound **24** (25.0 g, 100%) was used in the transimination reaction without purification.

When desired, **24** can be purified by recrystallization. The crude product was dissolved in absolute ethanol and neutralized with a 0.48 M ethanolic HCl solution (4 mL of 12 M HCl mixed with 96 mL of absolute ethanol). The ethanol was evaporated and the residue was recrystallized from absolute ethanol. **24**·HCl was dissolved in ether and washed with 150 mL of 1 M NaOH. The water layer was extracted two more times with ether. The combined ethereal layers were dried on $MgSO_4$, and the solvent was evaporated: yield 15.1 g (60%); $[\alpha]^{20}_D$ −70° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.28 (m, 5H, Ph), 4.65 (t, 1H, J = 5.7 Hz, CH), 2.82 (d, 2H, J = 5.7 Hz, CH_2), 1.24 (bs, 2H, NH_2), 0.91 (s, 9H, t-Bu), 0.06 (s, 3H, $SiCH_3$), −0.10 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 142.9, 128.0, 127.1, 126.0 (Ph), 76.6 (CH), 51.0 (CH_2), 25.8 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), −4.7 ($SiCH_3$), −5.0 ($SiCH_3$).

Bis[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethan-2-yl]amine (25). To a solution of 9.90 g (40 mmol) of **7** in 300 mL of dry ether was added 80 mL of a solution of 1 M DIBALH (80 mmol) in hexane at −80 °C. The reaction mixture was stirred at this temperature for 3 h. Then successively 50 mL of dry methanol and a solution of 25.1 g (100 mmol) of **24** in 25 mL of methanol were added at −90 °C. After stirring at room temperature for 2 h, the reaction mixture was cooled to 0 °C. $NaBH_4$ (3.00 g, 80 mmol) was added in small portions, after which the mixture was stirred overnight at ambient temperature. Water (500 mL) was added, and the layers were separated. The water layer was extracted two times with ether (300 mL). The ethereal layers were washed with brine and dried on $MgSO_4$, and the solvent was evaporated. Purification by flash column chromatography (eluent: triethylamine/petroleum ether 40–60 = 3/97) yielded 17.8 g (92%) of **25** and 11.3 g (75% of the excess) of **24**: $[\alpha]^{20}_D$ −72° (c = 1, $CHCl_3$); de 90% (HPLC); ^1H NMR δ (ppm) 7.27 (m, 10H, Ph), 4.77 (dd, 2H, J = 5.4 Hz, J = 7.9 Hz, CH), 2.88 (dd, 2H, J = 7.7 Hz, J = 11.9 Hz, CH_2), 2.65 (dd, 2H, J = 5.4 Hz, J = 11.9 Hz, CH_2), 1.62 (bs, 1H, NH), 0.83 (s, 18H, t-Bu), −0.01 (s, 6H, $SiCH_3$), −0.17 (s, 6H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.6, 128.1, 127.3, 126.1 (Ph), 74.5 (CH), 58.7 (CH_2), 25.9 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), −4.6, −4.8 ($SiCH_3$).

[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethan-2-yl][(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]amine (26). Prepared as described for **25**, using **16a** in the transimination reaction: yield 89%; $[\alpha]^{20}_D$ −59° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.25 (m, 10H, Ph), 4.71 (dd, 1H, J = 4.8 Hz, J = 7.5 Hz, $OCHCH_2$), 4.49 (d, 1H, J = 5.7 Hz, $OCHCH$), 2.74 (m, 3 H, CHN + CH_2N), 1.51 (bs, 1H, NH), 1.03 (d, 3H, J = 6.2 Hz, CH_3), 0.85 (s, 9H, t-Bu), 0.77 (s, 9H, t-Bu), 0.02 (s, 3H, $SiCH_3$), −0.10 (s, 3H, $SiCH_3$), −0.23 (s, 3H, $SiCH_3$), −0.25 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.9, 142.8, 128.0, 127.2, 127.1, 126.1 (Ph), 78.1, 75.3 (CHO), 60.0 (CHN), 56.8 (CH_2N), 25.8 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), 15.6 (CH_3), −4.1, −4.6, −4.9 ($SiCH_3$).

Bis[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]amine (27). To a suspension of 0.77 g (20 mmol) of $LiAlH_4$ in 5 mL of freshly distilled THF was added a solution of 2.60 g (5.1 mmol) of **19a** in 15 mL of THF at 0 °C. After 18 h of reflux the reaction mixture was cooled to 0 °C. Successively 0.8 mL of water, 0.8 mL of 4 M NaOH, and 2.4 mL of water were added. The suspension was stirred for another 30 min at room temperature and filtered. The residue was washed with ether (3 × 50 mL). The combined filtrates were dried on $MgSO_4$ and concentrated *in vacuo*: yield 1.43 g (99%); $[\alpha]^{20}_D$ +8° (c = 1, $CHCl_3$); mp 144 °C, de 92% (NMR); ^1H NMR: δ (ppm) 7.30 (m, 10H, Ph), 4.70 (d, 2H, J = 4.1 Hz, CHO), 3.09 (dq, 2H, J = 4.1 Hz, J = 6.7 Hz, CHN), 0.87 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm), 141.4, 127.8, 126.9, 125.9 (Ph), 75.5 (CHO), 54.8 (CHN), 14.7 CH_3).

Bis[(1*R*,2*S*)-1-hydroxy-1-phenylbutan-2-yl]amine (28). Prepared as described for **27**, using **20** as the starting material: yield 98%; $[\alpha]^{20}_D$ +4° (c = 1, $CHCl_3$); mp 127–130 °C; de 90% (NMR); ^1H NMR δ (ppm) 7.31 (m, 10H, Ph), 4.84 (d, 2H, J = 3.1 Hz, CHO), 3.03 (bs, 2H, OH), 2.79 (m, 2H, CHN), 1.32 (m, 5H, CH_2 + NH), 0.86 (t, 6H, J = 7.2 Hz, CH_3); ^{13}C NMR δ (ppm) 141.7, 128.1, 127.0, 125.9 (Ph), 72.9 (CHO), 62.1 (CHN), 21.1 (CH_2), 10.9 CH_3).

***N*,*N*-Bis[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]methylamine (29).** A mixture of 1.00 g (3.5 mmol) of **27** and 0.55 g (18 mmol) of paraformaldehyde in 20 mL of dry methanol was stirred for 1 h at ambient temperature. At 0 °C, 0.40 g (11 mmol) $NaBH_4$ was added in small portions. After stirring at room temperature for 18 h, 100 mL of water was added and the mixture was extracted with ether (3 × 70 mL). The combined ethereal layers were washed with 50 mL of brine, dried on $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (eluent: methanol/CH_2Cl_2 = 3/97) resulted in 0.90 g (86%) of **29**: $[\alpha]^{20}_D$ −74° (c = 1, $CHCl_3$); mp 85–86 °C; de 93% (NMR); ^1H NMR δ (ppm) 7.29 (m, 10H, Ph), 4.68 (d, 2H, J = 5.6 Hz, CHO), 2.95 (dq, 2H, J = 5.6 Hz, J = 6.7 Hz, CHN), 2.30 (s, 3H, CH_3N), 0.90 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.6, 127.9, 126.9, 125.8 (Ph), 74.3 (CHO), 60.9 (CHN), 34.1 (CH_3N), 10.5 (CH_3).

***N*,*N*-Bis[(1*R*,2*S*)-1-hydroxy-1-phenylbutan-2-yl]methylamine (30).** Prepared as was described for **29**, using **28** as the starting material: yield 89%; $[\alpha]^{20}_D$ −38° (c = 1, $CHCl_3$); de 91% (NMR); ^1H NMR δ (ppm) 7.30 (m, 10H, Ph), 4.93 (d, 2H, J = 3.6 Hz, CHO), 3.05 (bs, 2H, OH), 2.88 (m, 2H, CHN), 2.16 (s, 3H, CH_3N), 1.49 (m, 5H, CH_2 + NH), 0.96 (t, 6H, J = 7.5 Hz, CH_3); ^{13}C NMR δ (ppm) 142.7, 127.8, 126.7, 126.0 (Ph), 74.4 (CHO), 69.5 (CHN), 33.4 (CH_3N), 19.0 (CH_2), 12.1 (CH_3).

2-(Tetrahydropyranyloxy)ethanol (31). At −10 °C, 23.0 g (0.27 mmol) 3,4-2H-dihydropyran was added over a period of 45 min to a mixture of 50 mg of *p*-toluenesulfonic acid in 150 mL (2,7 mol) of ethylene glycol. The reaction mixture was stirred for 1 h at −10 °C and then for 2 h at room temperature. The mixture was poured into 500 mL of 1 M NaOH and extracted with CH_2Cl_2 (5 × 200 mL). The combined organic layers were dried on $MgSO_4$ and concentrated *in vacuo*. The crude product was distilled at reduced pressure from K_2CO_3: yield 32.0 g (80%); bp 70–72 °C (1.0 mmHg); ^1H NMR δ (ppm) 4.57 (bs, 1H, CHO_2), 3.74 (m, 6H, CH_2O), 2.84 (t, 1H, J = 5.2 Hz, OH), 1.69 (m, 6H, $(CH_2)_3$); ^{13}C NMR: δ (ppm) 99.5 (CHO_2), 69.9, 62.6, 61.6 (CH_2O), 30.4, 25.0, 19.5 (CH_2).

1-(Tetrahydropyranyloxy)-2-[(*p*-tolylsulfonyl)oxy]ethane (32). At 0 °C, 46.0 g (0.24 mol) of tosyl chloride was added in three portions to a solution of 34.9 g (0.24 mol) of **31** and 56 mL (0.40 mol) of triethylamine in 200 mL of CH_2Cl_2. After stirring for 24 h at 5 °C, the reaction mixture was concentrated. The residue was suspended in 100 mL of ether

and filtered. The residue was washed twice with 100 mL of ether. The combined filtrates were concentrated to obtain 71.0 g (99%) of **32** as a pale yellow oil: ^{1}H NMR δ (ppm) 7.81 (d, 2H, J = 8.2 Hz, Ph), 7.34 (d, 2H, J = 8.2 Hz, Ph), 4.55 (bs, 1H, CHO_2), 4.20 (t, 2H, J = 4.9 Hz, CH_2OTs), 3.67 (m, 4H, CH_2O), 2.45 (s, 3H, CH_3), 1.62 (m, 6H, $(CH_2)_3$); ^{13}C NMR δ (ppm) 144.6, 132.8, 129.6, 127.7 (Ph), 98.4 (CHO_2), 69.2, 64.4, 61.7, (CH_2O), 30.0, 25.1 (CH_2), 21.3 (CH_3), 18.8 (CH_2).

***N,N*-Bis[(1*R*,2*S*)-1-(2-hydroxyethoxy)-1-phenylpropan-2-yl]methylamine (33).** To a suspension of 0.42 g (14 mmol, 80% in mineral oil) of NaH in 5 mL of dry THF was added a solution of 1.60 g (5.4 mmol) of **29** in 10 mL of THF at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and then for 15 min at room temperature and refluxed for 1 h. Then every 30 min $^1/_7$ of a solution of 4.3 g (14 mmol) of **32** in 20 mL of THF was added to the refluxing solution. When the addition was complete, refluxing was continued for 40 h. After addition of 100 mL of water, the mixture was extracted with ether (3 × 50 mL). The combined ethereal layers were washed with brine, dried on $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in 15 mL of methanol and acidified with 1 M HCl. The reaction mixture was stirred overnight and poured into 150 mL of 1 M HCl. The acidic water layer was washed with ether (2 × 50 mL) and basified with solid NaOH. The water layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were dried on $MgSO_4$ and the solvent was evaporated: yield 1.64 g (79%); $[a]^{20}_D$ −66° (c = 1, $CHCl_3$); ^{1}H NMR δ (ppm) 7.30 (m, 10H, Ph), 5.50 (bs, 2H, OH), 4.69 (d, 2H, J = 3.1 Hz, CHO), 3.66 (m, 8H, CH_2O), 2.89 (dq, 2H, J = 3.1 Hz, J = 6.7 Hz, CHN), 2.61 (s, 3H, CH_3N), 0.94 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 140.5, 128.0, 126.9, 126.4 (Ph), 85.1 (CHO), 71.1 (CH_2OH), 62.6 (CHN), 62.4 (CH_2O), 35.0 (CH_3N), 9.9 (CH_3).

***N,N*-Bis-[(1*R*,2*S*)-1-phenyl-1-[2-[(*p*-tolylsulfonyl)oxy]-ethoxy]propan-2-yl]methylamine (34).** At 0 °C, 2.00 g (10 mmol) of tosyl chloride was added to 1.00 g (2.6 mmol) of **33** in 10 mL of pyridine. The reaction mixture was stirred for 40 h at 5 °C and then poured into 50 mL of water. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL), dried on $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 1/9): yield 0.60 g (35%); ^{1}H NMR δ (ppm) 7.76 (d, 4H, J = 8.2 Hz, Ph), 7.28 (m, 14H, Ph), 4.05 (t, 4H, J = 4.6 Hz, CH_2OTs), 3.97 (d, 2H, J = 5.7 Hz, CHO), 3.36 (t, 2H, J = 4.6 Hz, CH_2O), 3.30 (t, 2H, J = 4.6 Hz, CH_2O), 2.69 (dq, 2H, J = 5.7 Hz, J = 6.7 Hz, CHN), 2.44 (s, 6H, PhCH_3), 2.19 (s, 3H, CH_3N), 0.77 (d, 6H, J = 6.7 Hz, CH_3).

(2*R*,3*S*)-3,4-Dimethyl-2-phenylmorpholine (35). To a suspension of 78 mg (2.6 mmol, 80% in mineral oil) of NaH in 5 mL of dry THF was added a solution of 260 mg (0.86 mmol) of **29** in 15 mL of THF at 0 °C. After stirring for 30 min at 0 °C and for 2 h at room temperature, the reaction mixture was cooled to −80 °C. A solution of 600 mg (0.86 mmol) of **34** in 15 mL of THF was added and the reaction mixture was allowed to warm to room temperature. After stirring for 4 d, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was dissolved in 25 mL of CH_2Cl_2 and washed with 50 mL of water. The water layer was extracted two times with CH_2Cl_2 (25 mL). The combined organic layers were dried on $MgSO_4$, and the solvent was evaporated. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2/petroleum ether 40–60 = 3/10/87) gave 300 mg of a mixture of **29** and **35**. The components of this mixture were separated by a second flash column chromatography (eluent: triethylamine/ether/petroleum ether 40–60 = 4/48/48): yield 80 mg (49%) of **37**; ^{1}H NMR and ^{13}C NMR data were identical to literature data;[33] MS (EI) m/z 191 (M^+).

***N,N*-Bis[2-(2-hydroxyethoxy)ethyl]-*p*-toluenesulfonamide (38).** Prepared as described for **33**, using *N,N*-bis(2-hydroxyethyl)-*p*-toluenesulfonamide (**37**)[30] as the starting material: yield 95%; ^{1}H NMR δ (ppm) 7.70 (d, 2H, J = 8.0 Hz, Ph), 7.31 (d, 2H, J = 8.0 Hz, Ph), 3.70 (t, 8H, J = 5.7 Hz, CH_2O), 3.55 (t, 4H, J = 2.1 Hz, CH_2OH), 3.36 (t, 4H, J = 5.7 Hz, CH_2N), 2.43 (s, 3H, PhCH_3); ^{13}C NMR δ (ppm) 143.2, 135.8, 129.4, 126.8 (Ph), 72.1, 69.6, 61.0 (CH_2O), 48.7 (CH_2N), 21.1 (CH_3).

***N,N*-Bis[2-[2-[(*p*-tolylsulfonyl)oxy]ethoxy]ethyl]-*p*-toluenesulfonamide (39).** A mixture of 17.4 g (50 mmol) of **38** and 17.0 mL (120 mmol) of triethylamine in 250 mL of CH_2Cl_2 was cooled to 0 °C. Tosyl chloride (38.2 g, 200 mmol) was added in small portions. The reaction mixture was stirred for 48 h at 5 °C. After evaporating the solvent, the crude product was suspended in ether and filtered. The residue was washed twice with ether, and the combined filtrates were concentrated. The crude product was purified by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/30/67). Yield: 24.6 g (75%); ^{1}H NMR: δ (ppm) 7.78 (d, 4H, J = 8.2 Hz, Ph), 7.72 (d, 2H, J = 10.8 Hz, Ph), 7.34 (d, 4H, J = 8.2 Hz, Ph), 7.30 (d, 2H, J = 10.8 Hz, Ph), 4.09 (t, 4H, J = 4.6 Hz, CH_2OTs), 3.56 (m, 8H, CH_2O), 3.30 (t, 4H, J = 5.7 Hz, CH_2N), 2.44 (s, 6H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR δ (ppm) 144.8, 143.3, 136.6, 132.8, 129.8, 129.6, 127.8, 127.0 (Ph), 70.1, 69.3, 69.1 (CH_2O), 48.6 (CH_2N), 21.5, 21.4 (CH_3).

1,10-Bis(*p*-tolylsulfonyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (40). To a suspension of 400 mg (13.3 mmol, 80% in mineral oil) of NaH in 100 mL of dry THF at 0 °C was added a solution of 0.74 g (2.9 mmol) of **37** in 125 mL of THF. The reaction mixture was refluxed for 2 h. After cooling to 0 °C, a solution of 1.97 g (3.0 mmol) of **39** in 125 mL of THF was slowly added. The suspension was refluxed for 48 h, after which a few drops of water were added to destroy the excess NaH. The solvent was evaporated and 50 mL of water was added to the residue. The mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with 50 mL of water, dried on $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography (eluent: triethylamine/ethyl acetate/ether = 3/20/77), followed by crystallization from toluene: yield 0.54 g (33%); mp 162–163 °C (lit.[33] 164–165 °C); ^{1}H NMR δ (ppm) 7.48 (m, 8H, Ph), 3.65 (t, 8H, J = 5.9 Hz, CH_2O), 3.54 (s, 8H, CH_2O), 3.36 (t, 8H, J = 5.7 Hz, CH_2N), 2.41 (s, 6H, CH_3); ^{13}C NMR δ (ppm) 143.2, 136.4, 129.6, 127.0 (Ph), 70.7, 70.5 (CH_2O), 49.1 (CH_2N), 21.4 (CH_3).

(2*S*,3*R*,17*R*,18*S*)-3,17-Diphenyl-10-(*p*-tolylsulfonyl)-1,2,-18-trimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (41). Prepared as described for **40**, using **29** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/30/67): yield 28%; $[\alpha]^{20}_D$ +18° (c = 1, $CHCl_3$); ^{1}H NMR δ (ppm) 7.74 (d, 2H, J = 8.2 Hz, Ph), 7.25 (m, 12H, Ph), 3.91 (d, 2H, J = 4.6 Hz, CHO), 3.49 (m, 16H, CH_2), 3.00 (m, 2H, CHN), 2.42 (s, 3H, PhCH_3), 2.27 (s, 3H, CH_3N), 1.02 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.9, 142.0, 137.2, 129.5, 127.5, 127.0, 126.9, 126.9 (Ph), 85.8 (CHO), 70.6, 70.4, 68.3 (CH_2O), 61.2 (CHN), 48.7 (CH_2N), 34.3 (CH_3N), 21.4 (PhCH_3), 10.5 (CH_3).

(2*S*,3*R*,17*R*,18*S*)-2,18-Diethyl-3,17-diphenyl-1-methyl-10-(*p*-tolylsulfonyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (42). Prepared as described for **40**, using **30** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/20/77): yield 40%; $[\alpha]^{20}_D$ −16° (c = 1, $CHCl_3$); ^{1}H NMR δ (ppm) 7.68 (d, 2H, J = 8.2 Hz, Ph), 7.25 (m, 12H, Ph), 4.49 (d, 2H, J = 3.1 Hz, CHO), 3.43 (m, 16H, CH_2O + CH_2N), 2.83 (m, 2H, CHN), 2.42 (s, 3H, PhCH_3), 2.39 (s, 3H, CH_3N), 1.60 (m, 4H, CH_2), 0.82 (t, 6H, J = 7.3 Hz, CH_3); ^{13}C NMR δ (ppm) 142.9, 142.0, 136.6, 129.4, 127.5, 126.9, 126.8, 126.4 (Ph), 85.0 (CHO), 70.6, 70.0, 68.5 (CH_2O), 68.4 (CHN), 49.1 (CH_2N), 34.3 (CH_3N), 21.3 (PhCH_3), 19.6 (CH_2), 12.7 (CH_3).

***N,N*-Bis[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethan-2-yl]-*p*-toluenesulfonamide (43).** To a solution of 17.5 g (36 mmol) of **25** in 30 mL of pyridine was added at 0 °C 13.8 g (72 mmol) of tosyl chloride in small portions. The reaction mixture was stirred overnight at 5 °C. Then 4.0 mL of triethanolamine was added to destroy the excess tosyl chloride. After stirring at room temperature for 1 h, 350 mL of 1 M HCl was added. The mixture was extracted with ether (3 × 150 mL). The combined organic layers were washed with water and a saturated $NaHCO_3$ solution and dried on $MgSO_4$, and the solvent was evaporated. Purification by flash column chromatography (eluent: triethylamine/ether/petroleum ether 40–60 = 3/7/90) yielded 22.6 g (98%) of **43** as a white solid: $[\alpha]^{20}_D$ −70° (c = 1,

(33) Gelboke, M.; Blondiau, T.; Kone, B.; Lagrange, G.; Grimée, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 369.

$CHCl_3$); mp 103–104 °C; ^1H NMR δ (ppm) 7.77 (d, 2H, J = 8.2 Hz, Ph), 7.28 (m, 12H, Ph), 4.77 (dd, 2H, J = 3.4 Hz, J = 8.6 Hz, CHO), 3.77 (dd, 2H, J = 8.6 Hz, J = 14.9 Hz, CH_2N), 3.41 (dd, 2H, J = 3.4 Hz, J = 14.9 Hz, CH_2N), 2.44 (s, 3H, CH_3), 0.80 (s, 18H, t-Bu), −0.14 (s, 6H, $SiCH_3$), −0.31 (s, 6H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.0, 142.5, 139.0, 129.6, 128.2, 127.6, 127.2, 126.2 (Ph), 75.5 (CHO), 56.7 (CH_2N), 25.7 ($C(CH_3)_3$), 21.4 (CH_3), 17.8 ($C(CH_3)_3$), −4.8, −5.2 ($SiCH_3$).

***N*-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethan-2-yl]-*N*-[(1*R*,2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylpropan-2-yl]-*p*-toluenesulfonamide (44).** Prepared as described for **43**, using **26** as the starting material: reaction time 48 h; yield 75%; $[\alpha]^{20}_D$ −43° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.75 (d, 2H, J = 8.2 Hz, Ph), 7.21 (m, 12H, Ph), 5.04 (dd, 1H, J = 3.4 Hz, J = 8.4 Hz, O$CH$$CH_2$), 4.72 (d, 1H, J = 2.7 Hz, OCHCH), 3.71 (m, 2H, CHN + CH_2N), 3.26 (dd, 1H, J = 3.4 Hz, J = 15.4 Hz, CH_2N), 2.42 (s, 3H, PhCH_3), 1.26 (d, 3H, J = 6.9 Hz, CH_3), 0.82 (s, 9H, t-Bu), 0.79 (s, 9H, t-Bu) −0.02 (s, 3H, $SiCH_3$), −0.28 (s, 3H, $SiCH_3$), −0.33 (s, 3H, $SiCH_3$), −0.51 (s, 3H, $SiCH_3$); ^{13}C NMR δ (ppm) 143.2, 143.0, 142.9, 138.3, 129.4, 128.0, 127.7, 127.4, 127.4, 127.0, 126.4, 126.3 (Ph), 76.8, 74.5 (CHO), 60.5 (CHN), 54.1 (CH_2N), 25.8, 25.8 ($C(CH_3)_3$), 21.3 (PhCH_3), 18.0, 17.7 ($C(CH_3)_3$), 12.9 (CH_3), −4.6, −4.7, −5.5 ($SiCH_3$).

***N*,*N*-Bis[(*R*)-1-hydroxy-1-phenylethan-2-yl]-*p*-toluenesulfonamide (46).** A solution of 19.0 g (60 mmol) of TBAF·$3H_2O$ in 100 mL of THF was added to a solution of 16.0 g (25 mmol) of **43** in 100 mL of THF at 0 °C. The reaction mixture was stirred overnight at room temperature and then poured into 500 mL of water. The layers were separated. The water layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried on $MgSO_4$ and concentrated *in vacuo*. After flash column chromatography (eluent: triethylamine/petroleum ether 40–60/ether = 3/27/70) 9.70 g (95%) of **46** was isolated as a white solid: $[\alpha]^{20}_D$ −61° (c = 1, $CHCl_3$); mp 83–85 °C; ^1H NMR δ (ppm) 7.67 (d, 2H, J = 8.2 Hz, Ph), 7.34 (m, 12H, Ph), 5.13 (dd, 2H, J = 3.1 Hz, J = 9.5 Hz, CHO), 3.84 (bs, 2H, OH), 3.31 (dd, 2H, J = 14.4 Hz, J = 9.5 Hz, CH_2N), 3.16 (dd, 2H, J = 3.1 Hz, J = 14.4 Hz, CH_2N), 2.38 (s, 3H, CH_3); ^{13}C NMR δ (ppm) 143.5, 141.2, 134.8, 129.6, 128.3, 127.7, 127.2, 125.9 (Ph), 72.1 (CHO), 57.6 (CH_2N), 21.3 (CH_3).

***N*,*N*-Bis[(*R*)-1-(2-hydroxyethoxy)-1-phenylethan-2-yl]-*p*-toluenesulfonamide (47).** Prepared as described for **33**, using **46** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 4/96): yield 65%; $[\alpha]^{20}_D$ −76° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.68 (d, 2H, J = 8.2 Hz, Ph), 7.32 (m, 12H, Ph), 4.63 (dd, 2H, J = 3.1 Hz, J = 8.7 Hz, CHO), 3.48 (m, 12H, CH_2O + CH_2N), 2.85 (bs, 2H, OH), 2.41 (s, 3H, CH_3); ^{13}C NMR δ (ppm) 143.3, 142.5, 139.1, 129.5, 128.6, 128.1, 127.3, 126.5 (Ph), 80.9 (CHO), 70.2, 61.5 (CH_2O), 54.9 (CH_2N), 21.3 (CH_3).

***N*,*N*-Bis[(*R*)-1-phenyl-1-[2-[*p*-tolylsulfonyl)oxy]ethoxy]-ethan-2-yl]-*p*-toluenesulfonamide (48).** Prepared as described for **34**, using **47** as the starting material. Purification by flash column chromatography (eluent: petroleum ether 40–60/CH_2Cl_2 = 30/70): yield 65%; $[\alpha]^{20}_D$ −50° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.69 (d, 2H, J = 8.2 Hz, Ph), 7.64 (d, 4H, J = 8.5 Hz, Ph), 7.29 (m, 16H, Ph), 4.44 (dd, 2H, J = 3.4 Hz, J = 9.0 Hz, CHO), 3.99 (t, 4H, J = 4.9 Hz, CH_2OTs), 3.42 (m, 8H, CH_2N + CH_2O), 2.41 (s, 9H, PhCH_3); ^{13}C NMR δ (ppm) 144.5, 143.0, 138.5, 138.1, 132.6, 129.6, 129.4, 128.4, 128.0, 127.6, 126.8, 126.4 (Ph), 82.3 (CHO), 68.7, 66.1 (CH_2O), 55.1 (CH_2N), 21.3, 21.1 (CH_3).

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-3,8,12,17-Tetraphenyl-10-(*p*-tolylsulfonyl)-1,2,18-trimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (49). Prepared as described for **40**, using **29** and **48** as the starting materials. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/17/80): yield 29%; $[\alpha]^{20}_D$ −69° (c = 1, $CHCl_3$); mp 67–69 °C; ^1H NMR δ (ppm) 7.67 (d, 2H, J = 8.2 Hz, Ph), 7.30 (m, 22H, Ph), 4.41 (t, 2H, J = 6.5 Hz, O$CH$$CH_2$), 3.97 (d, 2H, J = 4.6 Hz, OCHCH), 3.33 (m, 14H, CH_2O + CH_2N + CHN), 2.41 (s, 3H, PhCH_3), 2.19 (s, 3H, CH_3N), 1.04 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.5, 142.1, 139.8, 135.9, 129.1, 128.2, 127.6, 127.5, 127.4, 127.0, 126.8, 126.6 (Ph), 86.5, 79.5 (CHO), 68.1 (CH_2O), 61.3 (CHN), 53.1 (CH_2N), 34.2 (CH_3N), 21.2 (PhCH_3), 10.6 (CH_3).

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-2,18-Diethyl-1-methyl-3,8,12,17-tetraphenyl-10-(*p*-tolylsulfonyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (50). Prepared as described for **40**, using **30** and **48** as the starting materials. Purification by flash column chromatography (eluent: triethylamine/ether/petroleum ether = 3/20/70): yield 24%; $[\alpha]^{20}_D$ −71° (c = 1, $CHCl_3$); mp 59–60 °C; ^1H NMR δ (ppm) 7.55 (d, 2H, J = 8.2 Hz, Ph), 7.27 (m, 20H, Ph), 7.14 (d, 2H, J = 8.2 Hz, Ph), 4.65 (d, 2H, J = 2.8 Hz, OCHCH), 4.60 (dd, 2H, J = 4.4 Hz, J = 8.0 Hz, O$CH$$CH_2$), 3.46 (m, 12H, CH_2O + CH_2N), 2.96 (m, 2H, CHN), 2.36 (s, 3H, PhCH_3), 2.29 (s, 3H, CH_3N), 1.55 (m, 4H, CH_2), 0.84 (t, 6H, J = 7.3 Hz, CH_3); ^{13}C NMR δ (ppm) 141.8, 139.7, 129.3, 128.4, 127.9, 127.8, 127.5, 127.0, 126.8, 126.7 (Ph), 85.4, 80.7 (CHO), 68.6 (CHN), 68.5, 68.3 (CH_2O), 54.8 (CH_2N), 33.9 (CH_3N), 21.4 (PhCH_3), 19.5 (CH_2), 12.7 (CH_3).

(3*R*,17*R*)-3,17-Diphenyl-1,10-bis(*p*-tolylsulfonyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (51). Prepared as described for **40**, using **39** and **46** as the starting materials. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether = 3/30/67): yield 55%; $[\alpha]^{20}_D$ −44° (c = 1, $CHCl_3$); mp 53–56 °C; de 93% (HPLC); ^1H NMR δ (ppm) 7.72 (d, 2H, J = 8.2 Hz, Ph), 7.42 (d, 2H, J = 8.2 Hz, Ph), 7.29 (m, 12H, Ph), 7.14 (d, 2H, J = 8.2 Hz, Ph), 4.54 (dd, 2H, J = 7.5 Hz, J = 4.8 Hz, CHO), 3.55 (m, 20H, CH_2N + CH_2O), 2.43 (s, 3H, PhCH_3), 2.37 (s, 3H, PhCH_3); ^{13}C NMR δ (ppm) 143.1, 142.6, 139.3, 137.0, 136.3, 129.5, 129.2, 128.3, 127.8, 127.0, 126.9, 126.6 (Ph), 81.0 (CHO), 70.4, 70.3, 68.2 (CH_2O), 52.6, 48.9 (CH_2N), 21.3 (CH_3).

(3*R*,8*R*,12*R*,17*R*)-3,8,12,17-Tetraphenyl-1,10-bis(*p*-tolylsulfonyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (52). Prepared as described for **40**, using **46** and **48** as the starting materials. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether = 3/10/30): yield 53%; $[\alpha]^{20}_D$ −54° (c = 1, $CHCl_3$); mp 78–79 °C; ^1H NMR δ (ppm) 7.41 (m, 28H, Ph), 4.64 (dd, 4H, J = 7.2 Hz, J = 5.5 Hz, CHO), 3.83 (dd, 4H, J = 7.2 Hz, J = 14.6 Hz, CH_2N), 3.56 (dd, 4H, J = 5.5 Hz, J = 14.6 Hz, CH_2N), 3.34 (s, 8H, CH_2O), 2.37 (s, 6H, CH_3); ^{13}C NMR δ (ppm) 142.5, 139.3, 137.1, 129.2, 128.4, 127.8, 127.2, 126.7 (Ph), 80.8 (CHO), 68.2 (CH_2O), 52.0 (CH_2N), 21.3 (CH_3).

(3*R*,17*R*)-3,17-Diphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (53). At 0 °C, 0.50 g (13 mmol) of $LiAlH_4$ was added to a solution of 1.00 g (1.3 mmol) of **51** in 15 mL of dry THF. The reaction mixture was slowly warmed and then refluxed for 48 h. The reaction was carefully quenched with water at 0 °C. After 150 mL of water had been added, the mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with 100 mL of water, dried on $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 3/97) afforded 320 mg (54%) of **53**: $[\alpha]^{20}_D$ −34° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.31 (m, 10H, Ph), 4.53 (dd, 2H, J = 10.0 Hz, J = 2.6 Hz, CHO), 4.08 (bs, 2H, NH), 3.56 (m, 12H, CH_2O), 3.10 (dd, 2H, J = 10.0 Hz, J = 12.8 Hz, CHCH_2N), 2.90 (m, 4H, CH_2CH_2N), 2.60 (dd, 2H, J = 2.6 Hz, J = 12.8 Hz, CHCH_2N); ^{13}C NMR δ (ppm) 140.1, 128.0, 127.3, 126.1 (Ph), 80.2 (CHO), 69.9, 69.1, 67.7 (CH_2O), 55.9, 48.4 (CH_2N).

(2*S*,3*R*,17*R*,18*S*)-3,17-Diphenyl-1,2,18-trimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (55). Prepared as described for **53**, using **41** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 3/97): yield 67%; $[\alpha]^{20}_D$ +2° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.23 (m, 10H, Ph), 3.45 (m, 14H, CHO + CH_2O), 2.98 (m, 2H, CHN), 2.86 (m, 4H, CH_2N), 2.36 (s, 3H, CH_3N), 1.05 (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.0, 127.3, 126.9, 126.4 (Ph), 84.9 (CHO), 70.0, 69.8, 67.9 (CH_2O), 61.3 (CHN), 49.1 (CH_2N), 33.8 (CH_3N), 10.3 (CH_3).

(2*S*,3*R*,17*R*,18*S*)-2,18-Diethyl-3,17-diphenyl-1-methyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (54). Prepared as described for **53**, using **42** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 3/97): yield 57%; $[\alpha]^{20}_D$ −28° (c = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.25 (m, 10H, Ph), 4.33 (d, 2H, J = 3.3 Hz, CHO), 3.51 (m, 12H, CH_2O), 2.78 (m, 6H, CHN + CH_2N), 2.54 (s, 3H, CH_3N), 2.10 (bs, 1H, NH), 1.66 (m, 4H, CH_2), 0.88 (t, 6H, J = 7.3 Hz, CH_3); ^{13}C NMR δ (ppm) 142.1, 127.6, 126.6, 126.4 (Ph), 85.4 (CHO),

70.2 (CH_2O), 70.0 (CHN), 68.5 (CH_2O), 49.4 (CH_2N), 33.0 (CH_3N), 20.0 (CH_2), 13.1 (CH_3).

(3*R*,8*R*,12*R*,17*R*)-3,8,12,17-Tetraphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (56). Prepared as described for **53**, using **52** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2/petroleum ether 40–60 = 3/20/77): yield 46%; $[\alpha]^{20}_D$ −88° (*c* = 1, $CHCl_3$); mp 41 °C; ^1H NMR δ (ppm) 7.29 (m, 20H, Ph), 4.61 (dd, 4H, *J* = 1.8 Hz, *J* = 9.0 Hz, CHO), 3.57 (t, 4H, *J* = 7.4 Hz, CH_2O), 3.50 (t, 4H, *J* = 7.4 Hz, CH_2O), 3.21 (dd, 4H, *J* = 9.0 Hz, *J* = 12.6 Hz, CH_2N), 2.66 (dd, 4H, *J* = 1.8 Hz, *J* = 12.6 Hz, CH_2N), 2.66 (bs, 2H, NH); ^{13}C NMR δ (ppm) 140.8, 128.2, 127.4, 126.4 (Ph), 80.7 (CHO), 68.4 (CH_2O), 56.6 (CH_2N).

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-3,8,12,17-Tetraphenyl-1,2,18-trimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (57). Prepared as described for **53**, using **49** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/30/67): yield 46%; $[\alpha]^{20}_D$ −67° (*c* = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.28 (m, 20H, Ph), 4.67 (dd, 2H, *J* = 2.6 Hz, *J* = 9.8 Hz, O*CH*CH_2), 4.00 (d, 2H, *J* = 4.6 Hz, O*CH*CH), 3.49 (m, 8H, CH_2O), 3.18 (dd, 2H, *J* = 9.8 Hz, *J* = 12.9 Hz, CH_2N), 3.09 (m, 2H, CHN), 2.71 (dd, 2H, *J* = 2.6 Hz, *J* = 12.9 Hz, CH_2N), 2.39 (s, 3H, CH_3N), 1.16 (d, 6H, *J* = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.1, 141.1, 128.3, 127.6, 127.5, 127.2, 126.7, 126.6 (Ph), 85.9, 81.2 (CHO), 68.9, 68.8 (CH_2O), 61.7 (CHN), 57.3 (CH_2N), 34.2 (CH_3N), 10.5 (CH_3).

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-2,18-Diethyl-1-methyl-3,8,12,17-tetraphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (58). Prepared as described for **53**, using **50** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl/petroleum ether 40–60 = 4/48/48): yield 49%; $[\alpha]^{20}_D$ −79° (*c* = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.27 (m, 20H, Ph), 4.62 (m, 4H, CHO), 3.53 (m, 8H, CH_2O), 3.11 (dd, 2H, *J* = 9.5 Hz, *J* = 12.8 Hz, CH_2N), 2.88 (m, 2H, CHN), 2.65 (dd, 2H, *J* = 2.2 Hz, *J* = 12.8 Hz, CH_2N), 2.51 (s, 3H, CH_3N), 1.71 (m, 4H, CH_2), 0.95 (t, 6H, *J* = 7.4 Hz, CH_3); ^{13}C NMR δ (ppm) 141.8, 140.9, 128.2, 127.6, 127.5, 126.8, 126.5 (Ph), 86.3, 81.5 (CHO), 70.5 (CHN), 69.4, 86.9 (CH_2O), 57.3 (CH_2N), 32.1 (CH_3N), 20.2 (CH_2), 13.1 (CH_3).

(3*R*,17*R*)-1,10-Dimethyl-3,17-diphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (1). Crown ether **53** (240 mg, 0.55 mmol) was heated to 100 °C with 0.50 mL (13 mmol) of formic acid and 0.50 mL (5.8 mmol) of a 35% aqueous formaldehyde solution for 20 h. A volume of 0.4 mL of 12 M HCl was added and the solution was concentrated. The residue was dissolved in 25 mL of 1 M NaOH and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried on $MgSO_4$, and the solvent was evaporated. The crude product was purified: yield 159 mg (62%); $[\alpha]^{20}_D$ −74° (*c* = 1, $CHCl_3$); ^1H NMR δ (ppm) 7.28 (m, 10H, Ph), 4.51 (dd, 2H, *J* = 4.6 Hz, *J* = 7.7 Hz, CHO), 3.59 (m, 12H, CH_2O), 2.96 (dd, 2H, *J* = 7.7 Hz, *J* = 13.4 Hz, CH*CH*$_2$N), 2.79 (dt, 4H, *J* = 2.5 Hz, *J* = 5.8 Hz, CH_2*CH*$_2$N), 2.65 (dd, 2H, *J* = 4.6 Hz, *J* = 13.4 Hz, CH*CH*$_2$N), 2.43 (s, 3H, CH_3), 2.36 (s, 3H, CH_3); ^{13}C NMR δ (ppm) 141.3, 128.0, 127.2, 126.7 (Ph), 80.8 (CHO), 70.1, 69.2, 68.1 (CH_2O), 63.9, 56.5, (CH_2N), 43.6 (CH_3); MS *m*/*z* 443 (M + H^+). Anal. Calcd for $C_{26}H_{38}N_2O_4$: C, 70.56; H, 8.65; N, 6.33; O, 14.46. Found: C, 70.10; H, 8.74; N, 6.05; O, 14.10.

(2*S*,3*R*,17*R*,18*S*)-3,17-Diphenyl-1,2,10,18-tetramethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (2). Prepared as described for **1**, using **54** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 3/97): yield 83%; $[\alpha]^{20}_D$ +8° (*c* = 1, $CHCl_3$); de 95% (NMR); ^1H NMR δ (ppm) 7.23 (m, 10H, Ph), 3.81 (d, 2H, *J* = 4.6 Hz, CHO), 3.71 (t, 4H, *J* = 5.7 Hz, CH_2O), 3.61 (t, 4H, *J* = 4.1 Hz, CH_2O), 3.34 (m, 4H, CH_2O), 2.87 (m, 6H, CHN + CH_2N), 2.34 (s, 3H, CH_3N), 2.28 (s, 3H, CH_3N), 1.06 (d, 6H, *J* = 6.6 Hz, CH_3); ^{13}C NMR δ (ppm) 142.0, 127.3, 127.0, 126.4 (Ph), 85.6 (CHO), 70.1, 69.4, 68.2 (CH_2O), 61.3 (CHN), 56.7 (CH_2N), 43.3, 34.0 (CH_3N), 10.6 (CH_3); MS *m*/*z* 471 (M + H^+); Anal. Calcd for $C_{28}H_{42}N_2O_4$: C, 71.46; H, 8.99; N, 5.95; O, 13.60. Found: C, 71.44; H, 9.15; N, 5.78; O, 13.00.

(2*S*,3*R*,17*R*,18*S*)-2,18-Diethyl-1,10-dimethyl-3,17-diphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (3). Prepared as described for **1**, using **55** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2 = 3/97): yield 60%; $[\alpha]^{20}_D$ −23° (*c* = 1, $CHCl_3$); de 94% (NMR); ^1H NMR δ (ppm) 7.24 (m, 10H, Ph), 4.43 (d, 2H, *J* = 3.1 Hz, CHO), 3.55 (m, 12H, CH_2O), 2.84 (m, 2H, CHN), 2.61 (dt, 4H, *J* = 2.6 Hz, *J* = 5.7 Hz, CH_2N), 2.41 (s, 3H, CH_3N), 2.27 (s, 3H, CH_3N), 1.60 (m, 4H, CH_2), 0.87 (t, 6H, *J* = 7.2 Hz, CH_3); ^{13}C NMR δ (ppm) 142.1, 127.5, 126.9, 126.3 (Ph), 85.0 (CHO), 70.4, 69.1 (CH_2O), 68.9 (CHN), 68.7 (CH_2O), 56.9 (CH_2N) 43.3, 33.9 (CH_3N), 20.0 (CH_2), 12.8 (CH_3); MS *m*/*z* 499 (M + H^+); Anal. Calcd for $C_{30}H_{46}N_2O_4$: C, 72.25; H, 9.30; N, 5.62; O, 12.83. Found: C, 72.70; H, 8.80; N, 5.57; O, 12.66.

(3*R*,8*R*,12*R*,17*R*)-1,10-Dimethyl-3,8,12,17-tetraphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (4). Prepared as described for **1**, using **56** as the starting material. Purification by flash column chromatography (eluent: triethylamine/CH_2Cl_2/petroleum ether 40–60 = 3/30/67): yield 89%; $[\alpha]^{20}_D$ −117° (*c* = 1, $CHCl_3$); mp 115–116 °C; ^1H NMR δ (ppm) 7.29 (m, 20H, Ph), 4.55 (dd, 4H, *J* = 4.6 Hz, *J* = 7.5 Hz, CHO), 3.53 (t, 4H, *J* = 8.6 Hz, CH_2O), 3.46 (t, 4H, *J* = 8.6 Hz, CH_2O), 3.08 (dd, 4H, *J* = 7.5 Hz, *J* = 13.4 Hz, CH_2N), 2.76 (dd, 4H, *J* = 4.6 Hz, *J* = 13.4 Hz, CH_2N), 2.45 (s, 6H, CH_3); ^{13}C NMR δ (ppm) 142.6, 128.0, 127.2, 126.7 (Ph), 81.0 (CHO), 68.4 (CH_2O), 63.9 (CH_2N), 43.7 (CH_3); MS *m*/*z* 595 (M + H^+); Anal. Calcd for $C_{38}H_{46}N_2O_4$: C, 76.74; H, 7.79; N, 4.71; O, 10.76. Found: C, 77.12; H, 7.58; N, 4.55; O, 10.52.

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-1,2,10,18-Tetramethyl-3,8,12,17-tetraphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (5). Prepared as described for **1**, using **57** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/10/87): yield 68%; $[\alpha]^{20}_D$ −56° (*c* = 1, $CHCl_3$); mp 58–59 °C; de 94% (NMR); ^1H NMR δ (ppm) 7.29 (m, 20H, Ph), 4.38 (dd, 2H, *J* = 5.1 Hz, *J* = 6.7 Hz, O*CH*CH_2), 3.94 (d, 2H, *J* = 5.1 Hz, O*CH*CH), 3.46 (m, 8H, CH_2O), 3.16 (dq, 2H, *J* = 5.1 Hz, *J* = 6.7 Hz, CHN), 3.03 (dd, 2H, *J* = 5.1 Hz, *J* = 13.1 Hz, CH_2N), 2.83 (dd, 2H, *J* = 6.7 Hz, 13.1 Hz, CH_2N), 2.36 (s, 3H, CH_3N), 2.24 (s, 3H, CH_3N), 1.14 (d, 6H, *J* = 6.7 Hz, CH_3); ^{13}C NMR δ (ppm) 142.5, 142.0, 128.1, 127.5, 127.3, 127.2, 127.0, 126.6 (Ph), 86.1, 81.6 (CHO), 68.7, 68.1 (CH_2O), 63.9 (CH_2N), 61.6 (CHN), 44.2, 34.1 (CH_3N), 11.0 (CH_3); MS *m*/*z* 623 (M + H^+); Anal. Calcd for $C_{40}H_{50}N_2O_4$: C, 77.14; H, 8.08; N, 4.50; O, 10.27. Found: C, 77.07; H, 7.77; N, 4.36; O, 9.88.

(2*S*,3*R*,8*R*,12*R*,17*R*,18*S*)-2,18-Diethyl-1,10-dimethyl-3,8,12,17-tetraphenyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (6). Prepared as described for **1**, using **58** as the starting material. Purification by flash column chromatography (eluent: triethylamine/ethyl acetate/petroleum ether 40–60 = 3/10/87): yield 63%; $[\alpha]^{20}_D$ −83° (*c* = 1, $CHCl_3$); de 95% (NMR); ^1H NMR δ (ppm) 7.27 (m, 20H, Ph), 4.62 (d, 2H, *J* = 2.8 Hz, O*CH*CH), 4.53 (dd, 2H, *J* = 4.1 Hz, *J* = 7.8 Hz, O*CH*CH_2), 3.56 (m, 8H, CH_2O), 3.03 (m, 2H, CHN), 2.94 (dd, 2H, *J* = 13.6 Hz, *J* = 7.8 Hz, CH_2N), 2.61 (dd, 2H, *J* = 13.6 Hz, *J* = 4.1 Hz, CH_2N), 2.35 (s, 3H, CH_3N), 2.29 (s, 3H, CH_3N), 1.61 (m, 4H, CH_2), 0.90 (t, 6H, *J* = 7.3 Hz, CH_3); ^{13}C NMR δ (ppm) 142.0, 141.7, 128.2, 127.7, 127.4, 127.2, 126.8, 126.5 (Ph), 85.2, 81.6 (CHO), 69.1 (CH_2O), 69.0 (CHN), 68.7 (CH_2O), 64.9 (CH_2N), 44.2, 33.6 (CH_3N), 20.0 (CH_2), 12.8 (CH_3); MS *m*/*z* 651 (M + H^+); Anal. Calcd for $C_{42}H_{54}N_2O_4$: C, 77.50; H, 8.36; N, 4.30; O, 9.83. Found: C, 77.90; H, 8.35; N, 3.98; O, 9.47.

Supplementary Material Available: Copies of the ^1H NMR spectra for compounds **1–6**, **12–14**, **16**, **19**, **20**, **22**, **24–33**, **38**, **39**, **41–44**, and **46–58** (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.