Stepwise Approach toward First Generation Nonenzymatic Hydrolases

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The synthesis and reactivity study of a first generation serine protease mimic is described. Central in the design stands the possibility of stabilization of the transition state by an amino triol such as **8t**. En route to **8t**, a series of amino alcohols (**4**−**8**) was obtained, the reactivity of which was studied toward esterification by acetylimidazole (AcIm) and by *p*-nitro-2,2,2-trifluoroacetanilide (PNTFA). Interesting reactivity differences were observed between the *cis*- and the *trans*-series, especially between **7c** and **7t** (AcIm), and between **8c** and **8t** (PNTFA). In both cases the results are explained by invoking extra stabilization of the tetrahedral oxyanion.

Introduction

To match enzymatic efficiency remains one of the major quests in organic chemistry.[1] Even if impressive successes in synthetic efficiency have been recorded, they more often than not relate to unnatural processes, e.g., the Sharpless epoxidation, where a high level of selectivity, usually expressed in terms of ee's, is considered as evidence of performance. However, the efficiency of the enzymatic machinery as expressed in turnover and rate, remains largely unequalled. A typical example in the field of classic organic chemistry is the hydrolysis of the unactivated amide bond. Compared to the acidic or basic hydrolysis the efficiency of chymotrypsin, a protease responsible for the cleavage of peptide bonds with a specificity for large hydrophobic residues, is enormous.[2] In contrast, the development of synthetic mimics for proteases has only been marginally successful.[3] The design of hydrolase candidates has mainly rested on the incorporation of functional groups on a potential binding site such as a cyclodextrin,[4] a crown ether,[5] or a structural moiety that can bind a possible candidate via hydrogen bonding.[6] Almost as a rule the substrates of which the cleavage was studied were activated esters,[7] with a preference for phenyl esters, and in most cases the observed reaction involved a transesterification rather than a hydrolysis. Recently, a 29 residue cyclic peptide was synthesized that was reported to possess nearly the same catalytic activity and specificity as the pancreatic serine protease, trypsin.[8] However, several groups have subsequently questioned these results.[9] Probably the most successful mimic until now is the one described by Stewart and co-workers.[10] Computer modeling was used to design a bundle of four short parallel amphipatic helical peptides bearing the serine protease catalytic residues. The peptide has affinity for chymotrypsin ester substrates. However, no activity toward amides, the natural substrates of chymotrypsin, was reported. So, the real challenge is still intact.

Several years ago we have embarked on a program aiming at the development of synthetic hydrolases with the focus on gaining a better understanding of the enzymatic process. In this respect we wish to set forth the following criteria for evaluating a successful undertaking. The process should follow the basic steps of the enzymatic mechanism, should allow for turnover, and eventually operate on unactivated amides. In pursuance of this goal we decided to work first at the optimization of the chemical machinery in terms of the nature and the relative orientation of the required functional groups, and to include an appropriate binding site only in a subsequent phase of the program. In an ideal case this would allow for an eventual combination of general efficiency and specificity on demand. In the present paper we report on the synthesis and the reactivity of a first generation of model hydrolases.

Even if there still exists some controversy with regard to the relative importance of the individual steps, the mechanism of the hydrolysis by chymotrypsin is rather well understood and involves in the first place an almost cooperative action of a triad consisting of serine, histi-

(1) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721.
(2) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 707.
(3) "... but amide cleavage is one of the most daunting challenges for manmade catalysts, and so far we are not even close.": see ref 2, p 709.
(4) (a) Bender, M. L.; D'Souza, V. T. *Acc. Chem. Res.* **1987**, *20*, 146. (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146.
(5) Lehn, J. M.; Sirlin, C. *J. Chem. Soc., Chem. Commun.* **1978**, 949.
(6) (a) Cram, D. J.; Lam, P. Y.; Ho, P. S. *J. Am. Chem. Soc.* **1986**, *108*, 839. (b) Tecilla, P.; Jubian, V.; Hamilton, A. D. *Tetrahedron* **1995**, *51*, 435.
(7) For a recent and noteworthy exception involving the esterification of 4-(hydroxymethyl)pyridine by acetylimidazole both being bound inside the cavity of a cyclic porphyrin trimer, see: Mackay, L. G.; Wylie, R. S.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1994**, *116*, 3141.
(8) Atassi, M. Z.; Manshouri, T. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *90*, 8282.
(9) (a) Matthews, B. W.; Craik, C. S.; Neurath, H. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4103. (b) Corey, D. R.; Phillips, M. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4106. (c) Wells, J. A.; Fairbrother, W. J.; Otlewski, J.; Laskowski Jr., M.; Burnier, J. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4110.
(10) Hahn, K. W.; Klis, W. A.; Stewart, J. M. *Science* **1990**, *248*, 1544.
(11) Blow, D. M. *Acc. Chem. Res.* **1976**, *9*, 145.

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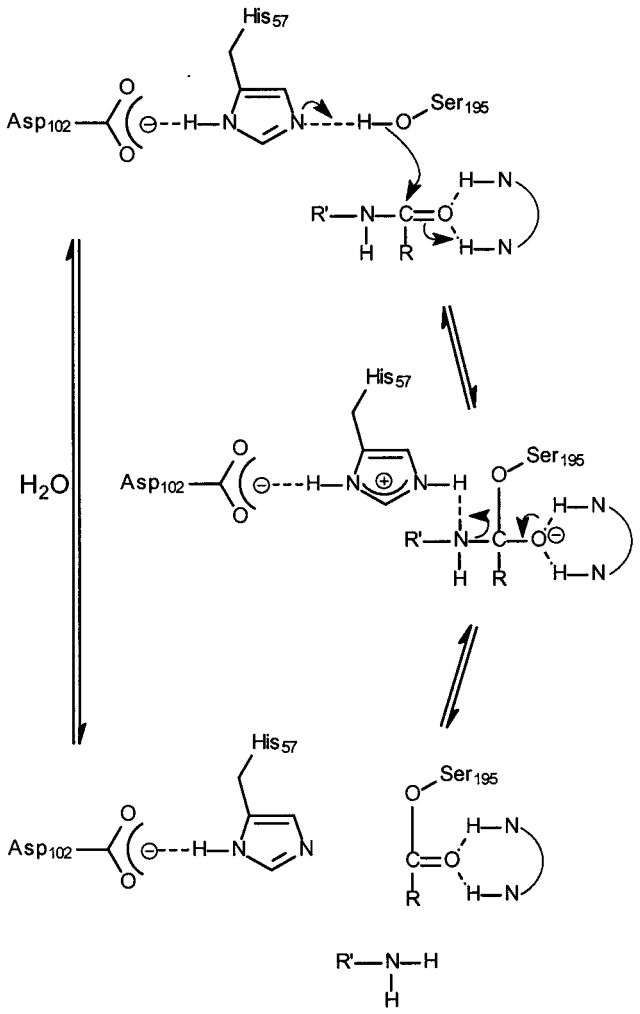


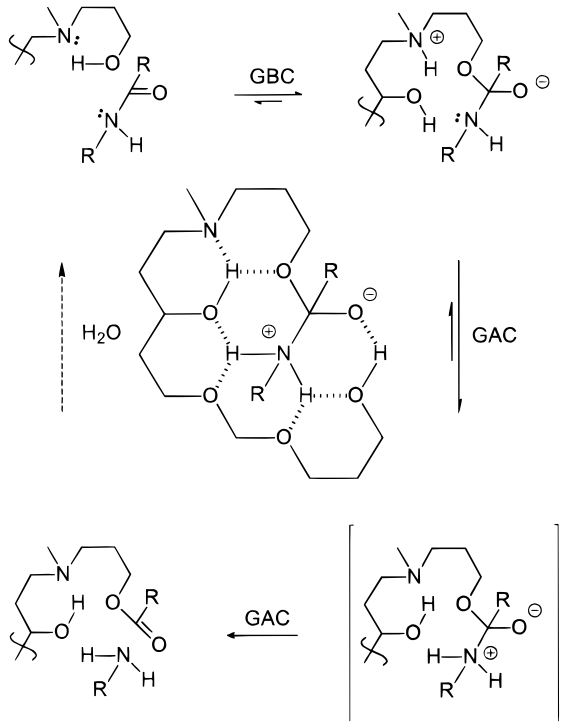
Figure 1. *Charge stabilization* mechanism for the peptide hydrolysis by α-chymotrypsin.

dine, and aspartate (Figure 1).[11] Attack by serine, which is made more nucleophilic by the proximate histidine functioning as a general base (GBC), leads to a tetrahedral intermediate, the oxyanion in which is stabilized by hydrogen bonding with the backbone peptide bonds. The role of aspartate probably consists here in stabilizing the protonated imidazole moiety.[12] The latter is essential in a general acid-catalyzed (GAC) breakdown of the tetrahedral intermediate leading to an acylated enzyme derivative. Further cleavage of the acylated derivative by water following the reverse mechanism completes the process with regeneration of the enzyme. The crucial part in the process are the GBC and GAC steps which have been suggested to occur in an almost simultaneous (cooperative) manner.[13] The knowledge that this very triad is operative as well in the mammalian serine proteases (cf. chymotrypsin) as in bacterial serine proteases (cf. subtilisin) is a striking example of independent convergent evolution.[14]

Results and Discussion

Design of the First Generation. Inspired by the mechanism of chymotrypsin we set out to evaluate the

Scheme 1

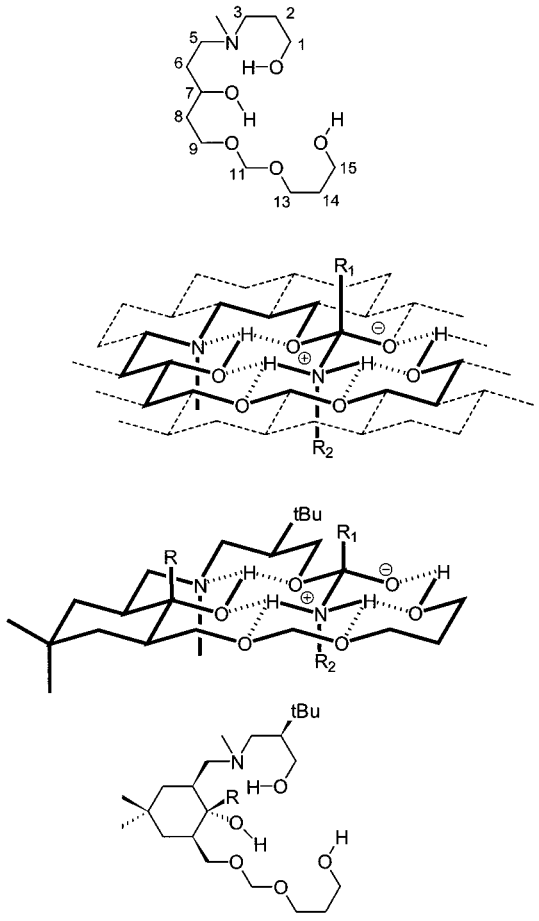


potential of Scheme 1 in the context of the hydrolysis of an unactivated amide bond as final goal. The molecule represented in the center corresponds to the protonated tetrahedral intermediate, a species that we consider as being closest to the two transition states (cf. GBC and GAC) that are involved in the acylation process. The dashed lines indicate the various hydrogen bonds that are implicated in the transition state stabilization. Next to the hydrogen bonding to the oxyanion, we consider the presence of four oxygen atoms that can stabilize the ammonium part of the intermediate as an important asset in the mechanism. Indeed, Gandour and coworkers recently reported on the catalytic behavior of open chain polyethers in the butylaminolysis of aryl acetates.[15] They found that catalysis proceeds via a complex in which four oxygens in a polyether subunit stabilize the ammonium part of the transition state. The core of the proposed molecule consists of an array of functional groups, i.e., one tertiary amine, two primary hydroxy groups, one secondary hydroxy group, and two ether functions, that are incorporated in a 15-atom linear framework designed in such a way as to enable all proton transfers or hydrogen bonds to occur via six-membered ring geometries. In a stepwise fashion the proposed mechanism involves GBC/GAC steps in which the tertiary amine functions as the general base and the secondary hydroxy group as a proton shuttle in the acid-catalyzed breakdown of the tetrahedral intermediate. The second primary hydroxy group should assist in stabilizing the oxyanion.

As mentioned above, the molecule has been further conceived in a way that all heavy atoms occupy corner positions on a diamond grid (Scheme 2). As a corollary the transition state stabilization is expected to occur via a low energy fully staggered geometry. To ease the entropic burden it is further desirable to incorporate

(12) Zimmerman, S. C.; Korthals, J. S.; Cramer, K. D. *Tetrahedron* **1991**, *47*, 2649.
(13) Warshel, A.; Russell, S. *J. Am. Chem. Soc.* **1986**, *108*, 6569.
(14) Neurath, H. *Science* **1984**, *224*, 350.
(15) Hogan, J. C.; Gandour, R. D. *J. Org. Chem.* **1991**, *56*, 2821.

Scheme 2



structural features that will ensure the proximity of the different functional groups that need to cooperate. Among many possibilities, we like to focus here on derivatives in which a *tert*-butyl substituent at C-2 and a chair cyclohexane ring incorporated at C-6, C-7, and C-8 assist in the GBC and the GAC steps, respectively. Finally, four oxygen atoms are involved in the stabilization of the ammonium moiety in accord with Gandours findings. The derivative depicted in Scheme 2 is one in which the substitution pattern of the cyclohexane ring involves the *all-trans* stereochemistry. The R-substituent at C-7 shows the possibility of incorporating in a next generation a binding site designed so as to fit the acyl group R_1 of the amide.

The absence of a substrate binding site at this stage of the program is obviously a major shortcoming. Indeed missing the entropic advantage of the formation of a Michaelis complex, which renders the chemical reaction an essentially unimolecular transformation, will result in an intrinsic low reactivity. Hence, if any reaction is to be observed at all, one will be forced to have recourse to activated substrates, the choice of which is crucial. In the context of this work we will focus on the cleavage of two electronically activated amides, acetyl imidazole (AcIm) and *p*-nitro-2,2,2-trifluoroacetanilide (PNTFA). The former will be used in order to evaluate the GBC, the latter the GAC portion of the mechanism. Activated esters, such as phenyl esters, are considered inappropriate for our purpose since evidence has been presented that in most cases the cleavage involves nucleophilic catalysis.[16,17]

Table 1. Half-Live Values (*pseudo* first-order conditions) for Reaction of Amino Alcohols 1−8 with Acetylimidazole (AcIm) and *p*-Nitro-2,2,2-trifluoroacetanilide (PNTFA) in Acetonitrile[a]

compound	$t_{1/2}$ AcIm[b]	$t_{1/2}$ PNTFA[c]
1,6-hexanediol + Et_3N[d]	2240[c]	412
1	721	112
2	198	107
3	151	206
4c	925	−
4t	6900	−
5c	255	−
5t	420	−
6c	306	−
6t	450	−
7c	26	353
7t	480	271
8c	169	873
8t	446	181

[a] Determined via ^{1}H NMR integration, 500 MHz, 23 °C, concentration (amino alcohol): 0.05 mol L^{-1} (see Supporting Information). [b] Half-live values in minutes. [c] Half-live values in hours. [d] Concentrations: 0.05 mol L^{-1}.

A Convergent Synthesis of 8. During the development of our target as defined in Scheme 2, a series of amino alcohols was obtained of which the reactivity toward the cleavage of AcIm was studied (Table 1). The 13 derivatives that were selected for study of reactivity are shown in Chart 1. The synthesis of the most evolved amino triol **8t** involves a convergent strategy implying first a reductive amination and second an alkylation as key-steps for the attachment of the two side-chains on the central cyclohexane ring (Scheme 3). The order that was chosen for performing these key transformations allowed us to synthesize a series of amino alcohols of increasing complexity, the reactivity of which toward a GBC esterification by AcIm was studied in the first place.

The synthesis of the central aldehyde that will be used in the reductive amination is shown in Scheme 4. Starting from the known 4,4-dimethylcyclohexanone **9**,[18] reaction with dimethyl carbonate led to **10**,[19] and further selective alkylation of the corresponding dianion (LDA, THF) with (benzyloxy)methyl chloride gave cyclohexanone *rac*-**11**,[20] which appears as the enol form (cf. ^{1}H NMR). Reduction of the carbonyl with sodium borohydride and cerium(III) chloride led to a ca. 1:1 mixture of alcohols *rac*-**12c** and *rac*-**12t** (77% combined yield), that was separated by HPLC. The structural assignment follows from analysis of the ^{1}H NMR spectral data: (1) the relative *cis*-orientation of the two equatorial substituents at C-2 and C-6 follows from the coupling pattern of H_2 and H_6 in both derivatives, i.e., $J(H_2-H_{3ax})$ and $J(H_6-H_{5ax}) \approx 13.3$ Hz in **12c** and **12t**, (2) distinction between the *all-cis* and *all-trans* alcohols follows from the coupling pattern of H_1 (sum of coupling constants = 3 Hz for **12c** and 20 Hz for **12t**). The further synthesis

(16) (a) Anoardi, L.; Tonellato, U. *J. Chem. Soc., Chem. Commun.* **1977**, 401. (b) Somayaji, V.; Skorey, K. I.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 4866. (c) Khan, M. N. *J. Org. Chem.* **1985**, *50*, 4851.

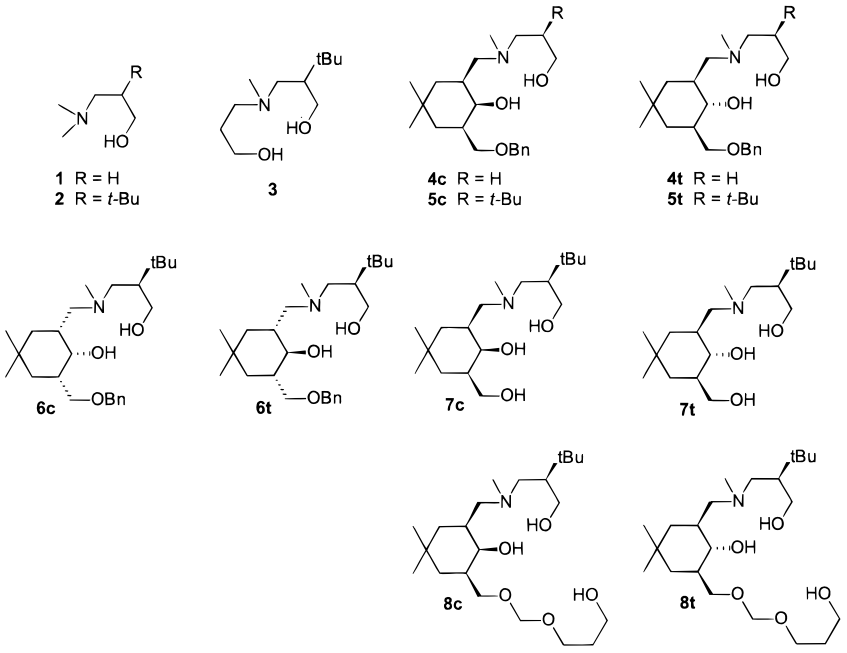
(17) However, examples of GBC-hydrolysis of PNPA were reported, see: (a) Hine, J.; Khan, M. N. *J. Am. Chem. Soc.* **1977**, *99*, 3847. (b) Werber, M. M.; Shalitin, Y. *Bioorg. Chem.* **1973**, *2*, 202.

(18) (a) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399. (b) Meyer, W. L.; Brannon, M. J.; da Burgos, C. G.; Goodwin, T. E.; Howard, R. W. *J. Org. Chem.* **1985**, *50*, 438.

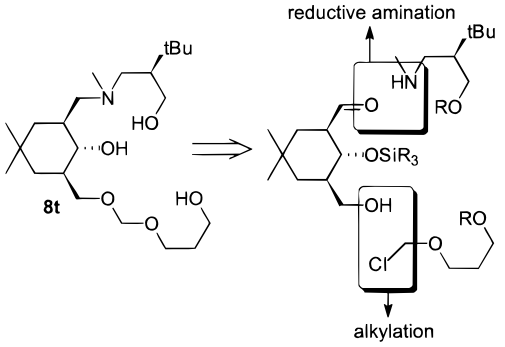
(19) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

(20) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

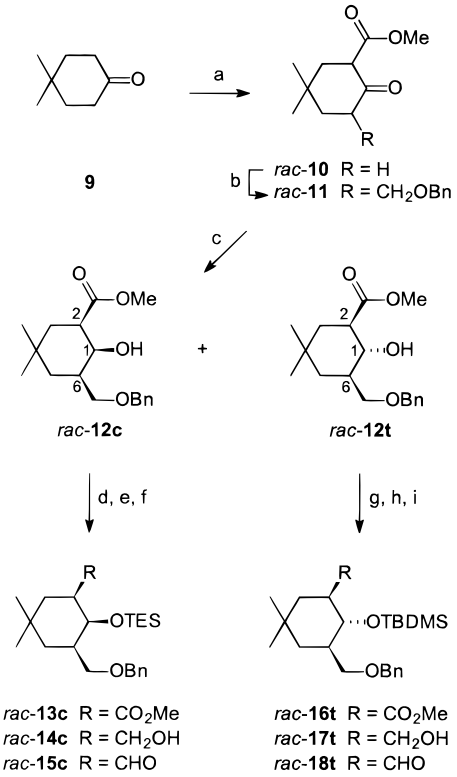
Chart 1



Scheme 3



Scheme 4[a]



[a] TES = triethylsilyl. Reagents: (a) NaH, MeOCOOMe, 95%; (b) i. LDA, THF, ii. $PhCH_2OCH_2Cl$; 65%; (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 77%; (d) TESCl, imidazole, 99%; (e) DIBALH, toluene, −78 °C, 99%; (f) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 93%; (g) TBDMSCl, imidazole, 99%; (h) DIBALH, toluene, −78 °C, 99%; (i) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 94%.

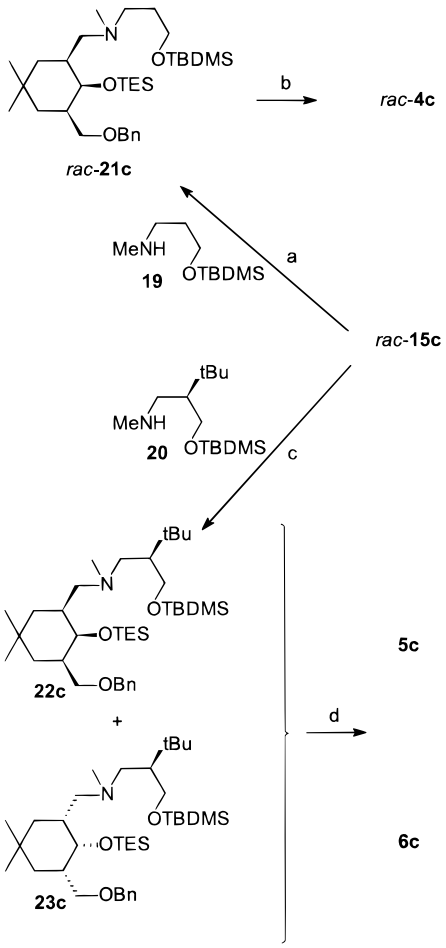
of the aldehyde was performed in each separate series and involved a three-step sequence: (1) protection of the secondary hydroxyl group as silyl ether (triethylsilyl ether (TES) in the *all-cis* series; *tert*-butyldimethylsilyl ether (TBDMS) in the *all-trans* series);[21] (2) reduction of the ester *rac*-**13c** and *rac*-**16t** with DIBALH; (3) oxidation of the obtained primary alcohols *rac*-**14c** and *rac*-**17t** with sulfur trioxide−pyridine complex in DMSO.

The synthesis of the three amino diols *rac*-**4c**, **5c**, and **6c** in the *cis*-series (see Chart 1) is shown in Scheme 5. Comparison of the reactivity of **4** and **5** should reveal the effect of the anchoring *tert*-butyl substituent on the GBC part of the mechanism. Central in the synthesis stands a reductive amination sequence. The therefore required secondary amine derivatives **19** and **20** were obtained using classical procedures that are included in the Supporting Information section. After considerable experimentation the successful transformation was realized using titanium(IV) isopropoxide in the condensation step, followed by sodium cyanoborohydride reduction.[22] Coupling of the aldehyde *rac*-**15c** with amine **19** led to *rac*-**21c** (54% yield) and after desilylation with tetrabutylammonium fluoride (TBAF) to amino diol *rac*-**4c**. The analogous coupling with the *tert*-butyl-substituted amine was performed with the enantiomerically pure (*R*)-derivative **20**.[23] The reductive amination sequence led to a ca. 1:1 mixture of the two diastereomers **22c** and **23c** that could not be separated at this stage. Desilyla-

(21) Originally the TBDMS protective group was also chosen for the *all-cis* series. Problems encountered during later deprotection steps led us eventually to use the TES ether as protective group.

(22) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.

Scheme 5[a]



[a] TES = triethylsilyl. Reagents: (a) i. 2 equiv $Ti(iPrO)_4$; ii. $Na(CN)BH_3$, EtOH, 54%; (b) Bu_4NF, THF, 58%; (c) i. 2 equiv **20**, 2 equiv $Ti(iPrO)_4$; ii. $Na(CN)BH_3$, EtOH, 94%; (d) Bu_4NF, THF, 73%.

tion led to the corresponding amino diols **5c** and **6c** that were isolated in pure form after HPLC separation. The analogous sequence was performed on the *all-trans* aldehyde *rac*-**18t**. In this manner amino diols *rac*-**4t**, **5t**, and **6t** were obtained (see Supporting Information).

The assignment of the structures of the diastereomeric amino diols **5c** and **6c** became possible via X-ray diffraction analysis of a later intermediate. After debenzylation of **5c**, the obtained amino triol **7c** was converted to the corresponding ammonium sulfonate salt by treatment with (*S*)-camphorsulfonic acid in dichloromethane. Figure 2a shows the ammonium salt as deduced from the X-ray data. At this point it is interesting to compare this result with the preferred calculated conformation of the free amino triol **7c** which is represented in Figure 2b.[24] Table 2 shows ^{1}H NMR coupling constants for the amino triols **7c** and **7t** which provide a nice indication of the anchoring capacity of the *tert*-butyl substituent in the GBC part of the molecule.

(23) The synthesis of the corresponding enantiomer has been described before: Steels, I.; De Clercq, P. J.; Declercq, J. P. *Tetrahedron: Asymmetry* **1992**, *3*, 599.

(24) Figure 2b shows the global energy minimum among several minimal energy conformations that were found. The geometry was calculated using *MacroModel V3.0*: Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W.; Department of Chemistry, Columbia University, New York, 10027.

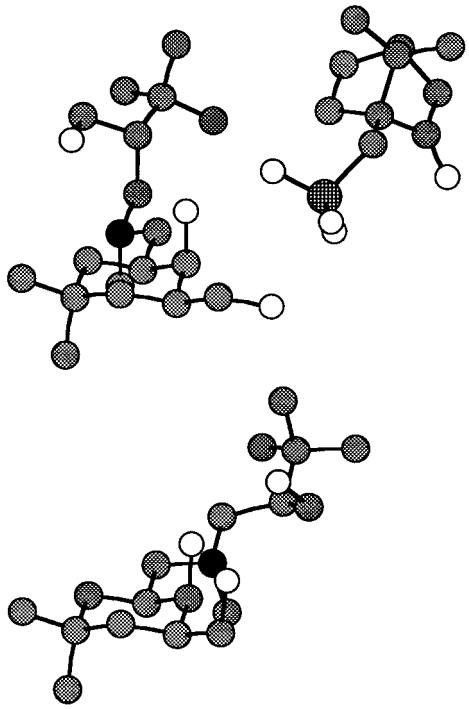
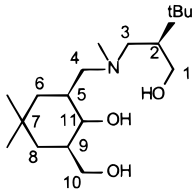


Figure 2. Ball-and-stick model of the X-ray structure of the (*S*)-camphor sulfonate salt of **7c** (top) and the calculated global minimum energy conformation of **7c** (bottom).

Table 2. ^{1}H NMR (500 MHz) Vicinal Coupling Constants for Amino Triols 7c and 7t

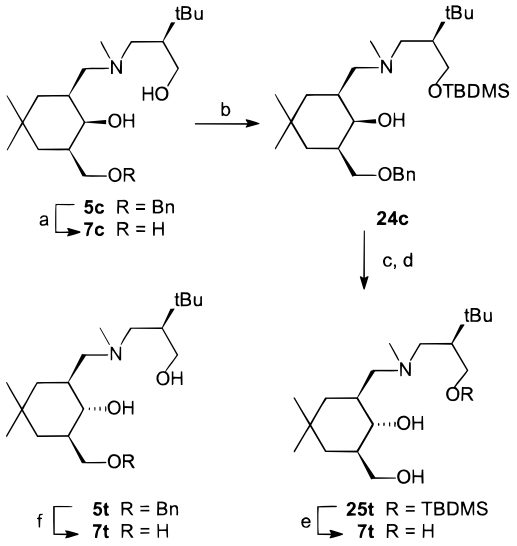


	J (Hz)	
position	**7c**[a]	**7t**[b]
1a-2	9.9	6.4
1b-2	3.4	3.8
2-3a	11.7	10.9
2-3b	2.6	2.9
4a-5	*c*	9.5
4b-5	*c*	4.9
5-6a	13.7	13.4
5-6b	3.1	3.5
5-11	*c*	9.7
8a-9	13.1	*c*
8b-9	3.6	3.3
9-10a	6.7	7.7
9-10b	5.0	4.1
9-11	*c*	9.7

[a] Recorded in CD_3CN. [b] Recorded in $CDCl_3$. [c] The individual coupling constants could not be determined from the observed ^{1}H NMR signal.

The structural assignment of the diastereomeric *trans*-derivatives **5t** and **6t**, that were obtained in a similar way, rests on the inversion sequence that is shown in Scheme 6. After selective protection of the primary hydroxy group in **5c** (leading to **24c**) and Dess−Martin oxidation of the secondary alcohol, the obtained cyclohexanone derivative was reduced under dissolved metal conditions which led to the expected *all-trans* diol **25t** exclusively. Desilylation gave amino triol **7t** which was

Scheme 6[a]



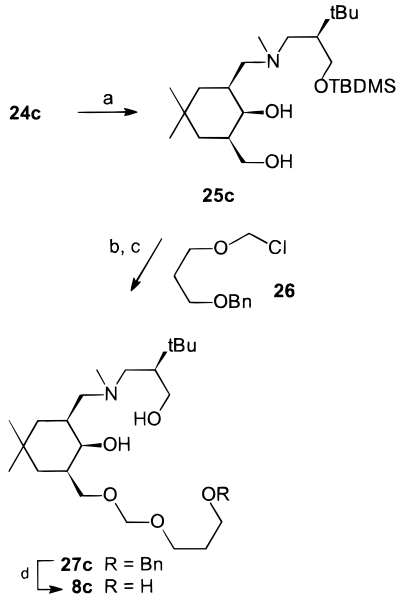
[a] Reagents: (a) Li, liquid NH_3, 69%; (b) TBDMSCl, Et_3N, DMAP, DMF, 78%; (c) Dess Martin, CH_2Cl_2, 55%; (d) Li, liquid NH_3, MeOH, 61%; (e) Bu_4NF, THF, 82%; (f) Li, liquid NH_3, 83%.

found identical with the derivative obtained via debenzylation of diastereomer **5t**.

The attachment of the final side chain involves an alkylation sequence that is shown in Scheme 7 for the *cis*-series. After selective protection of the primary hydroxy group in **5c** as TBDMS-ether (**24c**), debenzylation leads to diol **25c**. Upon deprotonation (1 equiv of *n*-butyllithium) followed by alkylation with chloride **26**, a selective reaction at the less hindered primary hydroxy group is observed.[25] Desilylation leads further to **27c** and final debenzylation to **8c**. The same sequence starting from **5t**, but involving *tert*-butyldiphenylsilyl as protective group, led to **8t** (see Supporting Information).

Reactivity Studies. As a measure of reactivity we first studied the esterification of the amino alcohols in Chart 1 by AcIm in acetonitrile using a large excess of amino alcohol to ensure the *pseudo* first-order conditions. Half-live values at 23 °C were determined by following the disappearance of AcIm (see Supporting Information) and are shown in Table 1.[26] In all cases the primary hydroxyl group at C-1 was found to be preferentially acylated. Especially in the cases of amino triols **7** and **8**

Scheme 7[a]



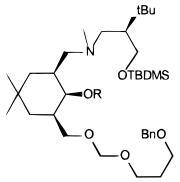
[a] Reagents: (a) Li, liquid NH_3, 100%; (b) i. 1.2 equiv *n*-BuLi, THF, −78 °C to −30 °C; ii. **26**, −78 °C, 68%; (c) Bu_4NF, THF, 80%; (d) Li, liquid NH_3, 93%.

this is indicative of a mechanism in which the tertiary amino group is actively involved. A somewhat reduced set of amino alcohols was also examined in their behavior toward *p*-nitro-2,2,2-trifluoroacetanilide (PNTFA). Here also half-live values were determined following the disappearance of PNTFA (Table 1). In this case the corresponding trifluoro-acetylated derivatives were not isolated. Presumably if formed, the acylated derivatives are further cleaved in a fast process involving the tertiary amine (vide infra).

With regard to AcIm, it has been shown that the amino alcohol catalyzed hydrolysis is subject to GBC.[16] Moreover, in a recent study of the influence of anchoring substitution in 1,3-amino alcohols on the rate of esterification by AcIm and by *p*-nitrophenylacetate (PNPA) in acetonitrile,[27] anchoring substitution was found to lead to (1) a rate decrease in the esterification with PNPA, and (2) a rate increase in the reaction with AcIm. These effects were ascribed to a nucleophilic mechanism for the reaction with PNPA and to a GBC mechanism for the reaction with AcIm.[28]

All studied derivatives in Chart 1 can be considered as derivatives of *N*-methyl-*N*-alkyl-3-amino-1-propanols. The simple derivatives **1**−**3** are included here for comparison. Their synthesis and reactivity behavior have been reported in detail before.[29] Comparison of the reactivity of **1** and **2** shows that the presence of an anchoring *tert*-butyl group is responsible for a reasonable 4-fold rate enhancement. This observation is in accord with a GBC mechanism. Indeed, the presence of a *tert*-butyl group induces the combined *anti*-orientation of the dimethylamino and hydroxy groups relative to the *tert*-

(25) Proof for the selective alkylation at the primary alcohol site was obtained indirectly via preparation of the mesylate; the ^1H NMR resonance at $\delta = 4.68$ ppm was found to integrate for the expected 1H.



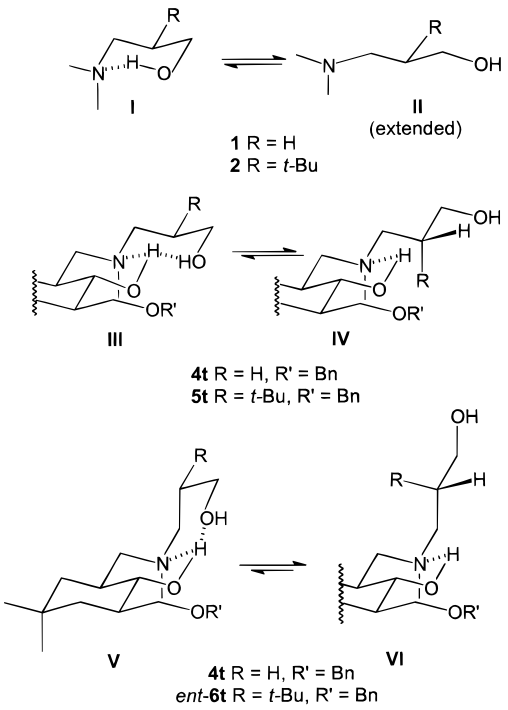
(26) Reactions were followed by ^1H NMR over a period of at least one half-life. Since the reactions were monitored by following the relative integrations of AcIm, a compound present in a very low concentration (cf. *pseudo* first-order conditions), monitoring over more extended time periods was inappropriate. However, in cases when half-lives were determined over at least five lifetimes using more sensitive UV methodology, values of the same order of magnitude are obtained (see ref 29b): 649, 144, and 108 min for **1**, **2**, and **3**, respectively. These values are consistently lower than those mentioned in Table 1, which is in line with the somewhat higher temperature at which the UV experiments were run (25 °C).

(27) Steels, I.; De Clercq, P. J.; Maskill, H. *J. Chem. Soc., Chem. Commun.* **1993**, 294.

(28) (a) Oakenfull, D. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 178. (b) Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188. (c) Fife, T. H. *Acc. Chem. Res.* **1993**, *26*, 325.

(29) (a) Madder, A.; De Clercq, P. J.; Maskill, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 851. (b) Madder, A.; Sebastian, S.; Van Haver, D.; De Clercq, P. J.; Maskill, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2787.

Scheme 8

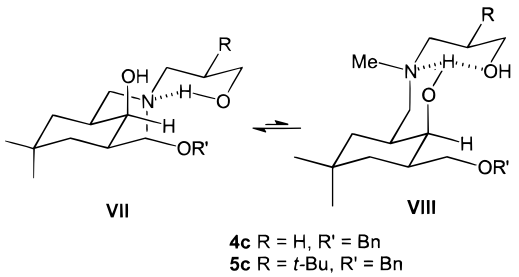


butyl group (cf. conformation **I** and **II**, Scheme 8); the induced proximity of the polar groups in the propane fragment favors the intramolecular hydrogen bonding between the tertiary amino group and the hydroxyl function, and hence the GBC mechanism. The presence of a second hydroxyl group in **3** further accelerates the reaction presumably through hydrogen bond assistance in stabilizing the tetrahedral oxyanion.[29a]

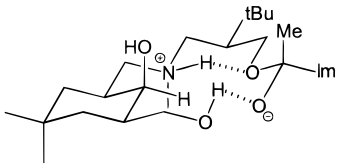
Inspection of Table 1 reveals that, with regard to the transesterification with AcIm, the maximum reactivity difference equals 28 (cf. $t_{1/2}$ of **1** and **7c**). It is further interesting to note that the presence of a *tert*-butyl group in the more elaborate derivatives **5** when compared to **4** leads to a sensible rate enhancement in the *cis*- and the *trans*-series. A following and unexpected observation is that the derivatives in the *cis*-series are consistently more reactive than the *trans*-analogues, i.e., a factor of approximately 7, 1.5, 1.5, 20, and 2.5 for **4**, **5**, **6**, **7**, and **8**, respectively. The very low reactivity of **4t** suggests that the normal intramolecular GBC mechanism is not operative here. Presumably, preferred hydrogen bonding of the tertiary amino group with the secondary hydroxyl group is taking place so that the product behaves as an ordinary primary alcohol. In this compound conformation **IV** is the preferred one (Scheme 8). Control experiments have shown that when AcIm is treated with 1,6-hexanediol in the presence of triethylamine the rate of the transesterification is negligible (cf. half-live of $\approx$ 2200 h). In contrast when considering the *tert*-butyl substituted derivative **5t,** the intramolecular hydrogen bonded form **IV** suffers from severe nonbonded interactions (i.e., *tert*-butyl (R) and *N*-methyl). Hence the **III** conformation should be the preferred one. This is in line with the observed rate enhancement compared to **4t**. In the case of the diastereomeric derivative **6t** the preferred conformation is expected to be **V** rather than **VI**,[30] with a very similar reactivity as observed for **5t** (cf. form **III**).

(30) Note that for reasons of clarity the enantiomer of **6t** is represented in the scheme.

Scheme 9



Scheme 10



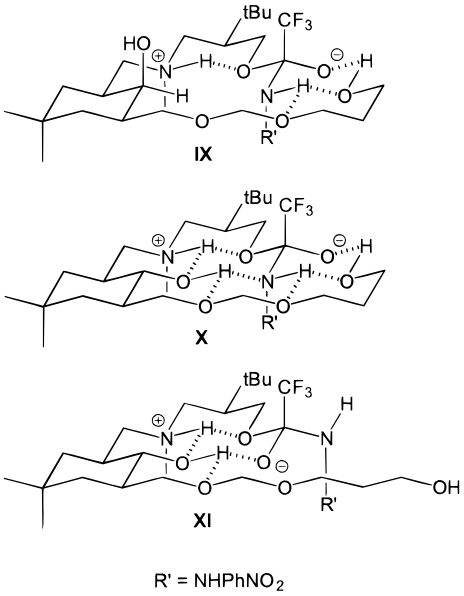
In the *cis*-derivative **4c** we note that the intramolecular hydrogen bonded form **VIII** (Scheme 9) is destabilized by nonbonded interactions originating from the *N*-methyl substituent so that the normal hydrogen bonded form **VII** is the expected one. The difference in reactivity that is now observed between **5c** and **4c** closely parallels the one that is observed between **2** and **1**.

A very interesting reactivity difference is observed when comparing amino triols **7c** and **7t**. The reactivity of **7t** is similar to the observed reactivities of the previously discussed *trans*-derivatives **5t** and **6t**. As for the *cis*-derivative the rate enhancement clearly indicates that an extra effect has to be involved. We like to suggest that the primary hydroxyl group that is not involved in the GBC portion of the mechanism can effectively help in stabilizing the tetrahedral oxyanion via intramolecular hydrogen bonding as illustrated in Scheme 10.

The introduction of the side chain (cf. **8c** and **8t**) that is expected to stabilize the ammonium intermediate is of course irrelevant here since the imidazole moiety does not allow for a GAC breakdown of the tetrahedral intermediate, both because of electronic and geometric reasons. For the sake of completeness, they have been included in the list and show, as can be expected, a reactivity behavior that is almost identical to **5c** and **5t**, respectively.

As a conclusion of this part we believe that as far as the GBC portion of the mechanism is concerned the study of this set of derivatives has been quite instructive. Especially, the knowledge that a correctly positioned hydroxy group for hydrogen bonding to the oxyanion intermediate (cf. Scheme 10) is effective, will be useful in the future. At the same time it is obvious that a further evaluation of the hydrolytic capacity of our set requires a substrate that can benefit from eventual hydrogen bond stabilization as shown in Scheme 2. On the other hand, for reasons that have been mentioned earlier, the intrinsic low reactivity will require an electronically activated substrate. We consider trifluoroacetanilides as a reasonable compromise. Indeed, the trifluoroacyl group should exhibit an enhanced reactivity toward nucleophilic attack, and the anilide moiety should have a propensity toward GAC breakdown of the tetrahedral intermediate. Previous studies involving trifluoroacetanilides have shown that the imidazole-catalyzed hydrolysis of a series of trifluoroacetanilides, among

Scheme 11



which the *p*-nitro derivative, proceeds via imidazolium GAC breakdown of the tetrahedral intermediate.[31]

The cleavage of PNTFA by the amino alcohols **1**, **2**, **3**, **7**, and **8** was followed in the same way as described above for AcIm (monitoring by ^{1}H NMR integration). The observation that the reaction led to the hydrolysis of PNTFA without isolation of the trifluoroacetyl ester of the amino alcohol implies that water is participating in the process.[32] At this point it is not clear whether water is involved in a direct hydrolysis of PNTFA via a process involving GBC or rather in the fast hydrolysis of the previously formed trifluoroacetyl ester of the amino alcohol under study. Although the mechanism is unclear, inspection of the reduced set that was investigated remains instructive (Table 1). The expected drop in overall reactivity is observed and can be roughly evaluated at a factor of 50−100 (cf. from minutes to hours). For the simple derivatives **1** and **2**, no anchoring effect is observed as in the case of AcIm. Furthermore, the *trans*-derivatives are now found to be more reactive than the corresponding *cis*-derivatives. Also, a general trend is observed in that the more structurally complex the molecule becomes (cf. **2** → **3** → **7** → **8**) the less reactive it behaves except for **8t**.

In the context of our work it is tempting to ascribe the higher reactivity of **8t**, when compared to **8c**, to the occurrence of GAC catalysis (compare **IX** and **X** in Scheme 11). However, this possibility has to be ruled out since a competition experiment in which the reactivity of **8t** was followed in the presence of a 1:1 mixture of PNTFA and the corresponding *p*-MeO-trifluoroacetanilide clearly showed the *p*-nitro derivative to be hydrolyzed faster.[33] Rather we believe that in the case of **8t**, reaction is occurring via GBC in which the oxyanion formation is assisted by the proximate secondary hydroxy group (cf. **XI**). It is likely that the expected mechanism represented in **X** will only be effective when the stabilization of the oxyanion by the terminal primary hydroxy group will be enforced in the first place. The incorporation of anchoring structural moieties in the flexible polyether part of the molecule and/or the inclusion of unreactive terminal functional groups with more efficient hydrogen bonding capacity, such as a phosphonamidate or a sulfonamide,[34] should help solve this problem. These aspects will be further investigated in the future.

Finally, we like to stress the fact that the results in terms of intrinsic hydrolytic performance are not spectacular but that they were not expected to be so in the first place. Rather, the relative differences that have been observed within the series of Chart 1 indicate reactivity trends that are not only of general interest but very encouraging in the context of our final endeavor.

Experimental Section

General Information. All reactions involving air and/or moisture sensitive materials were conducted under atmospheres of N_2 or Ar, which were dried and purified by passage through a column containing copper on charcoal, anhydrous $CaSO_4$, and 4 Å molecular sieves. All solvents were purified before use. Et_2O and THF were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Et_3N and diisopropylamine (DIA) were distilled from CaH_2. CH_2Cl_2 was distilled from P_2O_5. DMSO was distilled from CaH_2 under vacuum and immediately stored over freshly activated 4 Å molecular sieves. Analytical and preparative thin-layer chromatography were performed using glass plates precoated (0.25-mm layer) with silica gel 60 F_{254}. Flash chromatography was performed using Merck silica gel 60 (70−235 or 230−400 mesh). The ^{1}H NMR spectra were obtained at 500, 360, and 200 MHz and the ^{13}C NMR spectra at 50.3 MHz. Chemical shifts are reported in parts per million (ppm) downfield from TMS using residual $CHCl_3$ (7.27 ppm) as internal standard. Melting points are uncorrected. Infrared (IR) were recorded on a FT-IR spectrometer using KBr plates with film or in solution. Mass spectra (MS) were recorded at 70 eV. Commercial AcIm was recrystalized from dry Et_2O. PNTFA was prepared according to a literature procedure, [35] recrystalized from water, and dried in vacuo (P_2O_5).

***rac*-[Methyl (1*R*,2*S*,3*R*)-3-[(Benzyloxy)oxy]-2-hydroxy-5,5-dimethylcyclohexane-1-carboxylate] (12c) and *rac*-[Methyl (1*R*,2*R*,3*R*)-3-[(Benzyloxy)oxy]-2-hydroxy-5,5-dimethylcyclohexane-1-carboxylate] (12t).** To a suspension of oil-free sodium hydride (8.94 g of a 60% suspension in mineral oil, 372 mmol) in 400 mL of THF was added dimethyl carbonate (74.6 mL, 885 mmol). The mixture was heated to reflux and a solution of 4,4-dimethylcyclohexanone (21.53 g, 170 mmol) in 200 mL of THF was added dropwise over 45 min. The mixture was maintained at reflux for 2 h after the addition was complete. The reaction mixture was added to 300 mL of saturated aqueous NH_4Cl and the aqueous phase extracted twice with Et_2O (2 × 300 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was bulb-to-bulb distilled at 89 °C (0.2 mmHg) to yield 29.83 g (95%) of **10** as a colorless oil: IR (neat): 3434, 2953, 2867, 1725, 1697, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (6H, s), 1.44 (t, 2H, J = 6.7 Hz), 2.02 (s, 2H), 2.29 (t, 2H, J = 6.7 Hz), 3.74 (s, 3H), 12.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.22, 27.46, 28.59, 33.99, 35.74, 50.96, 95.98, 170.90, 172.82; MS *m*/*z* (relative intensity) 184 (M^+, 70).

To a solution of diisopropylamine (4.47 g, 6.20 mL, 44.21 mmol) in 80 mL of THF at 0 °C *n*-butyllithium (18.47 mL of a 2.5 M solution in hexanes, 46.18 mmol) was slowly added. After stirring for 20 min at 0 °C a solution of **10** (4 g, 21.71 mmol) in 20 mL of THF was added. After stirring for another

(31) Komiyama, M.; Bender, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 5977.

(32) It should be stressed that under the *pseudo* first-order conditions (10-fold excess of amino alcohol) minute amounts of water are sufficient for complete hydrolysis.

(33) Caplow, M. *J. Am. Chem. Soc.* **1969**, *91*, 3639.

(34) We acknowledge this particular suggestion by one of the referees.

(35) Henderson, J. W.; Haake, P. *J. Org. Chem.* **1977**, *42*, 3989.

20 min at 0 °C (benzyloxy)methyl chloride (3 mL, 3.40 g, 21.71 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with 50 mL of a 5 N HCl-solution and 100 mL of Et_2O. After separation of the layers, the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with H_2O until neutral. Purification by silica gel chromatography with pentane/EtOAc (98:2) yielded 4.28 g of the desired **11** (65%): IR (neat) 3500, 2953, 2864, 1748, 1715, 1651, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (s, 3H), 1.02 (s, 3H), 1.55 (dd, 1H, J = 13.2 and 11.4 Hz), 1.60 (ddd, 1H, J = 13.3, 6.5 and 2.2 Hz), 2.04 (dd, 1H, J = 15.6 and 2.5 Hz), 2.10 (ddd, 1H, J = 15.7, 2.0 and 1.4 Hz), 2.66 (m, 1H), 3.71 (dd, 1H, J = 9.1 and 6.2 Hz), 3.74 (dd, 1H, J = 9.1 and 3.8 Hz), 3.75 (s, 3H), 4.55 (s, 2H), 7.27−7.39 (m, 5H), 12.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.43, 28.51, 31.08, 36.00, 37.34, 38.78, 51.09, 70.23, 72.88, 97.09, 127.12, 127.55, 127.94, 138.08, 170.75, 173.06.

Cerium(III) chloride heptahydrate (45 g, 123.19 mmol) was added to a solution of *rac*-**11** (25 g, 82 mmol) in 500 mL of MeOH. The reaction mixture was stirred until a clear solution was obtained and subsequently cooled to −55 °C. Sodium borohydride (4.66 g, 123.19 mmol) was added portionwise. After complete conversion (TLC-control) the mixture was transferred to a 1 L flask. 200 mL of saturated aqueous NH_4Cl solution and 50 mL of H_2O were added, and most of the methanol was removed under reduced pressure. The residue was transferred into a separating funnel and, after addition of another 200 mL of NH_4Cl solution, extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified via flash silica gel chromatography followed by HPLC with isooctane:EtOAc (80:20) leading to 19.27 g of the pure isomers **12c** and **12t** (77% combined yield).

Alcohol 12c: R_f (pentane:EtOAc, 8:2) = 0.23; IR (neat) 3512, 2951, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (s, 3H), 0.99 (s, 3H), 1.08 (m, 1H), 1.42 (m, 1H), 1.48 (dd, 1H, J = 13.3 and 13.3 Hz), 1.77 (dd, 1H, J = 13.3 and 13.3 Hz), 1.87 (m, 1H), 2.55 (ddd, 1H, J = 13.5, 3.7 and 2.2 Hz), 3.46 (dd, 1H, J = 9.1 and 4.9 Hz), 3.59 (dd, 1H, J = 9.1 and 7.0 Hz), 3.71 (s, 3H), 4.35 (m, 1H), 4.52 (s, 2H), 7.22−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.25, 29.95, 32.26, 34.68, 34.89, 37.42, 43.55, 54.41, 66.44, 72.35, 70.02, 127.22, 127.97, 128.00, 137.89, 175.63. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.54; H, 8.45.

Alcohol 12t: R_f (pentane:EtOAc, 8:2) = 0.15; IR (neat) 3498, 3031, 2952, 1738, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (s, 3H), 0.99 (s, 3H), 1.01 (dd, 1H, J = 13.2 and 13.2 Hz), 1.31 (ddd, 1H, J = 13.5, 3.2 and 3.2 Hz), 1.37 (dd, 1H, J = 13.3 and 13.3 Hz), 1.58 (ddd, 1H, J = 13.3, 3.3 and 3.3 Hz), 1.96 (m, 1H), 2.60 (ddd, 1H, J = 13.6, 10.2 and 3.6 Hz), 3.50 (dd, 1H, J = 8.7 and 8.7 Hz), 3.56 (dd, 1H, J = 4.3 and 9.1 Hz), 3.70 (dd, 1H, J = 10.1 and 10.1 Hz), 3.71 (s, 3H), 3.95 (m, 1H), 4.51 (s, 2H), 7.22−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.79, 30.02, 31.77, 38.74, 39.76, 40.45, 47.22, 51.83, 73.57, 75.62, 75.80, 127.61, 127.78, 128.40, 137.47, 175.55; MS *m/z* (relative intensity) 306 ($M^{\bullet+}$, 1), 200 (23), 167 (43), 107 (26), 91 (100). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.51; H, 8.55.

***rac*-[Methyl (1*R*,2*S*,3*R*)-3-[(Benzyloxy)oxy]-2-(triethylsilyloxy)-5,5-dimethylcyclohexane-1-carboxylate] (13c).** To a solution of alcohol **12c** (0.1 g, 0.33 mmol) in DMF (1 mL) was added imidazole (67 mg, 0.99 mmol), followed by triethylsilyl chloride (82 μL, 0.49 mmol). The reaction mixture was stirred overnight at room temperature after which it was poured into ice−water, extracted with Et_2O, and washed with a saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash silica gel chromatography with hexane:EtOAc (95:5). This yielded 137 mg (99%) of the desired product **13c**: IR (neat) 2951, 2874, 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.53 (q, 6H, J = 7.9 Hz), 0.89 (s, 3H), 0.92 (t, 9H, J = 7.9 Hz), 0.97 (s, 3H), 1.00 (m, 1H), 1.30 (dd, 1H, J = 13.0 and 13.0 Hz), 1.39 (m, 1H), 1.80 (dd, 1H, J = 13.3 and 13.3 Hz), 1.85−1.92 (m, 1H), 2.46 (ddd, 1H, J = 13.3, 3.5 and 1.9 Hz), 3.18 (dd, 1H, J = 9.0 and 5.6 Hz), 3.42 (dd, 1H, J = 8.8 and 8.8 Hz), 3.67 (s, 3H), 4.43 (d, 1H, J_{AB} = 11.6 Hz), 4.54 (d, 1H, J_{AB} = 11.5 Hz), 4.55 (m, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 5.27, 6.96, 24.87, 30.01, 32.84, 34.26, 35.46, 39.59, 45.47, 51.32, 68.15, 72.13, 73.14, 127.53, 127.81, 128.30, 138.27, 174.20; MS *m/z* (relative intensity) 391 ($M^{\bullet+}$ − 29, 8), 91 (100), 45 (23), 41 (24). Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 68.53; H, 9.58. Found: C, 68.58; H, 9.54.

***rac*-[(1*S*,2*R*,3*R*)-[3-[(Benzyloxy)oxy]-2-[(triethylsilyl)-oxy]-5,5-dimethylcyclohexyl]methanol] (14c).** Ester **13c** (1 g, 2.38 mmol) was dissolved in dry toluene (1.5 mL) and cooled to −78 °C. After stirring for 1 h at −78 °C, 3.45 mL of DIBALH (1.5 M in toluene, 5 mmol) was added, and the reaction mixture was stirred for 2 h. Subsequently 4 mL of Na−K tartrate was added, and the resulting mixture stirred for 1 h at room temperature. After extraction with Et_2O, the organic layer was dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash silica gel chromatography with pentane:EtOAc (from 95:5 to 90:10). This yielded 937 mg (100%) of alcohol **14c**: IR (neat) 3410, 2955, 2921, 2875, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (q, 6H, J = 7.9 Hz), 0.92 (s, 3H), 0.93 (s, 3H) 0.95 (t, 9H, J = 8.0 Hz), 1.00−1.04 (m, 2H), 1.31 (dd, 2H, J = 12.9 and 12.9 Hz), 1.70−1.77 (m, 1H), 1.82−1.88 (m, 1H), 3.18 (dd, 1H, J = 8.9 and 5.7 Hz), 3.39−3.43 (m, 1H), 3.43 (dd, 1H, J = 8.7 and 8.7 Hz), 3.53−3.56 (m, 1H), 4.17 (m, 1H), 4.44 (d, 1H, J_{AB} = 11.7 Hz), 4.54 (d, 1H, J_{AB} = 11.7 Hz), 7.27−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 5.41, 7.14, 25.50, 30.23, 33.04, 35.96, 36.21, 39.48, 41.84, 64.55, 67.33, 72.52, 73.09, 127.52, 127.83, 128.32, 138.30; MS *m/z* (relative intensity) 391 ($M^{\bullet+}$ − H, 1), 363 ($M^{\bullet+}$ − CH_2CH_3, 2), 91 (100), 49 (19). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.36; H, 10.27. Found: C, 70.46; H, 10.14.

***rac*-(1*R*,2*S*,3*R*)-3-[(Benzyloxy)oxy]-2-(triethylsilyloxy)-5,5-dimethylcyclohexanecarbaldehyde (15c).** Triethylamine (3.19 mL, 22.92 mmol) was added to a solution of alcohol **14c** (3 g, 7.64 mmol) in CH_2Cl_2 (17 mL) and DMSO (17 mL) at 0 °C. Then sulfur trioxide−pyridine complex (3.04 g, 19.10 mmol) was added portionwise. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and poured into 20 mL of ice−water. Extraction with CH_2Cl_2 was followed by drying over Na_2SO_4. After filtration and removal of the solvent in vacuo the residue was purified by flash silica gel chromatography hexane:EtOAc (from 98:2 to 95:5). This yielded 2.68 g (90%) of aldehyde **15c**: IR (neat) 2953, 2875, 1727, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.55 (q, 6H, J = 8.0 Hz), 0.90 (s, 3H), 0.91 (t, 9H, J = 7.9 Hz), 0.99 (s, 3H) 1.01 (ddd, 1H, J = 12.9, 3.1 and 2.6 Hz), 1.32 (dd, 1H, J = 13.0 and 13.0 Hz), 1.40 (ddd, 1H, J = 13.2, 3.1 and 2.3 Hz), 1.71 (dd, 1H, J = 13.1 and 13.1 Hz), 1.92 (m, 1H), 2.33 (ddd, 1H, J = 13.0, 3.4 and 1.9 Hz), 3.20 (dd, 1H, J = 8.9 and 5.2 Hz), 3.43 (dd, 1H, J = 9.0 and 9.0 Hz), 4.44 (d, 1H, J_{AB} = 11.6 Hz), 4.55 (d, 1H, J_{AB} = 11.6 Hz), 4.64 (m, 1H), 7.25−7.40 (m, 5H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 5.27, 6.92, 24.86, 29.83, 32.52, 32.72, 35.71, 39.44, 52.56, 66.32, 71.69, 73.14, 127.57, 127.79, 128.30, 138.00, 204.64; MS *m/z* (relative intensity) 391 (1), 239 (10), 91 (100), 89 (56). Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.80. Found: C, 70.62; H, 9.98.

***rac*-[(1*S*,2*S*,3*R*)-3-[(Benzyloxy)oxy]-2-[(*tert*-butyldimethylsilyl)oxy]-5,5-dimethylcyclohexylmethanol] (17t).** Imidazole (11.33 g, 166.53 mmol) and a few milligrams of DMAP were added to a solution of TBDMSCl (12.55 g, 83.24 mmol) in 100 mL of dry DMF. The solution was cooled to 0 °C after which a solution of alcohol *rac*-**12t** (12.07 g, 39.38 mmol) in 30 mL of dry DMF was added. The reaction mixture was stirred for 12 h at room temperature and was subsequently poured into ice−water (100 mL). After extraction with pentane, the combined organic layers were washed with brine and dried ($MgSO_4$). The excess of solvent was removed under reduced pressure and the residue purified by flash silica gel chromatography with hexane:EtOAc (95:5) yielding 16.39 g (99%) of **16t**: IR (neat) 2928, 2856, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.06 (s, 3H), 0.015 (s, 3H), 0.82 (s, 9H), 0.94 (s, 3H), 0.98 (s, 3H), 1.29 (dd, 1H, J = 13.3 and 13.3 Hz), 1.40 (dd, 1H, J = 13.2 and 13.2 Hz), 1.50 (ddd, 1H, J = 13.2, 3.5 and 3.5 Hz), 1.56 (ddd, 1H, J = 13.6, 3.4 and 3.4 Hz), 1.78 (m,

1H), 2.63 (ddd, 1H, J = 13.4, 9.9 and 3.8 Hz), 3.43 (dd, 1H, J = 8.8 and 6.5 Hz), 3.50 (dd, 1H, J = 8.8 and 2.9 Hz), 3.65 (s, 3H), 3.78 (dd, 1H, J = 10.0 and 10.0 Hz), 4.48 (d, 1H, J_{AB} = 12.1 Hz), 4.54 (d, 1H, J_{AB} = 12.1 Hz), 7.30−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.41, −4.24, 18.24, 24.68, 26.03, 30.12, 32.16, 40.93, 41.42, 42.20, 49.16, 51.48, 71.60, 72.95, 127.41, 127.50, 128.28, 138.62, 175.96; MS m/z (relative intensity) 363 ($M^{\bullet+}$ − 57, 3), 271 (10), 91 (100).

The ester **16t** was then reduced to the corresponding alcohol using DIBALH in toluene at −78 °C as described for **13c**: IR (neat) 3443, 2976, 2956 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.95 (s, 3H), 0.98 (s, 3H), 1.13 (dd, 1H, J = 13.2 and 13.2 Hz), 1.18 (dd, 1H, J = 13.2 and 13.2 Hz), 1.40 (br, s, 1H), 1.45 (ddd, 1H, J = 13.3, 3.3 and 3.3 Hz), 1.59 (ddd, 1H, J = 13.6, 3.5 and 3.5 Hz), 1.72 (m, 1H), 1.83 (m, 1H), 3.30 (dd, 1H, J = 10.0 and 10.0 Hz), 3.33 (dd, 1H, J = 8.8 and 7.0 Hz), 3.52 (dd, 1H, J = 8.8 and 3.1 Hz), 3.54 (m, 1H), 3.68 (dd, 1H, J = 10.5 and 3.8 Hz), 4.41 (d, 1H, J_{AB} = 12.1 Hz), 4.53 (d, 1H, J_{AB} = 12.2 Hz), 7.30−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 0.00, 17.92, 24.92, 25.72, 29.71, 32.31, 41.01, 41.29, 41.62, 43.08, 64.65, 71.59, 72.57, 127.01, 127.17, 127.91, 138.32; MS m/z (relative intensity) 335 ($M^{\bullet+}$ − 57, 4), 91 (100), 75 (25). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.36; H, 10.27. Found: C, 70.24; H, 10.33.

***rac*-[(1*R*,2*R*,3*R*)-3-[(Benzyloxy)oxy]-2-[(*tert*-butyldimethylsilyl)oxy]-5,5-dimethylcyclohexane-1-carbaldehyde] (18t).** The alcohol **17t** (2.31 g, 5.88 mmol) was oxidized to aldehyde **18t** using sulfur trioxide−pyridine complex as was described for the synthesis of aldehyde **15c** and led to 1.86 g (81%) of aldehyde **18t**: IR (neat) 2928, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz,) δ −0.02 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 0.97 (s, 3H), 0.98 (s, 3H), 1.26 (dd, 1H, J = 13.1 and 13.1 Hz), 1.31 (dd, 1H, J = 13.1 and 13.1 Hz), 1.35 (ddd, 1H, J = 13.4, 3.5 and 3.5 Hz), 1.54 (ddd, 1H, J = 13.8, 3.3 and 3.3 Hz), 1.82 (m, 1H), 2.59 (m, 1H), 3.45 (dd, 1H, J = 8.9 and 3.0 Hz), 3.49 (dd, 1H, J = 8.9 and 6.1 Hz), 3.81 (dd, 1H, J = 10.0 and 10.0 Hz), 4.41 (d, 1H, J_{AB} = 12.1 Hz), 4.55 (d, 1H, J_{AB} = 12.0 Hz), 7.30−7.35 (m, 5H), 9.64 (d, 1H, J = 3.79 Hz); ^{13}C NMR ($CDCl_3$) δ −4.14, −3.71, 18.09, 24.80, 25.90, 29.88, 31.20, 38.06, 40.93, 41.36, 55.11, 71.00, 71.64, 72.99, 127.41, 127.46, 128.22, 138.47, 204.73; MS m/z (relative intensity) 333 ($M^{\bullet+}$ − 57, 3), 213 (18), 121 (18), 105 (28), 91 (100), 77 (18). Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.80. Found: C, 70.58; H, 9.79.

***rac*-[(1*R*,2*R*,6*S*)-2-[(Benzyloxy)oxy]-6-[[*N*-(3-hydroxypropyl)-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol] (*rac*-4c).** A solution of aldehyde *rac*-**15c** (300 mg, 0.77 mmol), secondary amine **19** (312 mg, 1.54 mmol), and titanium(IV) isopropoxide (0.452 mL, 1.54 mmol) was stirred at room temperature in a round-bottomed flask with a calcium chloride drying tube for 4 h. The reaction mixture was diluted with absolute ethanol (0.8 mL) and subsequently sodium cyanoborohydride (31 mg, 0.5 mmol) was added. After stirring for 24 h, 1 mL of a 25% aqueous ammonia solution was added, and the mixture was diluted with Et_2O. After filtration of the inorganic salts the solvent was removed in vacuo. The residue was purified by flash silica gel chromatography with pentane:EtOAc (9:1). This yielded 239 mg (54%) of *rac*-**21c**: IR (neat) 2952, 2789, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 6H), 0.42 (q, 6H, J = 7.8 Hz), 0.89 (s, 9H), 0.90 (s, 3H), 0.91 (s, 3H), 0.95 (t, 9H, J = 8.0 Hz), 1.00 (m, 1H), 1.20 (m, 1H), 1.28 (dd, 1H, J = 12.5 and 12.5 Hz), 1.29 (dd, 1H, J = 13.1 and 13.1 Hz), 1.60−1.70 (m, 3H), 1.80−1.87 (m, 1H), 2.08 (dd, 1H, J = 12.1 and 5.2 Hz), 2.14 (s, 3H), 2.20−2.30 (m, 2H), 2.38−2.47 (m, 1H), 3.15 (dd, 1H, J = 8.9 and 5.6 Hz), 3.41 (dd, 1H, J = 8.7 and 8.7 Hz), 3.60−3.68 (m, 2H), 3.95 (m, 1H), 4.43 (d, 1H, J_{AB} = 11.7 Hz), 4.53 (d, 1H, J_{AB} = 11.7 Hz), 7.27−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.69, 6.21, 7.81, 18.94, 26.06, 26.57, 30.97, 33.67, 37.03, 37.36, 38.38, 40.59, 43.34, 55.58, 62.35, 70.42, 73.29, 73.74, 128.12, 128.48, 128.92, 139.06; MS m/z (relative intensity) 486 (3), 216 (12), 91 (20), 58 (100).

To a solution of amine *rac*-**21c** (214 mg, 0.37 mmol) in THF (2 mL) was added a 1 M solution of TBAF in THF (1.85 mL, 1.85 mmol, 5 equiv). After stirring for 15 h at room temperature, 1 mL of water was added, and the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash silica gel chromatography with pentane:acetone:25% ammonia solution (from 20:9.8:0.2 to 10:9.8:0.2). This yielded 75 mg (58%) of amino diol *rac*-**4c**: IR (neat) 3417, 2922, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (s, 3H), 0.93 (s, 3H), 1.01−1.09 (m, 2H), 1.23 (dd, 1H, J = 13.0 and 13.0 Hz), 1.27 (dd, 1H, J = 13.0 and 13.0 Hz), 1.58−1.69 (m, 2H), 1.72−1.78 (m, 1H), 1.80−1.87 (m, 1H), 2.10 (dd, 1H, J = 12.3 and 6.4 Hz), 2.18 (s, 3H), 2.42 (dd, 1H, J = 12.3 and 7.9 Hz), 2.45−2.52 (m, 2H), 3.33 (dd, 1H, J = 9.1 and 5.7 Hz), 3.50 (dd, 1H, J = 9.1 and 7.3 Hz), 3.58−3.64 (m, 2H), 3.85 (m, 1H), 4.47 (s, 2H), 7.26−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.08, 27.42, 30.52, 32.96, 35.59, 36.23, 37.77, 38.43, 42.74, 59.37, 60.27, 64.52, 67.54, 73.40, 73.62, 127.56, 127.66, 128.38, 138.28; MS m/z (relative intensity) 349 ($M^{\bullet+}$, 2), 334 ($M^{\bullet+}$ − CH_3, 5), 102 (100), 91 (25), 58 (57).

***(1R,2R,6S)*-2-[(Benzyloxy)oxy]-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (5c) and (1*S*,2*S*,6*R*)-2-[(Benzyloxy)oxy]-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (6c).** A mixture of aldehyde *rac*-**15c** (250 mg, 0.64 mmol), amine **20** (332 mg, 1.28 mmol), and titanium(IV) isopropoxide (0.377 mL, 1.28 mmol) was stirred at room temperature in a round-bottomed flask with a $CaCl_2$ drying tube. After 2 h the viscous solution was diluted with 2.5 mL of absolute EtOH (freshly distilled). Sodium cyanoborohydride (27 mg, 0.43 mmol) was added portionwise, and the resulting solution was stirred for 20 h. Dilution with 5 mL of Et_2O was followed by addition of 2 mL of a 25% ammonia solution, and the resulting inorganic precipitate was filtered and thoroughly washed with EtOH. The filtrate was then concentrated in vacuo. The residue was taken up in Et_2O, and water was added. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were then washed with brine and dried ($MgSO_4$). After filtration and concentration the residue was purified by flash silica gel chromatography with pentane:EtOAc (96.5:3.5) leading to 325 mg (0.51 mmol, 80%) of a mixture of diastereomers which could not be separated and was used as such in the following reaction.

The mixture of diastereomeric amines **22c** and **23c** (100 mg, 0.16 mmol) was dissolved in 0.2 mL of THF and 0.79 mL of a 1 M TBAF solution (0.79 mmol) was added. The reaction mixture was stirred overnight at room temperature. After removal of the solvent under reduced pressure the crude product was purified via HPLC with isooctane:acetone:25% ammonia solution (45:9.8:0.2) leading to 28 mg of amino diol **6c** and 19.3 mg of **5c** (combined yield 73%).

For **6c**: R_f (isooctane:acetone:25% ammonia solution (40:9.8:0.2)) = 0.28; IR (neat) 3428, 2958, 1459 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (s, 9H), 0.92 (s, 3H), 0.94 (s, 3H), 0.98 (m, 1H), 1.12 (m, 1H), 1.29 (dd, 1H, J = 12.8 and 12.8 Hz), 1.40 (dd, 1H, J = 13.1 and 13.1 Hz), 1.75−1.84 (m, 4H), 2.24 (s, 3H), 2.55 (dd, 1H, J = 12.2 and 12.2 Hz), 2.58 (m, 1H), 2.77 (dd, 1H, J = 10.7 and 10.7 Hz), 3.44 (dd, 1H, J = 9.0 and 5.3 Hz), 3.56 (dd, 1H, J = 9.0 and 6.6 Hz), 3.67 (dd, 1H, J = 10.4 and 10.4 Hz), 3.91 (m, 1H), 3.92 (m, 1H), 4.51 (s, 2H), 7.28−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): 25.12, 27.90, 30.06, 30.46, 31.16, 35.27, 36.35, 37.99, 38.34, 43.35, 44.27, 58.95, 62.20, 66.08, 66.53, 73.35, 127.50, 127.68, 128.35, 138.42; MS m/z (relative intensity) 405 ($M^{\bullet+}$, 1), 91 (34), 58 (100). For **5c**: R_f (isooctane:acetone:25% ammonia solution (40:9.8:0.2)) = 0.27; IR (neat) 3415, 2953, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 0.88 (s, 9H), 0.92 (s, 3H), 0.95 (s, 3H), 1.02 (m, 1H), 1.05 (m, 1H), 1.30 (dd, 1H, J = 12.8 and 12.8 Hz), 1.52 (dd, 1H, J = 13.2 and 13.2 Hz), 1.68 (m, 1H), 1.74 (m, 1H), 1.79 (m, 1H), 2.22 (s, 3H), 2.31 (dd, 1H, J = 12.1 and 6.5 Hz), 2.41 (dd, 1H, J = 12.1 and 7.6 Hz), 2.53−2.60 (m, 2H), 3.50−3.55 (m, 2H), 3.63 (dd, 1H, J = 10.2 and 10.2 Hz), 3.92 (m, 1H), 3.93 (m, 1H), 4.48 (d, 1H, J_{AB} = 12.0 Hz), 4.53 (d, 1H, J_{AB} = 12.0 Hz), 7.28−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): 25.02, 27.95, 30.53, 31.22, 35.80, 36.17, 37.48, 38.47, 41.22, 42.33, 44.97,

62.30, 66.40, 68.55, 73.44, 73.82, 127.65, 128.43, 138.12; MS *m*/*z* (relative intensity) 390 ($M^{\bullet+}$ − CH_3, 2), 158 (12), 91 (34), 58 (100).

(1*S*,2*R*,6*S*)-2-[(Benzyloxy)oxy]-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (5t) and (1*R*,2*S*,6*R*)-2-[(Benzyloxy)oxy]-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (6t). The synthesis of the *all-trans* amino diols is analogous to the synthesis of the corresponding *all-cis* amino diols and is fully detailed in the Supporting Information. Spectral data for **5t**: R_f (isooctane:acetone:25% ammonia solution (40:9.8:0.2)) = 0.50; IR (neat) 3410, 2952, 2855, 1365 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.81 (dd, 1H, J = 12.9 and 12.9 Hz), 0.89 (s, 12H), 0.95 (s, 3H), 1.02 (dd, 1H, J = 13.1 and 13.1 Hz), 1.36 (ddd, 1H, J = 13.3, 3.3 and 3.3 Hz), 1.44 (ddd, 1H, J = 13.4, 3.5 and 3.3 Hz), 1.46 (m, 1H), 1.73−1.79 (m, 2H), 2.20 (s, 3H), 2.19 (m, 1H), 2.37 (ddd, 1H, J = 12.4, 2.9 and 1.0 Hz), 2.52 (dd, 1H, J = 12.2 and 7.3 Hz), 3.02 (dd, 1H, J = 9.8 and 9.8 Hz), 3.42 (dd, 1H, J = 9.0 and 6.2 Hz), 3.50 (dd, 1H, J = 10.7 and 7.5 Hz), 3.57 (dd, 1H, J = 9.0 and 4.7 Hz), 3.68 (ddd, 1H, J = 10.7, 3.8 and 1.1 Hz), 4.47 (s, 2H), 7.26−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.03, 28.00, 30.26, 31.80, 32.53, 37.41, 39.81, 40.05, 41.59, 43.38, 45.42, 60.91, 61.56, 65.55, 73.52, 76.06, 78.94, 127.60, 127.72, 128.40, 137.63; MS *m*/*z* (relative intensity) 405 ($M^{\bullet+}$, 1), 404 ($M^{\bullet+}$ − H, 2), 390 ($M^{\bullet+}$ − CH_3, 3), 58 (100). Spectral data for **6t**: R_f (isooctane:acetone:25% ammonia solution (40:9.8:0.2)) = 0.50; IR (neat) 3410, 2951, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (dd, 1H, J = 13.1 and 13.1 Hz), 0.90 (s, 12H), 0.93 (m, 1H), 0.96 (s, 3H), 1.33−1.37 (m, 2H), 1.57 (m, 1H), 1.81 (m, 1H), 1.92 (m, 1H), 2.17 (m, 1H), 2.20 (s, 3H), 2.39 (m, 1H), 2.52 (dd, 1H, J = 11.9 and 11.9 Hz), 2.67 (dd, 1H, J = 12.2 and 6.9 Hz), 3.15 (dd, 1H, J = 9.7 and 9.7 Hz), 3.50−3.51 (m, 2H), 3.63 (dd, 1H, J = 10.9 and 7.1), 3.82 (ddd, 1H, J = 10.9, 3.9 and 1.2 Hz), 4.51 (s, 2H), 7.25−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.26, 28.06, 30.40, 31.63, 32.64, 36.78, 40.09, 40.32, 41.54, 41.93, 46.43, 60.30, 63.78, 64.42, 73.44, 74.71, 78.92, 127.62, 128.39, 138.04; MS *m*/*z* (relative intensity) 404 ($M^{\bullet+}$ − H, 1), 390 ($M^{\bullet+}$ − CH_3, 2), 91 (22), 58 (100).

(1*R*,2*R*,6*S*)-2-(Hydroxymethyl)-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (7c). Sodium metal was added in small portions to a solution of amino diol **5c** (95.6 mg, 0.236 mmol) in THF (1 mL) and 15 mL of freshly distilled ammonia until the solution remained deep blue. After stirring for 4 h at −33 °C, the excess sodium was destroyed by addition of solid ammonium chloride. The ammonia was allowed to evaporate, the residue was dissolved in CH_2Cl_2, and the inorganic precipitate was filtered off. The solvent was removed under reduced pressure, and the residue was purified via flash silica gel chromatography with isooctane:acetone:25% ammonia solution (70:29.4:0.6). This yielded 51.3 mg (69%) of amino diol **7c**: IR (neat) 3380, 2953, 1469, 1367 cm^{-1}; ^1H NMR (CD_3CN, 500 MHz) δ 0.88 (s, 6H), 0.92 (s, 9H), 1.02 (ddd, 1H, J = 12.9, 3.1 and 2.4 Hz), 1.09 (ddd, 1H, J = 13.0, 3.6 and 2.2 Hz), 1.20 (dd, 1H, J = 13.7 and 12.7 Hz), 1.31 (dd, 1H, J = 13.1 and 13.1 Hz), 1.58−1.67 (m, 2H), 1.75 (m, 1H), 2.19 (s, 3H), 2.29−2.30 (m, 2H), 2.49 (ddd, 1H, J = 12.3, 2.6 and 2.6 Hz), 2.58 (dd, 1H, J = 12.1 and 11.7 Hz), 3.45 (dd, 1H, J = 10.6 and 5.0 Hz), 3.51 (dd, 1H, J = 10.6 and 6.7 Hz), 3.56 (dd, 1H, J = 9.9 and 9.9 Hz), 3.78 (ddd, 1H, J = 10.1, 3.4 and 2.6 Hz), 3.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.11, 27.90, 30.46, 31.18, 32.98, 35.30, 35.62, 37.75, 39.84, 41.26, 44.70, 61.92, 62.73, 65.37, 66.37, 66.62; MS *m*/*z* (relative intensity) 315 ($M^{\bullet+}$, 1), 300 ($M^{\bullet+}$ − CH_3, 3), 58 (100), 44 (28). Anal. Calcd for $C_{18}H_{37}NO_3$: C, 68.53; H, 11.82; N, 4.44. Found: C, 68.04; H, 11.77; N, 4.28.

The structure of **7c** was further proven via X-ray diffraction analysis of the ammonium salt obtained in the following way: to a solution of (*S*)-(+)-camphorsulfonic acid (9 mg, 0.039 mmol) in CH_2Cl_2 (0.7 mL) was added a solution of amino triol **7c** (12.2 mg, 0.039 mmol) in CH_2Cl_2 (1 mL). After stirring for 30 min, the excess CH_2Cl_2 was removed under a stream of nitrogen. Recrystallization was performed in a mixture of isooctane and CH_2Cl_2.

(1*R*,2*R*,6*S*)-2-[(Benzyloxy)oxy]-6-[[*N*-[(2*R*)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (24c). To a solution of amino diol **5c** (76.7 mg, 0.189 mmol) in dry DMF (3 mL) was added triethylamine (0.058 mL, 0.416 mmol), followed by a few mg of DMAP. Subsequently TBDMSCl (32 mg, 0.208 mmol) was added in one portion. After stirring for 20 h at room temperature brine was added and the mixture extracted with Et_2O. After drying ($MgSO_4$), filtration and concentration in vacuo the residue was purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (90:9.8:0.2). This yielded 77 mg (78%) of silyl ether **24c** next to 12 mg (16%) of starting material: $[\alpha]^{23}_D = -23.72°$, $[\alpha]^{23}_{365} = -69.03°$ (c = 1.13, $CHCl_3$); IR (neat) 3437, 2955, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 0.91 (s, 3H), 0.93 (s, 9H), 0.95 (s, 3H), 1.07−1.12 (m, 2H), 1.25 (m, 1H), 1.40 (dd, 1H, J = 13.1 and 13.1 Hz), 1.47 (dd, 1H, J = 13.3 and 13.3 Hz), 1.68 (m, 1H), 1.83 (m, 1H), 2.18 (s, 3H), 2.19 (dd, 1H, J = 12.3 and 3.1 Hz), 2.28 (dd, 1H, J = 12.7 and 6.0 Hz), 2.34 (dd, 1H, J = 12.4 and 9.3 Hz), 2.38 (dd, 1H, J = 12.6 and 6.7 Hz), 3.48 (dd, 1H, J = 9.0 and 5.1 Hz), 3.58 (dd, 1H, J = 9.0 and 6.3 Hz), 3.69 (dd, 1H, J = 10.1 and 3.5 Hz), 3.73 (dd, 1H, J = 10.2 and 4.4 Hz), 4.02 (m, 1H), 4.50 (d, 1H, J_{AB} = 12.0 Hz), 4.53 (d, 1H, J_{AB} = 12.0 Hz), 7.28−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.52, −5.47, 18.13, 24.98, 25.88, 25.96, 28.45, 30.65, 32.31, 33.09, 36.33, 38.16, 38.59, 43.96, 48.12, 57.62, 61.78, 62.11, 69.19, 73.40, 73.43, 127.53, 127.61, 128.35, 138.43; MS *m*/*z* (relative intensity) 519 ($M^{\bullet+}$, <0.5), 504 ($M^{\bullet+}$ − CH_3, 0.5), 462 ($M^{\bullet+}$ − tBu, 4), 58 (100).

(1*S*,2*R*,6*S*)-2-(Hydroxymethyl)-6-[[*N*-[(2*R*)-2-(hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-4,4-dimethylcyclohexan-1-ol (7t). To a solution of alcohol **24c** (11 mg, 0.021 mmol) in CH_2Cl_2 (0.2 mL) was added Dess−Martin reagent (44 mg, 0.105 mmol). After complete conversion (TLC control) the reaction mixture was diluted with Et_2O, and 1 mL of a saturated sodium bicarbonate solution was added followed by 2 mL of a 5% sodium thiosulfate solution. The organic layer was separated and dried (Na_2SO_4). The excess solvent was removed under reduced pressure and the residue chromatographed on silica gel using isooctane:acetone:25% ammonia solution (95:4.9:0.01). This yielded 6 mg (55%) of the desired ketone (IR 1711 cm^{-1}) which was immediately taken into the next reaction. A solution of the ketone (10 mg, 0.019 mmol) in THF was transferred to a reaction flask containing 3 mL of predried liquid ammonia and 0.3 mL of dry methanol. Subsequently, lithium wire was added until the solution turned blue. After stirring for 15 min, solid ammonium chloride was added to destroy the excess lithium. The ammonia was evaporated, the residue was dissolved in CH_2Cl_2, and the inorganic salts were filtered. The filtrate was concentrated in vacuo yielding an oil which was purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (90:9.8:0.2). This yielded 5 mg (61%) of the desired amino diol **25t** which was not further characterized but immediately converted to the known amino triol **7t**.

To a solution of amino diol **25t** (2.5 mg, 0.0058 mmol) in THF (0.1 mL) was added a 1 M solution of TBAF in THF (12 mL, 0.012 mmol). The reaction mixture was stirred for 20 h at room temperature. The excess solvent was removed under reduced pressure and the residue purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (20:9.8:0.2). Thus 1.5 mg of amino triol **7t** (81%) was obtained: IR (neat) 3381, 2954, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (dd, 1H, J = 13.4 and 13.4 Hz), 0.89 (m, 1H), 0.90 (s, 3H), 0.92 (s, 9H), 0.98 (s, 3H), 1.21 (ddd, 1H, J = 13.4, 3.5 and 3.0 Hz), 1.28 (ddd, 1H, J = 13.4, 3.3 and 3.1 Hz), 1.47 (m, 1H), 1.79−1.89 (m, 2H), 2.24 (s, 3H), 2.31 (dd, 1H, J = 12.4 and 5.0 Hz), 2.39 (dd, 1H, J = 12.3 and 2.9 Hz), 2.53 (dd, 1H, J = 12.2 and 9.5 Hz), 2.55 (dd, 1H, J = 12.0 and 10.9 Hz), 3.27 (dd, 1H, J = 9.7 and 9.7 Hz), 3.58 (dd, 1H, J = 10.7 and 7.7 Hz), 3.60 (dd, 1H, J = 10.8 and 4.1 Hz), 3.65 (dd, 1H, J = 10.9 and 6.4 Hz), 3.80 (dd, 1H, J = 10.9 and 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 25.29, 28.04, 30.41, 31.92, 32.45, 36.10, 39.63, 41.23,

41.52, 41.94, 46.79, 59.49, 63.08, 63.15, 68.72, 82.29; MS *m*/*z* (relative intensity) 300 ($M^{\bullet+}$ − CH_3, 1), 258 (2), 58 (100). Anal. Calcd for $C_{18}H_{37}NO_3$: C, 68.53; H, 11.82; N, 4.44. Found: C, 67.54; H, 11.69; N, 4.41.

(1*R*,2*R*,6*S*)-6-[[*N*-[(2*R*)-2-[[(*tert*-Butyldimethylsilyl)-oxy]methyl]-3,3-dimethylbutyl]-*N*-methylamino]methyl]-2-(hydroxymethyl)-4,4-dimethylcyclohexan-1-ol (25c). The benzyl deprotection was performed under standard conditions with lithium in liquid ammonia as described above for the preparation of **7c**. The procedure led to 52 mg of the desired amino diol **25c** (100%): $[\alpha]^{23}_D = -26.29°$, $[\alpha]^{23}_{365} = -73.71°$ (*c* = 0.62, $CHCl_3$); R_f (isooctane:acetone:25% ammonia solution (85:14.7:0.3)) = 0.24; IR (neat) 3628, 3478, 2956, 2857, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.90 (s, 3H), 0.93 (s, 9H), 0.98 (s, 3H), 1.03 (m, 1H), 1.30 (m, 1H), 1.48 (dd, 1H, *J* = 13.0 and 13.0 Hz), 1.63 (m, 2H), 1.68 (m, 2H), 2.25 (m, 4H), 2.38 (m, 1H), 2.44 (m, 1H), 2.49 (dd, 1H, *J* = 12.9 and 5.4 Hz), 2.94 (m, 1H), 3.64 (m, 1H), 3.70 (dd, 1H, *J* = 10.3 and 3.5 Hz), 3.74 (m, 1H), 3.84 (m, 1H), 4.14 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −5.56, 18.13, 24.62, 25.96, 28.49, 30.69, 32.32, 33.09, 35.62, 36.09, 38.46, 38.86, 44.23, 48.16, 58.15, 61.93, 62.25, 67.10, 71.70; MS *m*/*z* (relative intensity) 429 ($M^{\bullet+}$, 1), 414 ($M^{\bullet+}$ − CH_3, 2), 372 ($M^{\bullet+}$ − tBu, 4), 58 (100).

(1*R*,2*R*,6*S*)-6-[[*N*-[(2*R*)-2-(Hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-2-[[(3-hydroxypropoxy)methoxy]methyl]-4,4-dimethylcyclohexan-1-ol (8c). To a solution of amino diol **25c** (50 mg, 0.116 mmol) in THF (1 mL) at −78 °C was added *n*-butyllithium (1.5 M in hexanes, 88 mL, 0.140 mmol). After stirring for 10 min at −78 °C, stirring was continued at −30 °C for 30 min. The reaction mixture was cooled again to −78 °C, and chloromethyl ether **26** (37 mg, 0.174 mmol) was added. Stirring was continued overnight while the solution was allowed to slowly reach rt. After dilution with Et_2O the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2. After the addition of a saturated ammonium chloride solution, the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (93:6.9:0.1). This yielded 48 mg (68%) of the desired product which was immediately further deprotected.

To a solution of the amino alcohol (47 mg, 0.077 mmol) in THF (0.8 mL) was added a 1 M solution of TBAF in THF (0.232 mL, 0.232 mmol). The reaction mixture was stirred for 12 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (85:14.7:0.3). This yielded 30.3 mg (80%) of amino diol **27c**: $[\alpha]^{23}_D = -28.07°$, $[\alpha]^{23}_{365} = -82.62°$ (*c* = 1.45, $CHCl_3$); IR (neat) 3384, 2924, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (s, 9H), 0.92 (s, 3H), 0.95 (s, 3H), 1.04 (m, 1H), 1.11 (m, 1H), 1.25 (br s, 1H), 1.29 (dd, 1H, *J* = 13.0 and 13.0 Hz), 1.41 (dd, 1H, *J* = 13.2 and 13.2 Hz), 1.67 (m, 1H), 1.74 (m, 1H), 1.79 (m, 1H), 1.90 (quintet, 2H, *J* = 6.3 Hz), 2.20 (s, 3H), 2.29 (m, 1H), 2.39 (dd, 1H, *J* = 11.9 and 7.8 Hz), 2.55 (m, 2H), 3.50 (dd, 1H, *J* = 9.5 and 4.7 Hz), 3.54−3.69 (m, 6H), 3.88 (m, 1H), 3.91 (m, 1H), 4.51 (s, 2H), 4.65 (s, 2H), 7.27−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.04, 27.93, 29.97, 30.48, 31.20, 32.94, 35.64, 36.07, 37.59, 38.32, 42.15, 44.95, 61.95, 62.34, 64.77, 66.40, 67.11, 67.46, 70.75, 72.91, 95.52, 127.56, 127.65, 128.37, 138.42; MS *m*/*z* (relative intensity) 492 ($M^{\bullet+}$ − H, <0.5), 478 ($M^{\bullet+}$ − CH_3, 1), 436 ($M^{\bullet+}$ − tBu, 1), 58 (100).

Deprotection of the benzyl ether was performed using lithium in liquid ammonia as described for the deprotection of **5c** (reflux time at −33 °C: 4 h). The obtained crude product was purified by flash silica gel chromatography with isooctane:acetone:25% ammonia solution (60:39.2:0.8). This yielded 23.5 mg (93%) of amino triol **8c**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (s, 9H), 0.90 (s, 3H), 0.93 (s, 3H), 1.03 (m, 2H), 1.21 (dd, 1H, *J* = 12. 8 and 12.8 Hz), 1.25 (dd, 1H, *J* = 13.0 and 13.0 Hz), 1.62 (dddd, 1H, *J* = 10.5, 10.5, 3.0 and 2.9 Hz), 1.72 (tt, 2H, *J* = 6.2 and 6.2 Hz), 1.78−1.83 (m, 2H), 2.18 (s, 3H), 2.19 (m, 1H), 2.38 (dd, 1H, *J* = 12.1 and 8.0 Hz), 2.50 (ddd, 1H, *J* = 12.3, 2.5 and 2.5 Hz), 2.58 (dd, 1H, *J* = 12.1 and 12.1 Hz), 3.26 (dd, 1H, *J* = 9.2 and 4.9 Hz), 3.48 (ddd, 1H, *J* = 9.5, 5.9 and 5.9 Hz), 3.53−3.61 (m, 4H), 3.67 (ddd, 1H, *J* = 9.5, 6.7 and 6.7 Hz), 3.77 (m, 1H), 3.78 (m, 1H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.70, 28.16, 30.79, 31.44, 32.35, 33.19, 35.30, 36.15, 38.08, 39.30, 40.73, 44.42, 58.88, 63.53, 63.39, 63.57, 64.30, 66.66, 69.66, 94.78.

(1*S*,2*R*,6*S*)-6-[[*N*-[(2*R*)-2-(Hydroxymethyl)-3,3-dimethylbutyl]-*N*-methylamino]methyl]-2-[[(3-hydroxypropoxy)methoxy]methyl]-4,4-dimethylcyclohexan-1-ol (8t). Amino triol **8t** was prepared in an analogous way which is fully detailed in the Supporting Information. Spectral data for **8t**: R_f (isooctane:acetone:25% ammonia solution (65:34.2:0.8) = 0.2; ^1H NMR($CDCl_3$, 500 MHz) δ 0.82 (dd, 1H, *J* = 12.9 and 12.9 Hz), 0.90 (s, 12H), 0.96 (s, 3H), 1.10 (dd, 1H, *J* = 13.2 and 13.2 Hz), 1.32 (ddd, 1H, *J* = 13.3, 3.3 and 3.3 Hz), 1.40 (ddd, 1H, *J* = 13.1, 3.2 and 3.2 Hz), 1.40−1.43 (m, 1H), 1.69 (tt, 2H, *J* = 6.5 and 6.5 Hz), 1.71−1.81 (m, 2H), 2.20 (s, 3H), 2.21 (m, 1H), 2.34 (dd, 1H, *J* = 12.5 and 2.8 Hz), 2.49 (dd, 1H, *J* = 12.4 and 10.1 Hz), 2.52 (dd, 1H, *J* = 12.3 and 8.3 Hz), 3.09 (dd, 1H, *J* = 9.9 and 9.9 Hz), 3.48−3.64 (m, 8H), 4.58 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 24.99, 28.00, 30.29, 31.59, 31.85, 32.22, 35.52, 39.89, 40.17, 40.76, 41.35, 46.52, 58.01, 58.71, 61.17, 62.47, 66.11, 68.14, 77.79, 94.30.

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Supporting Information Available: Schemes describing the synthesis of derivatives **19**, (*R*)-**20**, *rac*-**4t**, **5t**, **6t**, **8t** and experimental procedures including spectroscopic data for the preparation of these compounds. Detailed procedure for determination of half-live values. X-ray structure of the camphor sulfonate of amine **7c:** atomic coordinates and stereoscopic diagram. X-ray data are deposited with the Cambridge Crystallographic Data Centre. ^1H NMR and ^{13}C NMR spectra for compounds **4c**, **4t**, **5c**, **5t**, **6c**, **6t**, **7c**, **7t**, **8c**, **8t**, *rac*-**11c**, *rac*-**12c**, *rac*-**12t**, *rac*-**15c**, *rac*-**18t** and **24c** (44 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.

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