Design and Preparation of Potent, Nonpeptidic, Bioavailable Renin Inhibitors†

Olivier Bezençon,* Daniel Bur, Thomas Weller, Sylvia Richard-Bildstein, Luboš Remeň, Thierry Sifferlen, Olivier Corminboeuf, Corinna Grisostomi, Christoph Boss, Lars Prade, Stéphane Delahaye, Alexander Treiber, Panja Strickner, Christoph Binkert, Patrick Hess, Beat Steiner, and Walter Fischli

Drug Discovery and Preclinical Research, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

Received January 9, 2009

Starting from known piperidine renin inhibitors, a new series of 3,9-diazabicyclo[3.3.1]nonene derivatives was rationally designed and prepared. Optimization of the positions 3, 6, and 7 of the diazabicyclonene template led to potent renin inhibitors. The substituents attached at the positions 6 and 7 were essential for the binding affinity of these compounds for renin. The introduction of a substituent attached at the position 3 did not modify the binding affinity but allowed the modulation of the ADME properties. Our efforts led to the discovery of compound (+)-**26g** that inhibits renin with an IC_{50} of 0.20 nM in buffer and 19 nM in plasma. The pharmacokinetics properties of this and other similar compounds are discussed. Compound (+)-**26g** is well absorbed in rats and efficacious at 10 mg/kg in vivo.

Introduction

Cardiovascular diseases remain a main cause of mortality and morbidity around the world. In 2005, 17.5 million people died from cardiovascular diseases, more than from any other illness.[1] In particular, hypertension causes 7.1 million premature deaths per year.[2] Moreover, hypertension plays a major etiologic role in the development of cerebrovascular diseases, ischemic heart diseases, and cardiac and renal failures.

The renin−angiotensin−aldosterone system (RAAS[a]) is one of the major and most intensively studied regulating systems of the arterial blood pressure in humans. It plays a primordial role not only in cardiovascular diseases but also in renal diseases and other metabolic diseases as well.[3] The RAAS consists of a two-step cascade. First, the aspartic proteinase renin cleaves its only known substrate, angiotensinogen, in the rate-limiting step to the decapeptide angiotensin I. In a second step, angiotensin I is cleaved either by the metalloproteinase angiotensin-converting enzyme (ACE) or by the serine proteinase chymase to the tensoactive octapeptide angiotensin II. The exclusive and rate-determining function in the RAAS cascade makes renin an ideal pharmacological drug target.

However, from the point of view of a medicinal chemist, renin proved to be a very challenging target. First generation renin inhibitors were highly potent peptidomimetics, like compound **1** (zankiren, IC_{50} value in plasma of 1.1 nM,[4] Figure 1), which suffered from unacceptable low bioavailability. A second generation of inhibitors appeared in the late 1990s. On one hand a new compound class arose from the former peptidomimetic structures and culminated in compound **2** (aliskiren, IC_{50} value in buffer of 0.6 nM), which was approved and launched recently, despite a rather modest oral bioavailability of 4% in humans.[5] On the other hand, piperidine derivatives, which were initially identified from a screening effort, represent a completely new scaffold for renin inhibitors.[6] Extensive efforts in medicinal chemistry were conducted for new compounds that had no resemblance with the natural substrate. Compound **3** (Ro-66-1168; IC_{50} value in buffer of 0.039 nM) is a prominent member of this class.[6d] Unfortunately, these piperidine derivatives were not suitable for clinical development because of inadequate pharmacokinetic properties. Recently, ketopiperazine derivatives, which are a further development of this class, have been found to be renin inhibitors with IC_{50} values as low as 4 nM in buffer.[7] Very recently, 2,4-diaminopyrimidine derivatives were reported to inhibit renin quite potently as well.[8]

Design of a New Class of Renin Inhibitors

On the basis of the temporarily available structural information for piperidine derived renin inhibitors[6c] (e.g., compound **3**), we embarked on structure-based design of new compound classes with improved pharmacokinetic properties. In all three renin structures (PDB codes 1PR7, 1PR8, 1UHQ, meanwhile retracted from the data bank) a protonated secondary amine of the piperidine ring resides between the two catalytically important aspartate residues, thereby expelling the catalytic water. Two strong hydrogen bonds between the protonated ring nitrogen and each of the aspartate carboxylates anchor and orient the piperidine in the active site. Our initial design efforts started with a piperidine moiety located as found in the three template structures mentioned above. The renin inhibitor in 1UHQ occupies part of the S1 and S3 subpockets with its 3-substituent, while the long and flexible 4-substituent intrudes in a large newly formed pocket resulting from a reorientation of the β-hairpin loop, typically dubbed "flap", and synchronous side chain rearrangements of Trp41, Leu73, and Tyr75 (highlighted in red in Figure 2). The S2 pocket, as well as space typically occupied by the substrate backbone, remains unoccupied. It was

† Crystal structures are available at www.rcsb.org. PDB codes are as follows: 3G62, 3G70, 3G72.

* To whom correspondence should be addressed. Phone: +41 61 565 65 77. Fax: +41 61 565 65 00. E-mail: olivier.bezencon@actelion.com.

[a] Abbreviations: ACE, angiotensin cleaving enzyme; Ac, acetyl; ADME, absorption, distribution, metabolism, excretion; Ang, angiotensin; aq, aqueous; Ar, aryl; arom, aromatic; Boc, *tert*-butyloxycarbonyl; BSA, bovine serum albumine; Bu, butyl; *n*-BuLi, *n*-butyllithium; conc, concentrated; DIPEA, diisopropylethylamine; DMAP, 4-*N*,*N*-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; EDC·HCl, ethyl-*N*,*N*-dimethylaminopropylcarbodiimide hydrochloride; EDTA, ethylenediaminetetraacetic acid; EIA, enzyme immunoassay; equiv, equivalent(s); ELSD, evaporative light scattering detector; ESI, electrospray ionization; Et, ethyl; *F*, bioavailability; FC, flash chromatography; HOBt, hydroxybenzotriazol; HPLC, high performance liquid chromatography; LC, liquid chromatography; Me, methyl; org, organic; MS, mass spectrometry; PBS, phosphate buffered saline; Ph, phenyl; phe, phenyl; RAAS, renin angiotensin aldosterone system; R_f, retention factor; sat., saturated; SAR, structure−activity relationship; $T_{1/2}$, half-life; TBAF, tetrabutylammonium fluoride trihydrate; TBDMS, *tert*-butyldimethylsilyl; TBME, *tert*-butyl methyl ether; THF, tetrahydrofuran; T_{max}, time of maximum concentration; Tf, trifluoromethylsulfonyl; TLC, thin layer chromatography; t_R, retention time.

10.1021/jm900022f CCC: $40.75
Published on Web 04/09/2009

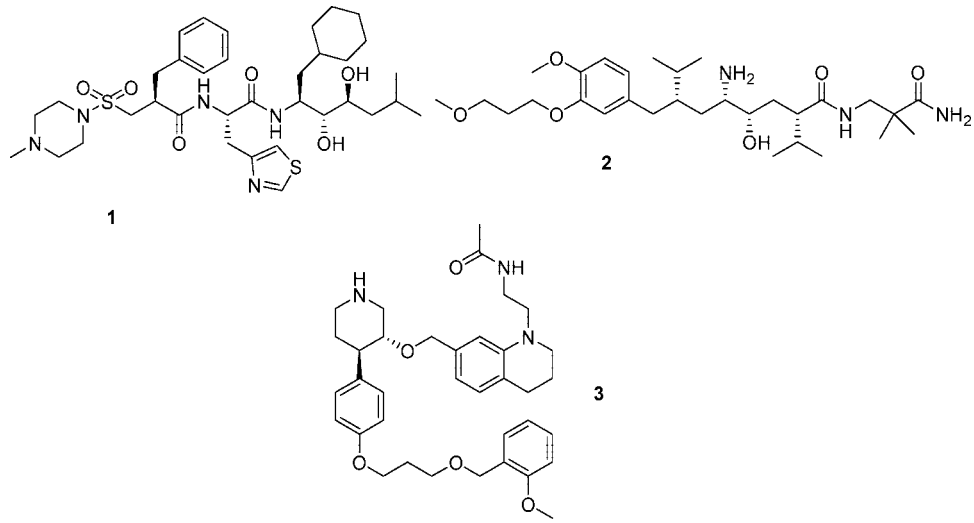


Figure 1. Chemical structures of zankiren (**1**), aliskiren (**2**), and Ro-66-1168 (**3**).

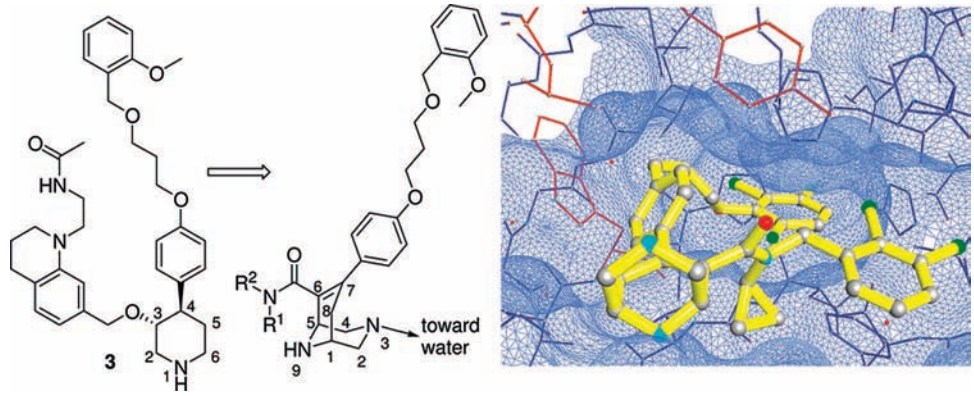


Figure 2. Design of the 3,9-diazabicyclononene template from the corresponding piperidine, with their numbering systems, and X-ray structure of human recombinant renin complexed with (+)-**26h**.

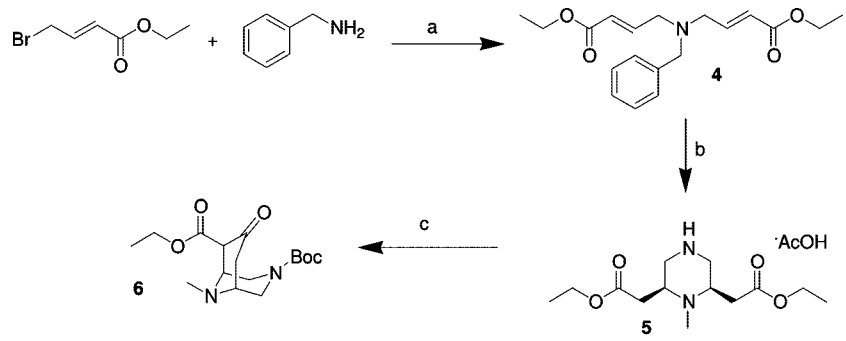
assumed that the extended hydrophobic interactions in the S1, S3 (filled by the tertiary amide in position 6 of the diazabicyclononene in Figure 2), and the "flap" pockets (filled by the substituent attached in position 7 of the diazabicyclononene in Figure 2) are key contributors to the high affinity of this inhibitor. In order to extend the number and direction of template exit vectors, positions 2 and 6 of the piperidine ring were bridged with a C−N−C unit to give a diazabicyclononene moiety (positions 2, 3, and 4 of the diazabicyclononene in Figure 2). This increased structural versatility would allow a better fine-tuning of the physicochemical parameters of our compounds. Introduction of a double bond at the 6,7-position of this bicyclic system simplified synthetic accessibility and diminished compound complexity with minor alteration of the respective exit vectors. The substituent at position 6 had to be altered, since we wanted to refrain from introducing ether substituents at this position in order to avoid the generation of unstable vinylic ethers. Fortunately it turned out that the ester group resulting from the applied synthesis pathway (vide infra) could be easily converted into an amide which led to very potent compounds after some further optimization. The substituent in position 4 of the piperidine ring was transformed to the newly generated position 7 in the bicyclic template but kept constant for initial compounds.

Chemistry

3,9-Diazabicyclononanone derivative **6** (Scheme 1) was prepared in three steps using a slightly modified literature procedure.[9] A double N-alkylation of benzylamine with ethyl 4-bromocrotonate led to tertiary amine **4**. Subsequent double Michael addition with methylamine yielded the corresponding piperazine in a 2:1 cis/trans mixture. After cleavage of the benzyl group, the acetate salt of the cis-isomer **5** crystallized selectively. A subsequent Dieckmann cyclization and protection of the secondary amine with a Boc group led to the racemic 3,9-diazabicyclononanone. Resolution by crystallization with (+)-tartaric acid afforded the pure enantiomer **6** as a key intermediate.[10]

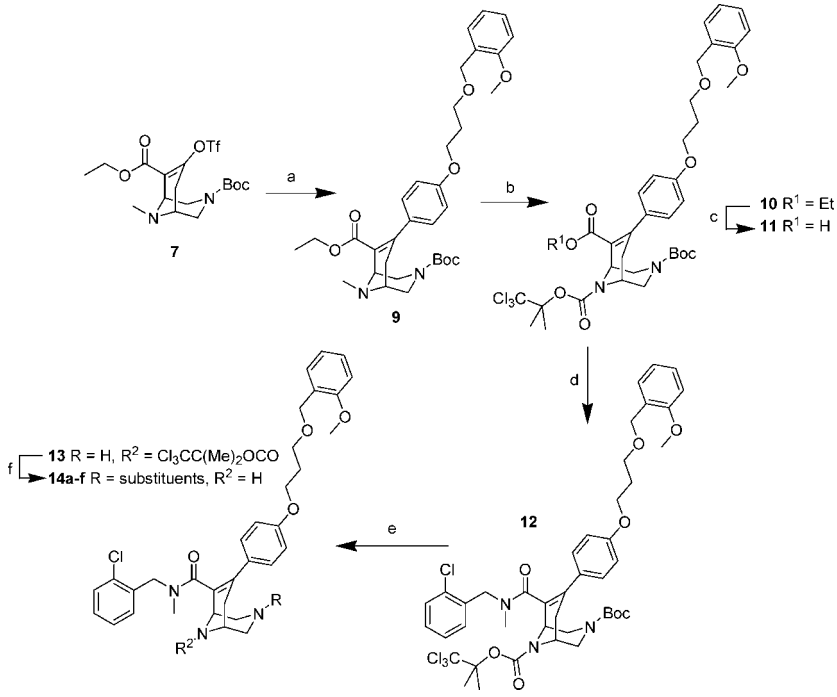
Vinylic triflate **7** (Scheme 2) was prepared from 3,9-diazabicyclononene **6**, using either triflic anhydride or triflimide. A Negishi coupling with 1-bromo-4-[3-(2-methoxybenzoxy)propoxy]benzene **8**[18] led to 3,9-diazabicyclononene **9** in excellent yield. Compound **9** still contained a methyl group at the 9-position of the diazabicyclononene system. Since such an *N*-methyl group on a tertiary amine is generally cleaved under rather harsh conditions, such as using an excess of a chloroformate at reflux in dichloroethane,[11] we decided to replace it by another group as early as possible in the synthesis. A direct transprotection with 2,2,2-trichloro-*tert*-butyl chloroformate yielded the orthogonally protected compound **10**.[12] Saponification of the ethyl ester proceeded at 80 °C to yield compound **11** together with another regioisomer, in which the double bond had shifted to its deconjugated 7,8-position (not represented in Scheme 3). These two compounds were not separated, and tertiary amide **12** was prepared together with its deconjugated regioisomer. At this stage both compounds were separated

Scheme 1[a]



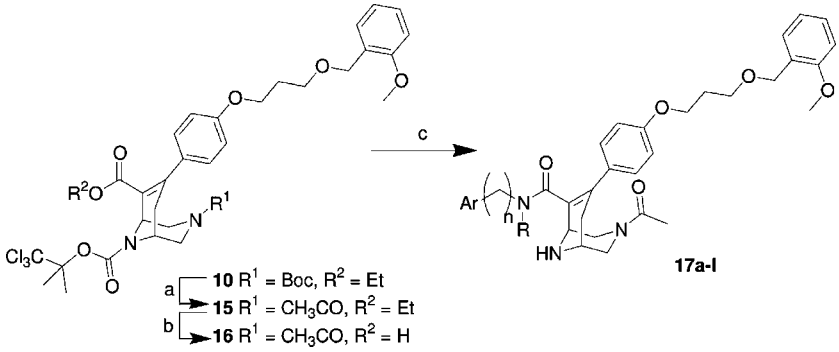
[a] Reagents: (a) Na_2CO_3, EtOH, 40 °C, 65%; (b) (i) $MeNH_2$, EtOH, H_2O, room temp; (ii) H_2, Pd/C, EtOH, AcOH, then *tert*-butyl methyl ether, 47%; (c) (i) NaH, THF, 45 °C; (ii) Boc_2O, Et_3N; (iii) (+)-tartaric acid, acetone, 24%.

Scheme 2[a]



[a] Reagents: (a) **8**, *n*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, THF, −78 °C to reflux, 65%; (b) $Cl_3CC(CH_3)_2OCOCl$, $ClCH_2CH_2Cl$, reflux, 46%; (c) NaOH, H_2O, EtOH, 80 °C; (d) 2-chlorobenzyl-*N*-methylamine, EDC·HCl, HOBt, DMAP, DIPEA, CH_2Cl_2, room temp, 29% over two steps; (e) HCl, dioxane, CH_2Cl_2, 0 °C to room temp, 45%; (f) (i) electrophile, base, CH_2Cl_2, room temp; (ii) Zn, AcOH, THF, room temp, 41−72% over two steps.

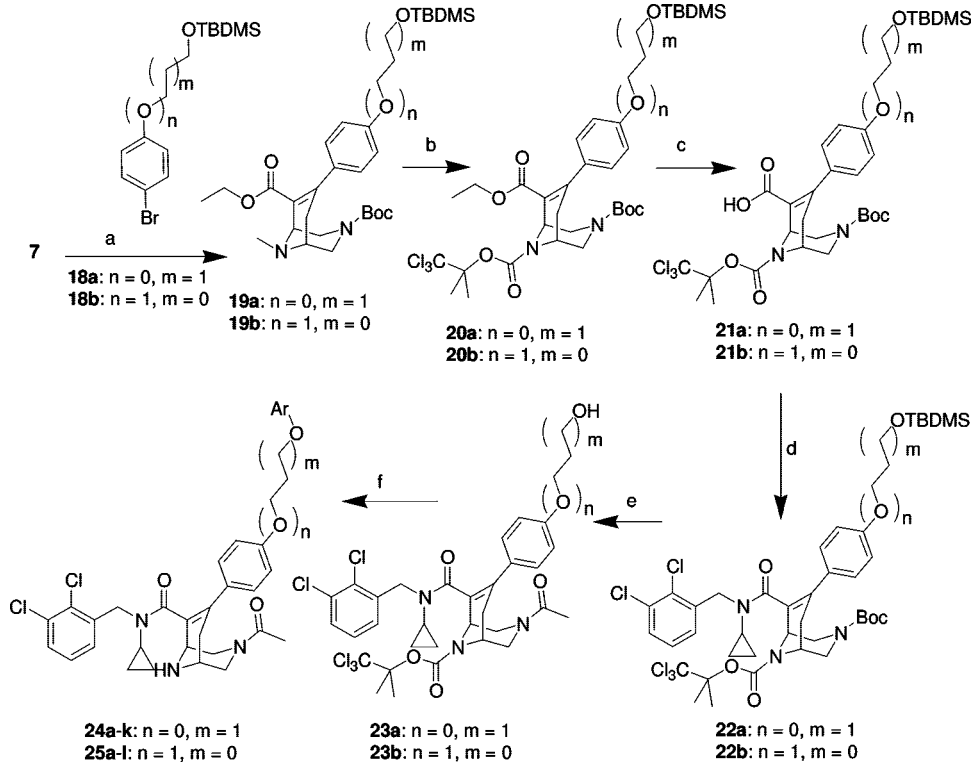
Scheme 3[a]



[a] Reagents: (a) (i) HCl, dioxane, CH_2Cl_2, room temp; (ii) AcCl, DIPEA, CH_2Cl_2, −78 °C, 68%; (b) NaOH, H_2O, EtOH, 80 °C; (c) (i) amine, EDC·HCl, HOBt, DMAP, DIPEA, CH_2Cl_2, room temp; (ii) Zn, AcOH, THF, room temp, 8−46% over three steps.

chromatographically. Selective cleavage of the Boc group yielded compound **13** as a first scaffold ready for parallel chemistry. Alkylation or acylation of compound **13** and final deprotection led to the desired compounds **14a**−**f**.

Scheme 4[a]



[a] Reagents: (a) *n*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, THF, −78 °C to reflux, 63−85%; (b) $Cl_3CC(CH_3)_2OCOCl$, CH_2ClCH_2Cl, reflux, 69−75%; (c) (i) NaOH, H_2O, EtOH, 80 °C, 95%; (ii) TBDMS-Cl, imidazole, DMF, room temp; (iii) K_2CO_3, THF, MeOH, H_2O, room temp; (d) 2,3-dichlorobenzylcyclopropylamine, EDC·HCl, HOBt, DMAP, DIPEA, CH_2Cl_2, room temp, 35−38% over four steps; (e) (i) HCl, dioxane, CH_2Cl_2; (ii) AcCl, DIPEA, CH_2Cl_2, −78 °C, 71−84%; (f) (i) ArOH, 1,1′-(azodicarbonyl)dipiperidine, PBu_3, toluene, 80 °C to reflux, 90 min; (ii) Zn, AcOH, THF, room temp, 11−39%.

The Boc group of compound **10** was cleaved as well, and subsequent acetylation yielded acetamide **15** (Scheme 3). Saponification of the ethyl ester led to carboxylic acid **16** that was directly used for amide couplings. Again, the amide products were obtained together with their corresponding, deconjugated regioisomers, and the two compounds were separated chromatographically before final deprotection. Subsequent removal of the trichloro-*tert*-butylcarbamate yielded compounds **17a**−**l**.

Finally modifications at the 7-position of the diazabicyclononene template were undertaken as well. The synthesis started by a Negishi coupling between vinylic triflate **7** and the corresponding bromophenyl derivatives **18a** and **18b**, respectively (Scheme 4, compounds **19a** and **19b**). A transprotection with 2,2,2-*tert*-butyl chloroformate yielded the corresponding 3,9-diazabicyclonene derivatives **20a** and **20b**. Saponification of these ethyl esters and reintroduction of the hydrolyzed silyl protecting groups afforded the corresponding carboxylic acids **21a** and **21b**, again together with their corresponding regioisomers presenting a shifted double bond at the 7,8-position. In these cases, subsequent amide couplings from these regioisomeric mixtures yielded the desired amide products **22a** and **22b**, respectively, with the double bond moving back to the desired position in a ratio ranging from 9:1 to 19:1, provided 1 equiv of HOBt and a secondary amine bearing an *N*-cyclopropyl substituent were engaged.[13] Acidic treatment of amides **22a** and **22b** cleaved both the Boc and silyl protecting groups; subsequent acetylations yielded alcohols **23a** and **23b**. Construction of libraries via Mitsunobu couplings and final deprotections yielded compounds **24a**−**k** and **25a**−**l**, respectively.

Proof of Concept

A small library generated by varying substituents at the N3-position of the diazabicyclononene template delivered compounds **14a**−**f**, yielding very promising IC_{50} values for renin inhibition (Table 1). The new diazabicyclononene template, with a tertiary amide substituent replacing the 1-(2-acetylaminoethyl)-1,2,3,4-tetrahydroquinolin-7-ylmethoxy substituent present at the corresponding position in compound **3**, was validated. Compounds **14a**−**f** are highly potent renin inhibitors displaying single digit nanomolar IC_{50} values in buffer. Variations at the N3-position of the 3,9-diazabicyclononene template did not result in a distinct structure−activity relationship (SAR). In agreement with our model predicting N3-substituents to reside at the interface of enzyme and solvent, a phenylacetyl (**14a**), a thiophenylacetyl (**14c**), or the much smaller acetyl derivative (**14d**) had similar inhibitory power. Even a sulfonyl group was tolerated equally well (**14b**), while very small substituents like a methyl group (**14e**) or hydrogen (compound **14f**) led to a marginal loss of affinity in buffer.

Table 1. Affinity of the First Diazabicyclononene Derivatives toward Renin

compd	R	IC_{50} in buffer[a]	IC_{50} in plasma[a]
14a	4-ClPhCH_2CO−	1.0	130
14b	PhCH_2SO_2−	4.8	170
14c	2-thiophenyl-CH_2CO−	1.6	278
14d	CH_3CO−	3.2	86
14e	Me−	5.2	86
14f	H−	6.8	129

[a] IC_{50} values determined in aqueous buffer or human plasma. Values in nM.

IC_{50} values were also determined in human plasma. Whether renin should be inhibited in blood, in tissue, or in both is still a matter of debate. Nevertheless, measuring the inhibitory affinity of our compounds in human plasma proved to be an excellent means to take into account the plasma protein binding and consequently the free fraction available in vivo for renin

Table 2. Optimization of the Amide Substituent at Position 6

compd[a]	*n*	R	Ar	IC_{50} in buffer[b]	IC_{50} in plasma[b]
17a	1	H	phenyl	458	7500
17b	1	H	2-Cl-phe	116	3600
17c	1	Me	phenyl	13	122
17d	2	Me	phenyl	8.3	167
17e	3	Me	phenyl	13	640
17f	1	cyclopropyl	2-Cl-phe	0.77	25
17g	1	cyclopropyl	3-Cl-phe	1.5	242
17h	1	cyclopropyl	4-Cl-phe	5.2	456
17i	1	cyclopropyl	2,3-di-Me-phe	0.25	8.8
17j	1	cyclopropyl	2,3-di-Cl-phe	0.20	9.1
17k	1	cyclopropyl	2-Me-3-MeO-phe	0.62	29
17l	1	cyclopropyl	2-Me-3-MeO-pyridin-4-yl	1.4	18

[a] For the preparation of noncommercially available amine, see Supporting Information. [b] IC_{50} values determined in aqueous buffer or human plasma. Values in nM.

inhibition. Except for compounds (+)-**26g** and (+)-**26h** (vide infra), which were more than 99% protein bound in human, rat, dog, and monkey plasma, plasma protein binding was not directly measured. Since the free fraction of all compounds was presumably very low, a precise, relevant measurement would have been very delicate. As a matter of fact, we observed an excellent correlation between IC_{50} values in plasma and the pharmacological effects for given inhibitor concentrations in blood, and we assumed that the ratio of the IC_{50} values measured in buffer and in plasma reflected the free fraction of our compounds in plasma. IC_{50} values determined in plasma for compounds **14a**−**f** are shifted upward by about a 100-fold over the values determined in buffer for compounds with hydrophobic N3 substituents (compounds **14a** and **14c**) and by about a 25-fold for a more polar sulfonamide (compound **14b**). Compounds **14e**−**f** with smaller groups at the N3-position displayed shifts in a range between 15 and 25, making them more potent in plasma than compounds **14a**−**c**. There seems to exist a certain correlation between the available free fraction, size and polarity of the inhibitors: for compounds **14a**−**c**, clogP varies from 5.5 to 6.3, while clogP varies between 4.1 and 4.4 for compounds **14d**−**f**. Similarly, the molecular weight varies from 699 to 729 for compounds **14a**−**c** and from 575 to 617 for compounds **14d**−**f**.

Optimization of the 6-Position

After validation of the central 3,9-diazabicyclononene as a useful template, improvement of the inhibitor potency by optimizing its substituents was undertaken. For the sake of minimal inhibitor size an acetyl at the N3-position of the bicyclic system was used in the following libraries. New substituents in position 6 were introduced by converting acid **16** to a library of secondary and tertiary amides, respectively (Table 2). While the secondary amide with an unsubstituted benzyl group (**17a)** was only weakly active, the 2-chloro derivative **17b** displayed a slightly improved affinity in buffer. However, converting compound **17a** to the tertiary methylamide **17c** improved this affinity by a factor of more than 30. The superiority of tertiary amides compared to secondary amides seems to have multiple reasons. (a) In the group of secondary amides (e.g., **17a**) the amide N−H has to be desolvated in an enthalpically unfavorable process before binding to renin. Since the inhibitor is unable to form a new hydrogen bond upon binding, a decreased binding energy and therefore inhibitory power emerge if compared with amide **17c**. (b) If compared with the secondary amide **17a**, the tertiary amide unit is forced into a different conformation, more favorable for binding to renin, in which the amide bond is perpendicular to the C6−C7 double bond. This is due to repulsions between the R- and Ar-substituents of compounds **17** on one hand, and the hydrogen atom attached at position 5 and the phenyl substituent attached at position 7 of the bicyclic system on the other hand. (c) The newly introduced R-substituents in the tertiary series point into a small subpocket of renin with a cyclopropyl ring (**17f** vs **14f**, Table 1), yielding best results. Interestingly the linker length between the terminal phenyl and amide unit did not discriminate IC_{50} values in the buffer assay (**17c**, **17d**, and **17e**) but the shortest (methylene) linker led to the lowest IC_{50} value in plasma. We therefore concentrated on easily available benzylamides ($n = 1$). Optimization of the terminal aryl group was lengthier. After extensive use of parallel chemistry, we found that small and hydrophobic ortho- and meta-substituents generally tended to improve affinity (e.g., **17f**, **17g**, vs **17h**) with optimal results obtained for the 2,3-dimethyl- (**17i**) and 2,3-dichloro-substituted compounds (**17j**), respectively. Interestingly, compound **17f**, with a 2-chloro substituent, displays a much lower IC_{50} value in plasma than compounds **17g** and **17h**, with a 3- and 4-chloro substituent, respectively. We do not have any explanation for this increased potency in plasma. The 2-methyl-3-methoxy pattern led to a slight loss in activity (**17k**). Introduction of a more polar, terminal 4-pyridinyl was well tolerated (**17l**) and had a slightly beneficial effect on affinity in plasma.

Replacement of the Lengthy Linker and Further Optimization at the 7-Position

After successfully optimizing position 6 of our template, we refocused our efforts on position 7. Unfortunately, until this time all compounds failed to display sufficient metabolic stability. Compound **17j** was rapidly metabolized in human and rat microsomal suspensions. The most labile part was postulated to be the terminal methoxybenzyl unit of the substituent in position 7. We strived to (a) replace this benzylic ether group and (b) to shorten the lengthy linker between the two aromatic rings. As suggested by modeling, we focused on two four-atom tethers, one being a propyl-3-oxy linker (**24** series) and the second a 1,2-ethylenedioxy linker (**25** series). The former was expected to be a bit longer, since the second is known to prefer a compact, gauche arrangement. A series of differently substituted terminal phenyl rings was modeled and eventually introduced.

Since **17j** was the most potent compound in our previous series (**17a**−**l**), its 2,3-dichlorobenzylcyclopropylamide moiety was kept in position 6 for further optimizations. Here again, the preparation of a large number of compounds led to a rather complex SAR for the terminal aromatic ring of the 7-substituent, which was divided into two sections depending on the linker type between the two aromatic rings (Table 3). The SAR proved to be a complex mix of steric and electronic effects on the phenyl ring. The optimal combination of substituents was found after an extensive use of parallel chemistry only. Both suggested linkers eventually delivered subnanomolar compounds; however, they required differently substituted terminal phenyl rings for optimal results. Indeed, while the propyl-3-oxy linker preferred to be in an extended conformation, the 1,2-ethylenedioxy unit is exclusively found in the preferred gauche conformation (Figure 3a). The conformational preferences of each linker affected their overall length, and therefore, substitution patterns at the terminal phenyl rings had to be chosen appropriately. In both series an unsubstituted terminal phenyl (**24a**, **25a**) turned out to be only moderately potent. While the introduction of a chloro substituent in position 2 was beneficial in both series

Table 3. Optimization of the Terminal Phenoxy Moiety at Position 7

	propyl-3-oxy linker			1,2-ethylenedioxy linker		
Ar	compd	IC_{50} in buffer[a]	IC_{50} in plasma[a]	compd	IC_{50} in buffer[a]	IC_{50} in plasma[a]
phe	**24a**	7.7	699	**25a**	8.5	590
2-Cl-phe	**24b**	1.4	188	**25b**	4.9	384
3-Cl-phe	**24c**	16	1560	**25c**	10	1100
4-Cl-phe	**24d**	38	1580	**25d**	7.0	694
2-MeO-phe	**24e**	19	1900	**25e**	6.6	415
2-Br-5-F-phe	**24f**	2.4	229	**25f**	4.6	582
2,6-diCl-4-Me-phe	**24g**	0.83	60	**25g**	0.16	7.1
2,6-diCl-4-F-phe	**24h**	1.0	257	**25h**	0.35	29
2,3,6-triF-phe	**24i**	0.48	26	**25i**	0.79	54
3-Cl-2,6-diF-phe	**24j**	0.28	50	**25j**	1.5	101
2-Cl-3,6-diF-phe	**24k**	0.29	24	**25k**	0.33	34
2,6-diCl-3,4-diMe-phe[b]				**25l**	0.30	40

[a] IC_{50} values determined in aqueous buffer or human plasma. Values in nM. [b] For preparation of the corresponding phenol, see Supporting Information.

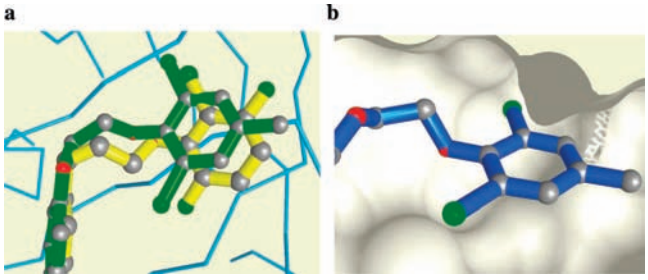


Figure 3. X-ray structure analysis: (a) linker and terminal aromatic ring of 7-substituents in (+)-**26h** (green) and (+)-**26g** (yellow); (b) view of 7-substituent of (+)-**26g** (blue) with 1,2-oxoethylene linker in preferred gauche conformation and exit vector of linker forced out of plane by two bulky chlorines in position 2,6 of terminal phenyl ring.

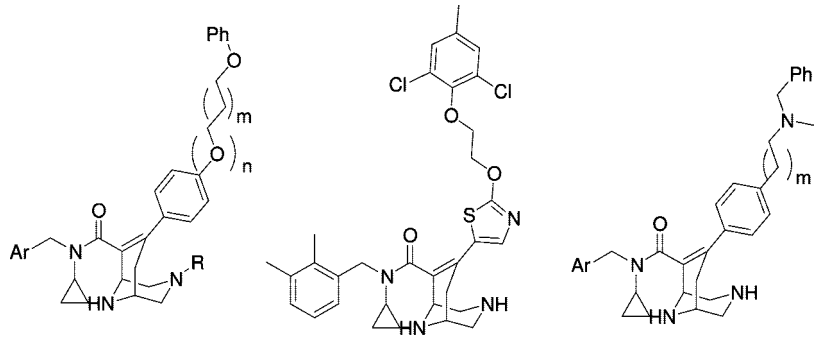
(**24b**, **25b**), shifting this halogen to the meta-position (**24c**) or especially the para-position (**24d**) turned out to be quite unfavorable in the series with the extended propyl-3-oxy linker. This negative trend was less pronounced in the second series (compare **24b**−**d** vs **25b**−**d**). With a very long and flexible linker as found in **3**, a terminal 2-methoxybenzyl substituent yielded a very potent inhibitor.[6] However, in our propyl-3-oxy linker series, a terminal 2-methoxyphenyl (**24e**) was even less active than the unsubstituted phenyl ring. All compounds comprising a terminal 2,6-disubstituted phenyl turned out to be superior to compounds lacking this substitution pattern (compare compounds **a**−**f** vs **g**−**l** in **24** and **25** series). Two reasons might be responsible for this required substitution pattern. First, the optimal hydrophobic 2-chloro substituent fits snuggly into a hydrophobic pocket while the 6-substituent fills a gap between the terminal aromatic rings of template substituents 6 and 7. Second, the two phenyl substituents force the O−C vector of the linker out of the plane defined by the phenyl ring. This conformationally strained arrangement is enforced by this 2,6-substitution pattern and turned out to be favorable for binding into the active site (Figure 3b). Inhibitors with an additional 4-phenyl substituent were slightly less potent in the longer propyl-3-oxy linker series (**24** series) probably because of steric repulsions (compare **24g** and **24h** with **25g**, and **25h**). The SAR for compounds comprising the shorter 1,2-ethylenedioxy linker was slightly different. Inhibitors comprising an unsubstituted phenyl (**25a**) or a monosubstituted phenyl (**25b**−**e**) displayed moderate affinities only. However, a substituent at the 4-position (**25d**) was well accepted here. An extensive study with polysubstituted phenoxy derivatives revealed the 2,6-dichloro-4-methylphenyl (**25g**) to be the optimal terminal aromatic in position 7. A smaller substituent in the para-position (**25h**) only slightly reduced potency. Shifting the para-substituent to meta-position and/or changing its size affected affinity only moderately (**25i**−**k**). Interestingly, an additional 3-methyl group added to our best terminal aromatic was well tolerated (**25l**). Noteworthy, compound **25g**, which comprises the same 6-substituent as **17j**, displays the same affinity in plasma, clearly demonstrating that the newly designed, short 1,2-dioxoethylene linker in substituent 7 is at least as good as its longer predecessor in **17j**. Compound **25g** was so far our most potent renin inhibitor in human plasma.

Further Optimizations

While optimizing the 6- and 7-positions of the diazabicyclononene, we kept investigating the effect of different substituents at the N3-position. As noticed earlier, the substitution at this position did not have a profound influence on the affinity in buffer. The substituted compounds (*rac*)-**26a** to (*rac*)-**26c**[14] displayed very similar values as compounds (+)-**26g** (ACT-077825, MK-8141), and (+)- and (−)-**26h** (Table 4). Interestingly, when both enantiomers of compounds **26h** were separated, we realized that they were almost equally potent toward renin inhibition. This proved to be generally the case for all diazabicyclononene derivatives that were not substituted at the N3-position (vide infra for a structural explanation). The upward shifts of the affinity in plasma tended to be elevated and not easily predictable for these N3-substituted compounds. Another common property of the acylated compounds at the N3-position (compounds (*rac*)-**26a** to (*rac*)-**26c**) was their poor bioavailability in Wistar rats (at 10 mg/kg), with very variable half-life times. Removing the polar amide substituent at the N3-position led to compounds (+)-**26g** and (+)-**26h** that were clearly more bioavailable. The replacement of the central phenyl ring by a thiazolyl (compound (+)-**26d**) represents another possibility to introduce some polarity in this type of lipophilic compounds. This led to some success, both in vitro and in vivo, but this compound finally did not display as promising properties as (+)-**26g** or (+)-**26h** regarding its potency in vivo. Furthermore, compound (+)-**26d** showed a significant time dependent inhibition for the CYP 3A4 (shift value of 25 after 30 min of preincubation). Introduction of polarity in the linker, with tertiary amines (e.g., compounds (*rac*)-**26e** and (*rac*)-**26f**), led to a significant loss of affinity for renin while only gaining little bioavailability. In general, permeation was most probably the limiting factor, since $T_{1/2}$ did not correlate with the bioavailability for compounds **26a** to (+)-**26h**. All these compounds are lipophilic, with clogP values varying between 6.6 (**26h**) and 4.8 (**26c**). Experimentally, the log *D* value of compound (+)-**26g** was higher than 4.9, and the log *D* value of compound (+)-**26h** was higher than 4.6 (pH 7.4). Enhancing the molecular weight (MW = 750 for **26a** vs 619 for **26g** or 645 for **26h**) and the number of hydrogen bond acceptors (eight acceptors for **26a**,**b** and seven acceptors for **26c**,**d** vs six for **26e**−**g** and five for **26h**) proved to be extremely detrimental for the bioavailability.

Fine optimization of the IC_{50} values in plasma by modulating the substituents at positions 6 and 7 with the finding described above led to the identification of two optimized compounds, one with a 1,2-ethylenedioxy linker at position 7 of the 3,9-diazabicyclononene (compound (+)-**26g**), and compound (+)-**26h** including the extended propyl-3-oxy linker at its 7-substituent. The substituents in position 6 were marginally different in compounds **26g** and **26h**, respectively. Interestingly, (+)-**26g** demonstrated decreased metabolic activation potential and

Table 4. Further Optimization at the N3-Position and Further Variations



26a-c, 26h: n = 0, m = 1
26g: n = 1, m = 0

26d

26e: m = 0
26f: m = 1

compd	Ar	Ph	R	IC_{50} in buffer[a]	IC_{50} in plasma[a]	$T_{1/2}$ [b]	T_{max} [c]	F [d]
(*rac*)-**26a**	2-Cl-phe	2-Br-5-F-phe	$CO(CH_2)_3CONH_2$	0.55	56	11	4.5	4
(*rac*)-**26b**	2-Cl-phe	2,3,6-triF-phe	$CO(CH_2)_2CONH_2$	0.55	56	2.3	6.0	3
(*rac*)-**26c**	2-Cl-phe	2,3,6-triF-phe	$COCH_2OH$	1.8	356	0.5	0.3	4
(+)-**26d**				0.67	23	5.2	0.5	15
(*rac*)-**26e**	2-Me-3-MeO-phe	2-Cl-3,6-diF-phe		2.9	41	3.6	3	12
(*rac*)-**26f**	2-Me-3-MeO-phe	2,3,6-triCl-phe		2.3	120	7.5	4	17
(+)-**26g**	2,3-diMe-phe	2,6-diCl-4-Me-phe	H	0.20	19	6.3	10	24
(+)-**26h**	2,3-diCl-phe	2-Cl-3,6-diF-phe	H	0.40	36	5.5	10	33
(−)-**26h**	2,3-diCl-phe	2-Cl-3,6-diF-phe	H	0.80	88			

[a] IC_{50} values determined in aqueous buffer or human plasma. Values in nM. [b] In h. [c] In h. [d] In %.

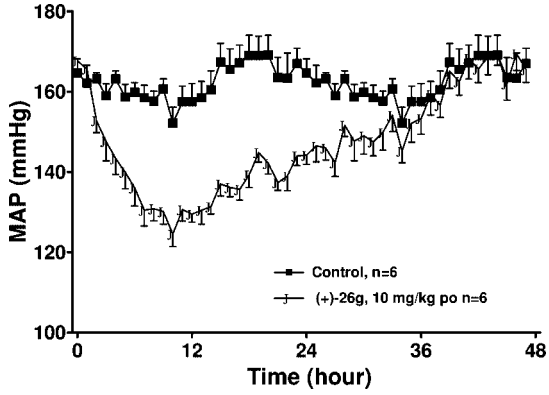


Figure 4. Mean arterial blood pressure (MAP) recordings before (control) and after a single oral administration of 10 mg/kg compound (+)-**26g** to double transgenic rats. Data are expressed as mean ± SEM.

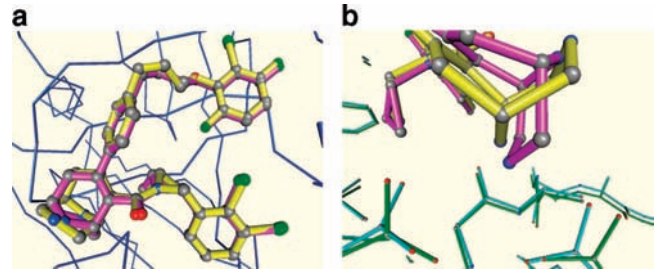


Figure 5. (a) Superposition of X-ray structures of human recombinant renin complexed with (+)-**26h** (yellow) and (−)-**26h** (magenta) respectively. (b) Side view of the bicyclic templates of (+)-**26h** (yellow, protein in blue) with (−)-**26h** superimposed (magenta, protein green).

less in vitro covalent binding to rat and human liver microsomal proteins than (+)-**26h**.[15]

Pharmacodynamics

Oral activity was assessed in female double transgenic rats implanted with a telemetry blood pressure transmitter as previously described.[16] These animals are expressing both human renin and angiotensinogen genes. If left untreated, they develop hypertension and severe albuminuria with serious vascular lesions in the kidney, resulting in ~50% mortality at 7−9 weeks of age.[17] The blood pressure recordings before and after oral administration of compound (+)-**26g** are shown in Figure 4. Compound (+)-**26g** at 10 mg/kg reduced the blood pressure by about 30 mmHg, and the duration of action was close to 36 h. This compound displayed a good pharmacodynamic−pharmacokinetic relationship, since the maximal effect on blood pressure was observed at about 11 h and T_{max} in Wistar rats was 10 h.

Structural Studies by X-ray Crystallography

During our medicinal chemistry campaign we prepared compound (+)-**26h** and its enantiomer (−)-**26h**. Much to our surprise, these two enantiomers were almost equally potent as renin inhibitors in buffer and plasma, respectively, a performance that is rarely seen for compounds of this size and structural complexity. X-ray structures of both compounds ((+)- and (−)-**26h**) complexed to human recombinant renin provided a stupefying simple explanation for this quite unexpected result. A superposition of these two structures revealed the two large substituents in positions 6 and 7 of our bicyclic template superimposed almost perfectly (Figure 5a). However, the central bicyclic template that is responsible for hydrogen bond contact with the two catalytically important aspartates was oriented quite differently. In compound (+)-**26h** nitrogen N9 that is located in the short bridge of the template is perfectly situated between the two aspartates, thereby expelling the catalytically important water and forming two strong H-bonds, one with each of the neighboring aspartates (Figure 5b). In (−)-**26h** the whole template is rotated 180° and shifted away from the aspartates

such that N3 of the three atom bridge is now perfectly located between the two aspartates also establishing hydrogen bonds with each of the aspartates. Obviously, the hydrophobic interactions dominate the positioning of these inhibitors with the pseudosymmetry of the central template being able to establish the necessary hydrogen bonds in either orientation. Substitution of either of the two nitrogen atoms abolishes this pseudosymmetry and completely abrogates this observed effect.

Conclusions

A series of renin inhibitors was discovered by de novo design and lead optimization. The most preferred compound of this series, compound (+)-**26g**, proved to be highly potent in renin inhibition, well absorbed in rats, and efficacious at 10 mg/kg in a double transgenic rat model.

Experimental Section

All solvents and reagents were purchased from commercial sources (Fluka, Aldrich, Lancaster, Acros, Riedel-de-Haen). Palladium catalysts were purchased from Strem Chemicals. Solvents were used undistilled. Dry solvents were purchased on molecular sieves and used directly. All reactions were run under a nitrogen atmosphere. TLC was run on glass plates from Merck coated with silica gel $60F_{254}$. Flash chromatography (FC) was run either in a glass column filled with silica gel 60 from Fluka under a slight positive pressure or using a Flash Master Personal from Argonaut, equipped with IsoluteSPE columns Flash Si II and with a Gilson FC204 fraction collector. Analytical LC−MS was run on one of the following columns: (a) Waters XBridge C18 column, 5 μm, 4.6 mm × 50 mm; (b) Zorbax Extend SB-AQ column, 5 μm, 4.6 mm × 50 mm. Gradient was from CH_3CN/H_2O (5:95) to 100% CH_3CN over 1.5 min. Flow was 4.5 mL/min. For the determination of the enantiomeric ratio, a ChiraCel OD column, 10 μm, 4.6 mm × 50 mm, was used under isocratic conditions (2% EtOH with 0.1% Et_3N and 98% hexane, flow rate of 0.8 mL/min, over 12 min). The LC−MS machines consisted of a Gilson Liquid Handler Micro 215, of Hewlett-Packard Agilent 1100 series pumps, of a Dionex P580 makeup pump, of a Dionex MS detector, of a Dionex UVD 340U UV detector, and of a Sedex 85 LT-ELSD detector. Chemical shifts are in ppm, using Me_4Si (0 ppm) or $CHCl_3$ (7.27 ppm) as reference. The attribution of the signals of the ^1H and ^{13}C NMR spectra was based on COSY, HSQC, and HMBC experiments; as much as is possible, an assignment of the NMR signals is described (see Supporting Information; aromatic signals are not attributed and are characterized with the subscript arom, and Cq stands for a nonattributed quaternally carbon atom). The NMR spectra of compounds **8**−**26** are complex; they consist of at least two rotamers and sometimes display broad signals. The minor rotamer is characterized with a superscripted R. Because of the complexity of the spectra, the integral could not always be determined unambiguously. Unless specified otherwise, the NMR spectra were recorded on a Bruker 400 MHz machine. Spectra measured at 300 MHz were recorded on a Varian machine. IR spectra were recorded on a Perkin-Elmer Spectrum One apparatus, with samples dissolved in $CHCl_3$ and prepared as films. Elemental analysis and Karl Fischer titrations were run at Solvias AG. Optical rotations were measured on a Jasco P-1030 apparatus. Purity of the final compounds was assessed by combustion analysis and/or LC−MS. When assessed by LC−MS, the purity was determined according to the UV trace at 230 and 254 nm.

4-[Benzyl(3-ethoxycarbonylallyl)amino]but-2-enoic Acid Ethyl Ester (4). A 100 L enamelled reactor was charged with EtOH (55 L). Ethyl 4-bromocrotonate (85%, 12.5 kg, 54.8 mol) was added, and the feeding tank was rinsed with EtOH (8 L). DIPEA (15 L, 86 mol) was added at room temperature, and the mixture was heated to 40 °C. Benzylamine (2.95 kg, 27.4 mol) was added over 25 min. The inner temperature increased from 38 to 55 °C. After complete addition, the mixture was stirred at 40 °C overnight. Since the conversion was incomplete, ethyl 4-bromocrotonate (420 mL, 2.29 mol) was added again, and the mixture was stirred at 40 °C for 4 h. The conversion was not complete yet, and ethyl bromocrotonate (150 mL, 0.82 mol) was added again. The mixture was stirred for 16 h at 40 °C. The conversion was complete. The solvents were removed to one-half under reduced pressure, and toluene (58 L) was added. The mixture was washed with water (2 × 28 L). The org layer was extracted with aq 1 M HCl (3 × 36 L). The combined aq extracts were covered with EtOAc (60 L), and the pH was adjusted to 12 by addition of aq 30% NaOH (40 L). The layers were separated, and the aq phase was extracted back with EtOAc (31 L). The combined org extracts were washed with water and evaporated under reduced pressure. EtOH (36 L) was added, and the solvents were removed under reduced pressure. The residue was dried under high vacuum to yield a crude mixture containing the title compound (5.9 kg, 65%). This mixture was use without further without purification. ^1H NMR ($CDCl_3$) 7.31−7.26 (m, 5H), 6.97 (ddd, $J_1 = 15.7$ Hz, $J_2 = J_3 = 5.8$ Hz, 2H), 6.05 (d, $J = 15.7$ Hz, 2H), 4.20 (q, $J = 7.2$ Hz, 4H), 3.63 (s, 2H), 3.24 (dd, $J_1 = 5.8$ Hz, $J_2 = 1.3$ Hz, 4H), 1.31 (t, $J = 7.2$ Hz, 6H). LC−MS: t_R = 0.79 min. MS (ESI): m/z 332.38 $(M + 1)^+$.

***cis*-(6-Ethoxycarbonylmethyl-1-methylpiperazin-2-yl)acetic Acid Ethyl Ester (5).** A solution of compound **4** (11.3 kg, 34.1 mol) in EtOH (70 L) was charged to a 100 L reactor. $MeNH_2$ (30% in EtOH, 5.2 L, 37.5 mol) was added at room temperature, and the mixture was stirred at room temperature overnight. Since the conversion was not complete, $MeNH_2$ (30% in EtOH, 250 mL, 1.84 mol) was added again, and the mixture was stirred overnight at room temperature. Since the conversion was not complete, $MeNH_2$ (30% in EtOH, 260 mL, 1.91 mol) was added again, and the mixture was stirred overnight at room temperature. AcOH (1.1 L) was added, and the pH was adjusted to 5−6. Pd/C (10% on charcoal, 628 g) was added, and the mixture was hydrogenated at 1230 mbar of H_2 at room temperature for 3 days. The mixture was filtered through Celite, and the filter cake was washed with EtOH. The filtrate was charged to a clean reactor and concentrated under reduced pressure. Toluene (34 L) was added, and the solvents were partially (11 L) removed under reduced pressure. The resulting solution was heated to 40 °C, and TBME (52 L) was added. The mixture was stirred for 20 min at 40 °C, was cooled within 3 h to 1 °C, and was stirred at this temperature overnight. The resulting suspension was filtered off, washed with cold TBME (2 × 15 L), and dried under a stream of N_2 for 4 days to yield the acetate salt of the title compound as a colorless solid (4.37 kg). The mother liquor (93 L) was charged to the reactor and was concentrated under reduced pressure. After removal of 70 L of solvents, the resulting solution was heated to 40 °C. TBME (40 L) was added, and the mixture was stirred at 40 °C for 20 min. The mixture was cooled to 1 °C over 2 h and stirred at this temperature overnight. The suspension was filtered, the filter cake was washed with TBME, and the colorless residue was dried overnight under a stream of N_2 to yield the acetate salt of the title compound as a colorless solid (730 g). The mother liquor (91 L) was charged to the reactor and was concentrated under reduced pressure. After removal of 66 L of solvents, the resulting solution was heated to 40 °C. The mixture was cooled to 1 °C over 2 h and stirred at this temperature for 3 days. The mixture was cooled to −10 °C for 2 h. The suspension was filtered, the filter cake was washed with TBME, and the colorless residue was dried for 4 h under a stream of N_2 to yield the acetate salt of the title compound as a colorless solid (251 g). The three crystallization crops were pulled together to yield the title compound as its acetate salt (5.35 kg, 47%). ^1H NMR (CD_3OD) 4.16 (q, $J = 7.1$ Hz, 4H), 3.16 (d, $J = 10.9$ Hz,2H), 2.97 (m, 2H), 2.90 (d, $J = 11.4$ Hz, 2H), 2.65 (dd, $J_1 = 15.8$ Hz, $J_2 = 4.2$ Hz, 2H), 2.56 (dd, $J_1 = 15.8$ Hz, $J_2 = 6.2$ Hz, 2H), 2.31 (s, 3H), 1.95 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 6H). LC−MS: $t_R = 0.57$ min. MS (ESI): m/z 273.41 $(M + 1)^+$.

(1*R*,5*S*)-9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester (6). Toluene (77 L) was charged to a 100 L reactor, and *t*-BuOK (6.48 kg, 57.7 mol) was added at room temperature. The suspension was heated to 40 °C, and the acetate salt of compound **5** (5.35 kg, 16.1 mol) was

added portionwise. The mixture was stirred at 40 °C for 16 h and was cooled to 0−5 °C. AcOH (8.0 L) was added, keeping the inner temperature below 8 °C. The resulting orange-brown suspension was concentrated under reduced pressure until a thick suspension was obtained (60 L of toluene removed). EtOAc (26 L) was added, and the mixture was cooled to 0−5 °C. Et_3N (14 L, 100 mol) was added until a pH of 8−9 was reached. A solution of Boc_2O (3.81 kg, 17.4 mol) in EtOAc (4.2 L) was added over 25 min. The reaction mixture was stirred for 2 h at 0−5 °C and allowed to warm to room temperature over 2 h. The mixture was stirred at room temperature overnight. The mixture was washed with aq 10% K_2CO_3 (16 L). Since the layer separation was sluggish, water (5 L) and EtOAc (10 L) were added. The layers separated overnight. The org layer was washed with water (2 × 16 L). The combined aq layers were extracted back with EtOAc (3 × 16 L). The combined org layers were concentrated under reduced pressure (83 L of org solvents removed). The remaining org mixture was diluted with toluene (40 L), and the resulting mixture was extracted with aq 2.5 M NaOH (3 × 20 L and 4 × 10 L). The combined aq extracts were acidified with aq 6 M HCl (18 L) to pH 6−7 and were extracted back with methylcyclohexane (4 × 40 L). The combined org extracts were filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum to yield the crude racemic title compound (*rac*)-**6** (4.13 kg, 80%) as a slightly yellow oil.

Compound (*rac*)-**6** (100 g, 306 mmol) was dissolved in acetone (500 mL). Separately, (+)-tartaric acid (18.4 g, 122 mmol) was dissolved in acetone (1.0 L). The tartaric acid solution was added dropwise to the bicyclononane solution under stirring. A few crystals of (1*S*,5*R*)-9-methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (+)-tartaric acid salt were added, and the suspension was continuously stirred for 18 h at room temperature. The suspension was filtered, and the precipitate was washed with acetone (100 mL). The precipitate was dried under high vacuum to yield (1*S*,5*R*)-9-methyl-7-oxo-3,9-diazabicyclo[3.3.1]-nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (+)-tartaric acid salt (40 g). The mother liquor was concentrated under reduced pressure, and the oily residue was diluted with methyl-*tert*-butyl ether (300 mL) and water (300 mL). $NaHCO_3$ (11 g) was slowly added under stirring until a pH value of 8 was reached. The layers were separated, and the aq layer was extracted with methyl *tert*-butyl ether (100 mL). The combined org extracts were washed with water (200 mL), and the solvents were removed under reduced pressure. The residue was dissolved in acetone (500 mL), and a solution of (−)-tartaric acid (21.9 g, 145 mmol) in acetone (500 mL) was added dropwise under stirring. A few crystals of (1*R*,5*S*)-9-methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (−)-tartaric acid salt were added, and the suspension was continuously stirred for 18 h at room temperature. The suspension was filtered, and the precipitate was washed with acetone (100 mL). The precipitate was dried under high vacuum to yield (1*R*,5*S*)-9-methyl-7-oxo-3,9-diazabicyclo[3.3.1]-nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (−)-tartaric acid salt (55 g). This salt was recrystallized from isopropanol (145 mL). The obtained crystals were dissolved in a stirred mixture of water (275 mL) and CH_2Cl_2 (275 mL). $NaHCO_3$ (27 g) was added in portions until a pH of 8 was reached. The layers were separated, and the aq layer was extracted with CH_2Cl_2 (150 mL). The combined org extracts were washed with water (275 mL), dried over Na_2SO_4, and filtered. The solvents were removed under reduced pressure to yield the title compound (30 g, 30% for the resolution step) that crystallized spontaneously. Mp = 54.8−55.3 °C. Chiral HPLC: t_R = 8.43 min, er = 99.9:0.01. ^{1}H NMR ($CDCl_3$, 400 MHz) 12.1 and 12.0 (s, broad, 1H), 4.23 (m, 2H), 4.13 and 3.92 (d and m, J = 12.9 Hz, 1H, rot), 3.92 and 3.80 (m and d, J = 12.7 Hz, 1H, rot), 3.57 and 3.53 (s, 1H, rot), 3.13 and 3.02 (m and d, J = 10.9 Hz, 1H, rot), 3.06 and 2.94 (d, and m, J = 12.8 Hz, 1H, rot), 2.94 (s, 1H), 2.63 (m, 1H), 2.34 (s, 3H), 2.13 and 2.01 (d and d, J = 19.2 and 18.8 Hz, 1H, rot), 1.41 and 1.34 (s, 9H, rot), 1.32 (m, 3H). IR (film): ν 2973, 2930, 2146, 1681, 1635 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.59; H, 7.87; N, 8.57.

(1*R*,5*S*)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester (7). A solution of compound **6** (50 g, 153 mmol) in dry THF (900 mL) under N_2 was cooled to 0 °C. NaH (55% in oil, 8.35 g, 191 mmol) was added slowly (gas evolution was seen) while keeping the temperature under 10 °C. The mixture was stirred for 1 h, and Tf_2NPh (65.7 g, 183 mmol) was added. The reaction mixture was stirred overnight while warming to room temperature. The reaction mixture was poured onto ice/distilled water mixture (1.5 L), and the solvents were partially removed under reduced pressure. The aq residue was extracted with EtOAc (3 × 350 mL). The combined org layers were washed with water (375 mL) and brine (350 mL). The org layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield a yellow oil. Purification of the crude by FC (EtOAc/heptane 5:95 to 3:7) yielded the title compound (61.3 g, 87%) as a yellow oil. R_f = 0.20 (EtOAc/heptane 1:4). ^{1}H NMR ($CDCl_3$) 4.33 (q, J = 7.0 Hz, 1H), 4.16 (d, J = 12.6 Hz, 1H), 4.09 (d, J = 12.3 Hz, 1H^R), 4.00 (d, J = 13.2 Hz, 1H), 3.83 (s, 1H^R), 3.77 (s, 1H), 3.19 (d, J = 12.7 Hz, 1H), 3.04 (broad, d, $J \approx$ 9.9 Hz, 2H), 2.75 (dd, J = 18.8, 6.4 Hz, 1H), 2.436 (s, 3H), 2.24 (d, J = 19.3 Hz, 1H), 1.40 (broad, s, 9H), 1.37 (t, J = 7.1 Hz, 3H). IR (film) ν 2977, 2934, 1694 cm^{-1}. Anal. Calcd for $C_{17}H_{25}F_3N_2O_7S$: C, 44.54; H, 5.50; F, 12.43; N, 6.11; S, 6.99. Found: C, 45.02; H, 5.42; F, 12.42; N, 6.04; S, 7.07. $[\alpha]_D^{25}$ +23.0 (1.0, MeOH). MS (ESI): t_R = 0.87, m/z 561.69 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester (9). A solution of bromide **8**[18] (53.5 g, 152 mmol) in THF (1050 mL) was treated at −78 °C with *n*-BuLi (1.6 M in hexane, 130 mL, 208 mmol) under N_2. After 30 min of stirring at −78 °C, a solution of $ZnCl_2$ (1 M in THF, 249 mL, 249 mmol) was added and the mixture was allowed to warm to room temperature. Triflate **7** (63.4 g, 138 mmol) in THF (40 mL) was added, followed by $Pd(PPh_3)_4$ (4.00 g, 3.00 mmol). The mixture was heated to 65 °C for 1 h and after cooling to room temperature was quenched with aq sat. NH_4Cl (400 mL). The mixture was partitioned between EtOAc and water. The org layer was concentrated, and the residue was purified by FC (5−50% gradient EtOAc in heptane) to provide the title compound (52.4 g, 65%). ^{1}H NMR ($CDCl_3$): 7.37 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 6.5 Hz, 1H^R), 7.26 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 4.59 (s, 2H), 4.24 (d, J = 13.0 Hz, 1H), 4.11 (t, J = 6.0 Hz, 2H), 4.06−3.87 (m, 2H and 2H^R), 3.94 (broad, d, $J \approx$ 13.6 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 1H), 3.72 (t, J = 5.9 Hz, 2H), 3.19 (d, J = 13.2 Hz, 1H), 3.12 (d, J = 12.7 Hz, 1H), 2.98 (broad, d, 1H), 2.57 (dd, J = 19.6, 6.3 Hz, 1H), 2.47 (s, 3H^R), 2.43 (s, 3H), 2.36 (d, J = 19.8 Hz, 1H), 2.12 (broad, t, $J \approx$ 6.0 Hz, 2H and 1H^R), 1.97 (d, J = 18.8 Hz, 1H), 1.42 (broad, s, 9H^R), 1.38 (broad, s, 9H), 0.94 (t, J = 6.8 Hz, 2H). IR (film) ν 2930, 1689 cm^{-1}. Anal. Calcd for $C_{33}H_{44}N_2O_7$: C, 68.25; H, 7.64; N, 4.82. Found: C, 66.35; H, 7.51; N, 4.73. $[\alpha]_D^{25}$ +7.0 (1.00, MeOH). LC−MS: t_R = 0.92 min. MS (ESI): m/z 581.51 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (10). A suspension of starting material **9** (20.6 g, 35 mmol), $NaHCO_3$ (29.8 g, 355 mmol), and β,β,β-trichloro-*tert*-butylchloroformate (17 g, 71 mmol) in 1,2-dichloroethane (360 mL) was stirred under N_2 at 80 °C overnight. After cooling to room temperature, the mixture was filtered, concentrated, and the residue was purified by FC (2−50% gradient EtOAc in heptane) to provide the title compound (12.6 g, 46%). ^{1}H NMR ($CDCl_3$) 7.38 (d, J = 7.3 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 6.5 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 5.27 (s, 1H), 5.23 (s, 1H^R), 5.12 (s, 1H^R), 4.58 (s, 2H), 4.42 (broad, s, 1H and 1H^R), 4.32 (d, J = 13.4 Hz, 1H), 4.13−3.92 (m, 3H and 5H^R), 4.10 (t, J = 6.1 Hz, 2H), 3.83 (s, 3H), 3.71 (t,

J = 5.8 Hz, 2H), 3.14 (d, J = 13.3 Hz, 1H and $1H^R$), 3.06 (d, J = 11.5 Hz, 1H and $1H^R$), 2.81 (dd, J = 19.6, 6.1 Hz, 1H), 2.53 (d, J = 19.8 Hz, 1H), 2.11 (t, J = 5.9 Hz, 2H), 1.99 (s, 3H), 1.95 (s, 3H), 1.41 (broad, s, $9H^R$), 1.38 (broad, s, 9H), 1.03 (t, J = 6.7 Hz, 2H). IR (film) ν 2978, 1695 cm^{-1}. Anal. Calcd for $C_{37}H_{47}N_2O_9Cl_3 \cdot 0.5H_2O$: C, 57.04; H, 6.16; N, 3.59. Found: C, 57.34; H, 6.09; N, 3.68. $[\alpha]_D^{25}$ −0.3 (0.99;, MeOH). LC−MS: t_R = 1.22 min. MS (ESI): m/z 771.41 $(M + 1)^+$.

(1*R*,5*S*)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (11). A mixture of ethyl ester **10** (5.20 g, 6.70 mmol) in aq 1 M NaOH (74 mL) and EtOH (176 mL) was stirred at 90 °C for 20 h. The EtOH was evaporated, and the mixture was diluted with EtOAc (400 mL) before aq 1 M HCl (30 mL) was added. The org layer was concentrated to provide the title compound together with its deconjugated regioisomer (5.10 g, quant), which was used in the next step without purification. LC−MS: t_R = 1.15 min. MS (ESI): m/z 743.47 $(M + 1)^+$.

(1*R*,5*S*)-6-[(2-Chlorobenzyl)methylcarbamoyl]-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic Acid 3-*tert*-Butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (12). A solution of acid **11** (4.9 g, 6.6 mmol), HOBt (1.1 g, 8.0 mmol), EDC·HCl (3.2 g, 117 mmol), DIPEA (3.4 g, 26 mmol), and DMAP (0.2 g, 1.6 mmol) in CH_2Cl_2 (140 mL) was stirred at room temperature for 30 min. 2-Chloro-*N*-methylbenzylamine[19] (3.10 g, 19.9 mmol) was added, and the reaction mixture was stirred at room temperature for 7 days. Aqueous 1 M HCl (40 mL) was added. The org layer was separated, concentrated, and the residue was purified by FC (1−4% gradient MeOH in CH_2Cl_2) to provide the title compound (1.70 g, 29% over two steps). ^1H NMR ($CDCl_3$) 7.39 (d, J = 7.2 Hz, 1H), 7.32−6.99 (m, 7H), 6.96 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.85−6.72 (m, 2H), 4.78 (d, J = 15.9 Hz, 1H), 4.75−4.37 (m, 6H and $5H^R$), 4.10 (broad, d, 2H), 3.83 (s, 3H), 3.74 (t, J = 5.6 Hz, 2H), 3.50−2.98 (m, 3H and $3H^R$), 2.74, 2.70, 2.54, and 2.43 (3H and $3H^R$), 2.37−2.21 (m, 1H and $1H^R$), 2.14 (t, J = 5.9 Hz, 2H), 1.99 (s, 3H), 1.94 (s, 3H), 1.33 (broad, s, $9H^R$), 1.29 (broad, s, 9H). IR (film) ν 2925, 1697, 1607 cm^{-1}. Anal. Calcd for $C_{43}H_{51}N_3O_8Cl_4$: C, 58.71; H, 5.84; N, 4.78. Found: C, 58.60; H, 5.83; N, 4.98. $[\alpha]_D^{25}$ +47.6 (1.02, MeOH). LC−MS: t_R = 1.26 min. MS (ESI): m/z 880.65 $(M + 1)^+$.

(1*R*,5*S*)-6-[(2-Chlorobenzyl)methylcarbamoyl]-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic Acid 2,2,2-Trichloro-1,1-dimethylethyl Ester (13). A solution of starting material **12** (6.6 g, 7.5 mmol) in CH_2Cl_2 (85 mL) was cooled to 0 °C. HCl (4 M in dioxane, 85 mL) was added, and the mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. Aqueous 2.5 M NaOH (100 mL) was carefully added. The org layer was separated, concentrated, and the residue was purified by FC (1−4% gradient MeOH in CH_2Cl_2) to provide the title compound (2.6 g, 45%). ^1H NMR ($CDCl_3$) 7.39 (d, J = 7.2 Hz, 1H), 7.33−6.99 (m, 7H), 6.96 (t, J = 7.4 Hz, 1H), 6.91−6.75 (m, 3H), 6.63 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 7.3 Hz, 1H), 4.76 (d, J = 15.7 Hz, 1H), 4.68−4.54 (m, 4H and $1H^R$), 4.43−4.26 (m, 1H and $2H^R$), 4.42 (d, J = 15.8 Hz, 1H and $1H^R$), 4.12 (broad, d, 2H), 3.83 (s, 3H), 3.75 (t, J = 5.6 Hz, 2H), 3.45, 3.41 (d and d, J = 12.1 Hz, J = 11.8 Hz, 2H), 3.28−2.87 (m, 2H and $3H^R$), 3.20 (d, J = 15.9 Hz, 1H), 2.75, 2.71, and 2.59 (3H and $2 \times 3H^R$), 2.25−2.03 (m, 2H and $1H^R$), 2.10 (t, J = 5.7 Hz, 2H), 2.00 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.86 (s, 3H). IR (film) ν 2908, 1698, 1606 cm^{-1}. Anal. Calcd for $C_{38}H_{43}N_3O_6Cl_4$: C, 58.55; H, 5.56; N, 5.39. Found: C, 58.40; H, 5.51; N, 5.40. $[\alpha]_D^{25}$ +18.6 (1.0, MeOH). LC−MS: t_R = 1.08 min. MS (ESI): m/z 780.11 $(M + 1)$.

General Procedure for the Preparation of Compounds 14a−d. To a solution of compound **13** (0.4 g, 0.51 mmol) and acyl chloride or sulfonyl chloride (0.56 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.67 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C. The mixture was diluted with CH_2Cl_2 (5 mL), and aq 1 M HCl (10 mL) was added. The org layer was concentrated, and the product was used in the next step without purification. A suspension of the obtained crude, acylated/sulfonated compound (∼0.4 mmol) and Zn powder (4 mmol) in THF (10 mL) was stirred in the presence AcOH (0.25 mL) at room temperature for 3 h. The mixture was filtered through Celite, and the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and aq 0.1 M EDTA (5 mL) was added. The mixture was stirred at room temperature for 6 h. The org layer was concentrated under reduced pressure, and the residue was purified by FC (1−5% MeOH in CH_2Cl_2) to provide compounds **14a−d**.

(1*R*,5*S*)-3-Acetyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic Acid 6-Ethyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (15). A solution of starting material **10** (37.1 g, 48.2 mmol) in CH_2Cl_2 (360 mL) was cooled to 0 °C. HCl (4 M in dioxane, 163 mL) was added, and the mixture was stirred at 0 °C for 20 min and at room temperature for 3.5 h. The mixture was diluted with CH_2Cl_2 (150 mL) before aq 10% Na_2CO_3 (200 mL) was carefully added. The org layer was concentrated under reduced pressure. The residue was dissolved under N_2 in THF (750 mL) and cooled to −78 °C. DIPEA (33 mL, 193 mmol), DMAP (0.59 g, 4.8 mmol), and AcCl (3.8 mL, 53 mmol) were added, and the mixture was stirred at −78 °C for 30 min. MeOH (250 mL) was added, the mixture was allowed to warm up to room temperature, and the solvents were evaporated under reduced pressure. The mixture was diluted with EtOAc (200 mL) before aq 1 M HCl (200 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (10−55% EtOAc in heptane) to provide the title compound (23.4 g, 68%). ^1H NMR ($CDCl_3$) 7.37 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.02−6.92 (m, 3H), 6.90−6.81 (m, 3H), 5.21 (broad, s, $1H^R$), 5.16 (s, 1H), 4.86 (d, J = 13.4 Hz, $1H^R$), 4.82 (d, J = 13.9 Hz, $1H^R$), 4.76 (d, J = 13.4 Hz, 2H), 4.58 (s, 2H), 4.51 (d, J = 7.2 Hz, $1H^R$), 4.46 (d, J = 6.5 Hz, 1H), 4.10 (t, J = 6.3 Hz, 2H), 4.06−3.91 (m, 3H), 3.83 (s, 3H), 3.78 (dd, J = 13.4, 2.2 Hz, $1H^R$), 3.71 (t, J = 6.1 Hz, 2H), 3.49 (dd, J = 13.4, 2.2 Hz, 1H and $1H^R$), 2.98−2.81 (m, 2H and $2H^R$), 2.42 (dd, J = 19.4, 2.2 Hz), 2.11 (t, J = 6.2 Hz, 2H), 2.00, 1.99, 1.96, 1.95 (4s, 4 × 3H), 0.98 (t, J = 7.1 Hz, 2H). IR (film) ν 2927, 1706, 1651 cm^{-1}. Anal. Calcd for $C_{34}H_{41}N_2O_8Cl_3$: C, 57.35; H, 5.80; N, 3.93. Found: C, 57.54; H, 5.87; N, 3.85. $[\alpha]_D^{25}$ +55.3 (1.01, MeOH). LC−MS: t_R = 1.17 min. MS (ESI): m/z 711.41 $(M + 1)^+$.

(1*R*,5*S*)-3-Acetyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic Acid 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (16). A mixture of ethyl ester **15** (20.1 g, 28.2 mmol) in aq 1 M NaOH (430 mL) and EtOH (600 mL) was stirred at 90 °C for 2 h. The EtOH was evaporated under reduced pressure, and the mixture was diluted with EtOAc (400 mL) before aq 1 M HCl (200 mL) was added. The org layer was concentrated to provide the title compound (17.8 g, 93%), which was used in the next step without purification. LC−MS: t_R = 1.07 min. MS (ESI): m/z 683.15 $(M + 1)^+$.

General Procedure for the Preparation of Compounds 17a−l. A solution of acid **16** (1.6 g, 2.3 mmol), HOBt (0.45 g, 3.2 mmol), EDC·HCl (1.2 g, 6.2 mmol), DIPEA (1.3 g, 10 mmol), and DMAP (80 mg, 0.6 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 30 min. The desired amine (7.0 mmol) was added, and the reaction mixture was stirred at room temperature for 1−5 days. The mixture was diluted with CH_2Cl_2 (25 mL) before aq 1 M HCl (25 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (35−50% gradient EtOAc in heptane) to provide the corresponding amide products. A suspension of these amide products (∼1 mmol) and Zn powder (14 mmol) in THF (20 mL) was efficiently stirred in the presence AcOH (0.5 mL) at room temperature for 3 h. The mixture was filtered through Celite, and the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and aq 0.1 M EDTA (5 mL) was added. The mixture was stirred at room temperature for 6 h. The org layer was concentrated under reduced pressure, and the residue was purified by FC (1−5% MeOH in CH_2Cl_2) to provide the products **17a−l**.

(1*R*,5*S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester (19a). A solution of bromide **18a** (55.6 g, 168.8 mmol) in THF (1000 mL) was treated at −78 °C with *n*-BuLi (1.6 M in hexane, 144 mL, 230 mmol) under N_2. After 30 min of stirring at −78 °C a solution of $ZnCl_2$ (1 M in THF, 276 mL, 276 mmol) was added, and the mixture was allowed to warm to room temperature. Triflate **7** (70.35 g, 153 mmol) in THF (200 mL) was added, followed by $Pd(PPh_3)_4$ (4.6 g, 3.8 mmol). The mixture was heated at 65 °C for 1 h and, after cooling to room temperature, was quenched with aq sat. NH_4Cl (500 mL). The mixture was partitioned between EtOAc and water. The org layer was concentrated, and the residue was purified by FC (CH_2Cl_2/MeOH = 98/2) to provide the title compound (54.4 g, 63%). ^{1}H NMR ($CDCl_3$) 7.13 (d, J = 7.4 Hz, 2H), 7.06 (d, J = 7.0 Hz, 2H), 4.24 (d, J = 12.9 Hz, 1H), 4.03−3.84 (m, 3H), 3.77 (s, 1H), 3.70 (s, 1H^R), 3.65 (t,, J = 6.0 Hz, 2H), 3.18 (d, J = 13.2 Hz, 1H), 3.12 (d, J = 12.7 Hz, 1H), 2.98 (broad, s, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.59 (dd, J = 19.7, 6.6 Hz, 1H), 2.47 (s, 3H^R), 2.43 (s, 3H), 2.36 (d, J = 19.8 Hz, 1H), 1.84 (q, 2H), 1.43 (broad, s, 9H^R), 1.39 (broad, s, 9H), 0.93 (s, 9H), 0.86 (t, J = 7.2 Hz, 2H), 0.12 (s, 6H). IR (film) ν 2929, 2857, 1693 cm^{-1}. Anal. Calcd for $C_{31}H_{50}N_2O_5Si$: C, 66.63; H, 9.02; N, 5.01. Found: C, 66.25; H, 8.92; N, 4.98. $[\alpha]_D^{25}$ +1.66 (1.28, MeOH). LC−MS: t_R = 0.98 min. MS (ESI): m/z 559.61 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester (19b). A solution of bromide **18b**[20] (14.7 g, 44.4 mmol) in THF (300 mL) was treated at −78 °C with *n*-BuLi (1.6 M in hexane, 37.8 mL, 60.5 mmol) under N_2. After the mixture was stirred for 30 min at −78 °C, $ZnCl_2$ (1 M in THF, 73 mL, 73 mmol) was added, and the mixture was allowed to warm to room temperature. Triflate **7** (18.5 g, 40.3 mmol) in THF (10 mL) was added, followed by $Pd(PPh_3)_4$ (1.4 g, 1.2 mmol). The mixture was heated at 65 °C for 1 h and, after cooling to room temperature, was quenched with aq sat. NH_4Cl (300 mL). The mixture was partitioned between EtOAc and water. The org layer was concentrated, and the residue was purified by FC (CH_2Cl_2/MeOH = 98/2) to provide the title compound (19.2 g, 85%). ^{1}H NMR ($CDCl_3$): 7.07 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.24 (d, J = 12.9 Hz, 1H), 4.08−3.87 (m, 7H), 3.77 (s, 1H), 3.18 (d, J = 14.5 Hz, 1H), 3.12 (d, J = 12.0 Hz, 1H), 2.98 (d, J = 5.8 Hz, 1H), 2.57 (dd, J = 20.1, 6.5 Hz, 1H), 2.42 (s, 3H, NCH_3), 2.35 (d, J = 19.7 Hz, 1H), 1.40 (broad, s, 9H), 0.93 (s, 12H), 0.12 (s, 6H). IR (film) ν 2928, 2856, 1683, 1607 cm^{-1}. Anal. Calcd for $C_{30}H_{48}N_2O_6Si$: C, 64.25; H, 8.63; N, 5.00. Found: C, 64.08; H, 8.44; N, 5.04. $[\alpha]_D^{25}$ +4.5 (1.0, MeOH). LC−MS: t_R = 0.98 min. MS (ESI): m/z 561.69 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (20a). A suspension of starting material **19a** (33.8 g, 60.4 mmol), $NaHCO_3$ (50 g, 604 mmol), and β,β,β-trichloro-*tert*-butylchloroformate (29.9 g, 121 mmol) in 1,2-dichloroethane (700 mL) was stirred under N_2 at 80 °C overnight. After cooling to room temperature, the mixture was filtered, concentrated under reduced pressure, and the residue was purified by FC (5−15% gradient EtOAc in heptane) to provide the title compound (30.7 g, 69%). ^{1}H NMR ($CDCl_3$) 7.13 (d, J = 7.5 Hz, 2H), 7.03 (d, J = 6. Hz, 2H), 5.67 (s, 1H), 5.24 (s, 1H^R), 5.14 (s, 1H^R), 4.41 (broad, s, 1H and 1H^R), 4.32 (d, J = 13.2 Hz, 1H), 4.13 (d, J = 11.8 Hz, 1H^R), 4.09 (d, J = 11.4 Hz, 1H), 4.05−3.87 (m, 2H), 3.65 (t, J = 6.1 Hz, 2H), 3.14 (d, J = 13.3 Hz, 1H and 1H^R), 3.07 (d, J = 13.0 Hz, 1H), 2.83 (broad, dd, $J \approx$ 20.0, 7.0 Hz, 1H), 2.68 (t, J = 7.4 Hz, 2H), 2.52 (d, J = 19.5 Hz, 1H), 2.36 (d, J = 19.8 Hz, 1H), 1.99 (s, 3H), 1.94 (s, 3H), 1.89−1.78 (m, 2H), 1.43 (broad, s, 9H^R), 1.39 (broad, s, 9H), 1.02−0.84 (m, 12H), 0.86 (t, J = 7.2 Hz, 2H), 0.07 (s, 6H). IR (film) ν 2977, 2932, 1694 cm^{-1}. $[\alpha]_D^{25}$ +1.44(1.45, MeOH). LC−MS: t_R = 1.37 min. MS (ESI): m/z 748.86 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 6-Ethyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (20b). A suspension of starting material **19b** (20 g, 35.7 mmol), $NaHCO_3$ (30 g, 356.6 mmol), and β,β,β-trichloro-*tert*-butylchloroformate (17.1 g, 71.3 mmol) in 1,2-dichloroethane (250 mL) was stirred under N_2 at 80 °C overnight. After cooling to room temperature, the mixture was filtered and concentrated under reduced pressure, and the residue was purified by FC (2−15% gradient EtOAc in heptane) to provide the title compound (20.1 g, 75%). ^{1}H NMR ($CDCl_3$): 7.04 (broad, d, $J \approx$ 7.5 Hz, 2H), 6.84 (d, J = 8.1 Hz, 2H), 5.26 (broad, s, 1H^R), 5.23 (broad, s, 1H), 5.12 (broad, s, 1H^R), 4.41 (broad, s, 1H and 1H^R), 4.31 (d, J = 13.5 Hz, 1H), 4.15−3.89 (m, 7H), 3.22−2.93 (m, 2H and 2H^R), 2.84 (dd, $J \approx$ 18.2, 7.6 Hz, 1H), 2.78 (dd, $J \approx$ 18.1, 7.0 Hz, 1H^R), 2.53 (broad, d, $J \approx$ 19.7 Hz, 1H and 1H^R), 1.99 (s, 3H), 1.94 (s, 3H), 1.41 (broad, s, 9H^R), 1.37 (broad, s, 9H), 1.02 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 6H). IR (film) ν 2929, 2857, 1697, 1604 cm^{-1}. Anal. Calcd for $C_{34}H_{51}N_2O_8Cl_3Si$: C, 54.43; H, 6.85; N, 3.73. Found: C, 54.48; H, 6.77; N, 3.74. $[\alpha]_D^{25}$ +1.5 (1.02, MeOH). LC−MS: t_R = 1.28 min. MS (ESI): m/z 751.52 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (21a). A mixture of ethyl ester **20a** (25.0 g, 33.5 mmol) in aq 1 M NaOH (370 mL) and EtOH (870 mL) was stirred at 80 °C for 12 h. The EtOH was evaporated under reduced pressure, and the mixture was diluted with EtOAc (400 mL), before aq 1 M HCl (240 mL) was added. The org layer was concentrated under reduced pressure to provide a mixture of the desilylated acid together with its deconjugated regioisomer (24.5 g), which was used in the next step without purification.

A solution of this crude acid mixture (24.5 g), imidazole (9.1 g, 134 mmol), and TBDMS-Cl (13.3 g, 83.7 mmol) in DMF (500 mL) was stirred under N_2 overnight. The mixture was partitioned between heptane (450 mL) and aq sat. NH_4Cl (450 mL). The org layer was concentrated, and the residue was diluted in THF (420 mL). MeOH (140 mL), water (140 mL), and K_2CO_3 (4.5 g, 32.6 mmol) were added, and the mixture was stirred at room temperature for 1.5 h. The MeOH was evaporated under reduced pressure, and the mixture was diluted with Et_2O (300 mL) before aq sat. NH_4Cl (300 mL) was added. The org layer was concentrated to provide the crude title compound mixed with its deconjugated regioisomer (24.5 g), which was used in the next step without purification. LC−MS: t_R = 1.23 min. MS (ESI): m/z 721.41 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic Acid 3-*tert*-Butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (21b). A mixture of ethyl ester **20b** (49.3 g, 65.7 mmol) in aq 1 M NaOH (788 mL) and EtOH (1100 mL) was stirred at 90 °C for 5 h. The EtOH was evaporated under reduced pressure, and the mixture was diluted with EtOAc (400 mL) before aq 1 M HCl (240 mL) was added. The org layer was concentrated under reduced pressure to provide the crude desilylated carboxylic acid together with its deconjugated regioisomer (40 g). MS (ESI): m/z 607.34 (M + 1)$^+$. A solution of this crude product (40 g), imidazole (13.4 g, 197.2 mmol), and TBDMS-Cl (29.7 g, 197 mmol) in DMF (350 mL) was stirred under N_2 overnight. The mixture was partitioned between heptane (450 mL) and aq sat. NH_4Cl (450 mL). The org layer was concentrated under reduced pressure, and the residue was diluted in THF (450 mL). MeOH (250 mL), water (120 mL), and K_2CO_3 (22.8 g, 164 mmol) were added, and the mixture was stirred at room temperature for 1.5 h. The solvents were partially evaporated under reduced pressure, and the mixture was diluted with Et_2O (450 mL) before aq sat. NH_4Cl (450 mL) was added. The org layer was concentrated under reduced pressure to provide the title compound mixed with its deconjugated regioisomer (45.4 g), which was used in the next step without purification. LC−MS: t_R = 1.20 min. MS (ESI): m/z 723.39 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic Acid 3-*tert*-butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (22a). A solution of acid **21a** (23.9 g, 33.2 mmol), HOBt (5.50 g, 39.9 mmol), EDC·HCl (16.2 g, 83.0 mmol), DIPEA (17.5 g, 132.8 mmol), and DMAP (1.0 g, 8.3 mmol) in CH_2Cl_2 (530 mL) was stirred at room temperature for 30 min. *N*-Cyclopropyl-*N*-(2,3-dichlorobenzyl)amine (21.5 g, 99.6 mmol) was added, and the reaction mixture was stirred at room temperature for 7 days. The mixture was diluted with CH_2Cl_2 (300 mL) before aq 1 M HCl (400 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (3−7% gradient acetone in heptane) to provide the title compound (18.7 g, 35% over two steps). ^{1}H NMR ($CDCl_3$) 7.36 (d, J = 7.6 Hz, 1H), 7.17−6.99 (m, 5H), 6.96 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H^R), 4.78 (broad, d, $J \approx$ 15.2 Hz, 2H), 4.73−4.44 (m, 2H and 4H^R), 4.35 (d, J = 15.4 Hz, 1H), 4.23 (d, J = 13.0 Hz, 1H), 4.09 (d, J = 13.0 Hz, 1H^R), 3.70−3.57 (m, 2H), 3.31−2.98 (m, 1H and 3H^R), 3.16 (broad, d, $J \approx$ 12.8 Hz, 1H), 3.04 (d, J = 12.5 Hz, 1H), 2.77−2.58 (m, 2H), 2.34 (d, $J \approx$ 18.2 Hz, 1H), 2.27 (d, $J \approx$ 18.0 Hz, 1H^R), 2.01 (s, 3H), 1.97 (s, 3H), 1.92−1.57 (m, 3H and 1H^R), 1.54 (broad, s, 9H^R), 1.48 (broad, s, 9H), 0.94 (s, 9H), 0.96−0.74 and 0.68−0.17 (m, 1H and 1H^R), 0.07 (s, 6H). IR (film) ν 2928, 2856, 1698 cm^{-1}. Anal. Calcd for $C_{43}H_{58}N_3O_6Cl_5Si$: C, 56.24; H, 6.37; N, 4.58. Found: C, 56.79; H, 6.59; N, 4.65. $[\alpha]_D^{25}$ +139.9 (0.98, MeOH). LC−MS: t_R = 1.45 min. MS (ESI): m/z 917.87 (M + 1)$^+$.

(1*R*,5*S*)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic Acid 3-*tert*-Butyl Ester 9-(2,2,2-Trichloro-1,1-dimethylethyl) Ester (22b). A solution of acid **21b** (40 g, 55.4 mmol), HOBt (9.9 g, 72.0 mmol), EDC·HCl (28.4 g, 145.2 mmol), DIPEA (29.2 g, 221.5 mmol), and DMAP (1.7 g, 13.8 mmol) in CH_2Cl_2 (650 mL) was stirred at room temperature for 30 min. *N*-Cyclopropyl-*N*-(2,3-dichlorobenzyl)amine (34.0 g, 157.3 mmol) was added, and the reaction mixture was stirred at room temperature for 7 days. The mixture was diluted with CH_2Cl_2 (650 mL) before aq 1 M HCl (450 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (3−20% gradient acetone in heptane) to provide the title compound (21.0 g, 41% over two steps). ^{1}H NMR ($CDCl_3$) 7.33 (broad, s, 1H), 7.17−7.02 (m, 3H), 6.85−6.69 (m 3H), 4.81−4.32 (m, 5H and 5H^R), 4.23 (d, J = 13.5 Hz, 1H), 4.13−3.93 (m, 4H and 1H^R), 3.28−3.0 (m, 2H and 3H^R), 3.04 (broad, d, $J \approx$ 12.6 Hz, 1H), 2.32 (d, $J \approx$ 18.0 Hz, 1H), 2.26 (d, $J \approx$ 18.1 Hz, 1H^R), 2.17 (broad, d, $J \approx$ 21.7 Hz, 1H^R), 2.01 (s, 3H), 1.97 (s, 3H), 1.82−1.59 (m, 1H and 1H^R), 1.53 (broad, s, 9H^R), 1.48 (broad, s, 9H), 0.94 (s, 9H), 0.94−0.73 and 0.68−0.17 (m, 1H and 1H^R), 0.13 (s, 6H). IR (film) ν 2928, 2856, 1698, 1608 cm^{-1}. Anal. Calcd for $C_{42}H_{56}N_3O_7Cl_5$: C, 54.82; H, 6.13; N, 4.57. Found: C, 55.02; H, 6.09; N, 4.56. $[\alpha]_D^{25}$ +126.0 (1.0, MeOH). LC−MS: t_R = 1.34 min. MS (ESI): m/z 920.65 (M + 1)$^+$.

(1*R*,5*S*)-3-Acetyl-6-[cyclopropyl(2,3-dichlorobenzyl)carbamoyl]-7-[4-(3-hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic Acid Trichloromethyl Ester (23a). A solution of starting material **22a** (18.5 g, 20.1 mmol) in CH_2Cl_2 (180 mL) was cooled to 0 °C. HCl (4 M in dioxane, 68 mL) was added, and the mixture was stirred 0 °C for 20 min and at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (100 mL) before aq 1 M NaOH (100 mL) was carefully added. The org layer was concentrated under reduced pressure, the residue was dissolved under N_2 in THF (380 mL), and the solution was cooled to −78 °C. DIPEA (13.8 mL, 80.5 mmol), DMAP (0.246 g, 2.0 mmol), and CH_3COCl (1.36 mL, 19.1 mmol) were added, and the mixture was stirred at −78 °C for 15 min. MeOH (100 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (150 mL) before aq 1 M HCl (150 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (CH_2Cl_2/MeOH 98.2) to provide the title compound (12.7 g, 84%). ^{1}H NMR ($CDCl_3$) 7.36 (t, J = 6.6 Hz, 1H), 7.18−7.00 (m, 4H), 6.77 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.74 (s, 1H and 1H^R), 4.72 (broad, d, $J \approx$ 14.9 Hz, 1H), 4.68 (broad, d, $J \approx$ 16.3 Hz, 1H), 4.65−4.00 (m, 1H and 2H^R, H-1), 4.48 (broad, d, J = 12.8 Hz, 1H), 4.41 (d, J = 15.9 Hz, 1H^R), 4.38 (d, J = 15.7 Hz, 1H), 3.73−3.61 (m, 2H), 3.46 (d, J = 14.7 Hz, 1H), 3.22 (dd, J = 18.3, 7.5 Hz, 1H), 3.13 (d, J = 18.1, 7.4 Hz, 1H^R), 2.88 (broad, d, J = 12.8 Hz, 1H), 2.70 (q, J = 7.4 Hz, 2H), 2.38−2.21 (m, 1H and 1H^R), 2.29 (s, 3H), 2.27 (s, 3H^R), 2.03 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H^R), 1.93−1.60 (m, 3H and 1H^R), 0.95−0.77, 0.73−0.51, 0.45−0.31 and 0.29−0.19 (m, 4H and 4H^R). ^{13}C NMR ($CDCl_3$) 173.07, 172.87, 171.24, 171.21 (CO and CO^R), 151.59 (Cq), 150.61 (Cq^R), 142.59 (Cq), 142.44 (Cq^R), 138.49 (Cq), 138.22 (Cq^R), 137.14 (Cq), 137.07 (Cq^R), 133.06 (Cq), 133.00 (Cq^R), 131.30 (Cq^R), 131.00 (Cq), 129.04 (CH$_{arom}$), 129.02 (CH$_{arom}$), 128.79 (CH$_{arom}$), 128.70 (CH$_{arom}$), 128.60 (CH$^R_{arom}$), 128.53 (CH$^R_{arom}$), 127.42 (CH$^R_{arom}$), 127.26 (CH$_{arom}$), 127.15 (CH$_{arom}$), 127.07 (CH$_{arom}$), 126.73 (CH$^R_{arom}$), 126.56 (CH$_{arom}$), 126.47 (CH$_{arom}$), 126.36 (CH$_{arom}$), 126.18 (CH$^R_{arom}$), 125.42 (Cq), 106.65 (CCl_3), 106.53 (C^RCl_3), 89.32 ($Me_2\underline{C}$−O), 88.95 (Cq, $Me_2\underline{C}^R$−O), 62.02 (C12), 51.00, 49.54 (C5 and C5^R), 50.52 (C4), 49.97 (C4^R), 49.33, 49.02 (C14 and C14^R), 47.55, 45.82 (C1 and C1^R), 46.92, 46.77 (C2 and C2^R), 34.23 (C11^R), 33.97 (C11), 33.17, 32.83 (C8 and C8^R), 31.73 (C10), 31.21, 31.12 (C15 and C15^R), 21.77, 21.69, 21.61, 21.32, and 21.29 ($\underline{C}H_3CO$, $\underline{C}^RH_3CO$, $(\underline{C}H_3)_2C$−O, $(\underline{C}^RH_3)_2C$−O), 10.72, 10.54, 6.58, 6.00 (C16 and C16^R). IR (film) ν 2925, 2159, 2025, 1703, 1620 cm^{-1}. Anal. Calcd for $C_{34}H_{38}N_3O_5Cl_5$: C, 54.75; H, 5.13; N, 5.63. Found: C, 54.52; H, 5.15; N, 5.34. $[\alpha]_D^{25}$ +177.0 (1.02, MeOH). LC−MS: t_R = 1.15 min. MS (ESI): m/z 746.43 (M + 1)$^+$.

(1*R*,5*S*)-3-Acetyl-6-[cyclopropyl(2,3-dichlorobenzyl)carbamoyl]-7-[4-(2-hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic Acid 2,2,2-Trichloro-1,1-dimethylethyl Ester (23b). A solution of starting material **22b** (20.4 g, 22.2 mmol) in CH_2Cl_2 (250 mL) was cooled to 0 °C. HCl (4 M in dioxane, 75 mL) was added, and the mixture was stirred 0 °C for 20 min and at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (150 mL) before aq 1 M NaOH (100 mL) was carefully added. The org layer was concentrated under reduced pressure, the residue was dissolved under N_2 in THF (250 mL), and the solution was cooled to −78 °C. DIPEA (15.2 mL, 88.7 mmol), DMAP (0.27 g, 2.2 mmol), and AcCl (1.6 mL, 22.2 mmol) were added, and the mixture was stirred at −78 °C for 15 min. MeOH (250 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (200 mL) before aq 1 M HCl (200 mL) was added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (EtOAc) to provide the title compound (11.8 g, 71%). ^{1}H NMR ($CDCl_3$) 7.36 (t, J = 6.7 Hz, 1H), 7.18−7.02 (m, 3H), 6.83 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (t, J = 9.7 Hz, 1H), 4.74 (s, 1H and 1H^R), 4.72 (broad, d, $J \approx$ 14.4 Hz, 1H), 4.62 (broad, d, $J \approx$ 16.0 Hz, 1H and 2H^R), 4.58−4.47 (m, 1H and 2H^R), 4.46 (broad, d, J = 10.4 Hz, 1H and 1H^R), 4.40 (d, J = 12.4 Hz, 1H^R), 4.36 (d, J = 16.2 Hz, 1H), 4.11−4.02 (m, 2H), 4.01−3.92 (m, 2H), 3.48 (d, J = 14.1 Hz, 1H^R), 3.44 (d, J = 14.0 Hz, 1H), 3.20 (dd, J = 18.1, 7.4 Hz, 1H), 3.10 (d, J = 17.9, 7.4 Hz, 1H^R), 2.88 (broad, d, $J \approx$ 11.1 Hz, 1H), 2.38−2.20 (m, 1H and 1H^R), 2.29 (s, 3H), 2.27 (s, 3H^R), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H^R), 1.97 (s, 3H), 1.82−1.66 (m, 1H and 1H^R), 0.92−0.77, 0.72−0.50, 0.47−0.30, and 0.29−0.19 (m, 4H and 4H^R). IR (film) ν 2925, 1703, 1607 cm^{-1}. Anal. Calcd for $C_{33}H_{36}N_3O_6Cl_5$: C, 52.99; H, 4.85; N, 5.62. Found: C, 54.21; H, 5.30; N, 5.25. $[\alpha]_D^{25}$ +117.3 (1.0, MeOH). LC−MS: t_R = 1.12 min. MS (ESI): m/z 748.36 (M + 1)$^+$.

General Conditions for the Preparation of Compounds 24a−k and 25a−l. To a solution of alcohol **23a** (1.0 g, 1.3 mmol) or **23b** (1.66 g, 2.2 mmol), 1,1′-(azodicarbonyl)dipiperidine (2.7 mmol/4.5 mmol), and the desired phenol (2.7 mmol/4.4 mmol) in toluene (30 mL) was added PBu_3 (85%, 4.0 mmol/6.7 mmol) at room temperature, and the reaction mixture was stirred at 80 °C for 12 h. Heptane (75 mL) was added, and the mixture was filtered. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (40 mL). At 0 °C aq H_2O_2 (25% in water, 8 mL) was added and the mixture was stirred at 0 °C for 5 min and

at room temperature for 1.5 h. Aqueous 1 M NaOH (20 mL) and brine (20 mL) were added. The org layer was concentrated under reduced pressure, and the residue was purified by FC (20−35% EtOAc in heptane) to provide the corresponding crude phenyl ether. A suspension of this crude product and of Zn powder (6.6 mmol) in THF (20 mL) was stirred in the presence of AcOH (0.4 mL) at room temperature for 3 h. The mixture was filtered through Celite, the solvents were evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (3 mL). Aqueous 0.1 M EDTA (5 mL) was added. The mixture was stirred at room temperature for 6 h. The org layer was concentrated, and the residue was purified by FC (3−5% MeOH in CH_2Cl_2) to provide the corresponding title product.

Acknowledgment. We thank Remy Dureau, Patrick Eckert, Martin Faes, Sven Glutz, Luke Harris, Bela Humer, Daniel Marchal, Sophie Moujon, Emmanuelle André, Pascal Rebmann, Daniel Trachsel, Gabriela Vorburger, Alain Chambovey, Antoinette Amrein, Geoffroy Bourquin, Fabienne Drouet, Aude Weigel, Markus Rey, and Daniel Wanner for their help and engagement on this program. We thank Synphabase AG as well for the preparation of compound **6** in kilogram scale. We thank Dr. Clemens Schulze-Briese, Takashi Tomizaki, and their group for their support in setting up the beamline.

Supporting Information Available: Experimental details of some precursors, full spectroscopic data of all compounds with assignments of the ^1H and ^{13}C NMR signals, X-ray structure analysis results, and details of the inhibition assay, pharmacokinetic experiments on the rat, and pharmacodynamic experiments on double transgenic rats. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM900022F