Synthetic and structural studies on macrocyclic amino cyclitols – conformational chameleons†

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Starting from quinic acid **7** the synthesis of 1,4-butanediol-linked macrocyclic aminocyclitols **30**, **32**, **34**, **36** and **38** is described. Assembly was achieved by olefin cross-metathesis of appropriate cyclohexyl allyl ethers followed by ring-closing metathesis of bis-*O*-allyl homodimers. In all five cases studied, the only products that were formed were those resulting from direct ring-closing metathesis; the formation of larger rings was not detected. These macrocycles exhibited diverse conformational behaviour which included formation of stable separable conformers **31a** and **31b** as well as conformationally dynamic macrocycles **35** in which a ring flip in one cyclohexane chair conformer induces a ring flip of the other cyclohexane ring through the linking chains of the macrocycles. The activation energy for the inversion of the chair conformation in this process was determined to be about 38 kJ mol^{-1}, which is about 7 kJ mol^{-1} lower than the activation energy for the ring flip of the unsubstituted cyclohexane ring. In all cases, the conformational studies strongly suggest that intramolecular H-bonding between 1,3-diaxially oriented amido and alcohol or ether groups exerts a decisive contribution to the overall stabilisation of the preferred cyclohexane chair conformation.

Introduction

Many natural products of pharmaceutical relevance are composed of macrocycles with embedded smaller rings such as pyrans or furans (often present as lactols or lactones). Typical examples are the polyketides bryostatin and sorangicin, and the diterpene tonantzitlolone. Their ability to target their receptors is very likely closely related to their conformational flexibility. On one hand the macrocycle adopts a preferred global conformation when being bound to the biomacromolecule.[1] But besides the influence imposed by the receptor it can be assumed that the conformational characteristics of the embedded five- or six-membered rings will also influence the macrocycle conformation in a relay type mode of action. Relay of conformational information has emerged as a new important research field for so-called small molecules.[2–4]

Recently, we and other research groups have been involved in synthesising aminoglycoside antibiotics and derivatives as well as mimetics that are able to selectively bind to biomacromolecules.[5–8] In this context, we described the first preparation of novel macrocyclic 1,4-butanediol-linked aminodeoxyglycosides **3** and **4** (Fig. 1),[8] which can be regarded as glycomimetics derived from aminoglycoside antibiotics. Like the natural products described above, these glycosides are composed of a macrocycle with embedded pyranose rings. In detailed NMR studies,[9] we showed that the conformational flexibility of the macrocycle, as well as conformational changes in the pyranose units, were responsible for **3** forming a complex with TAR RNA.[10]

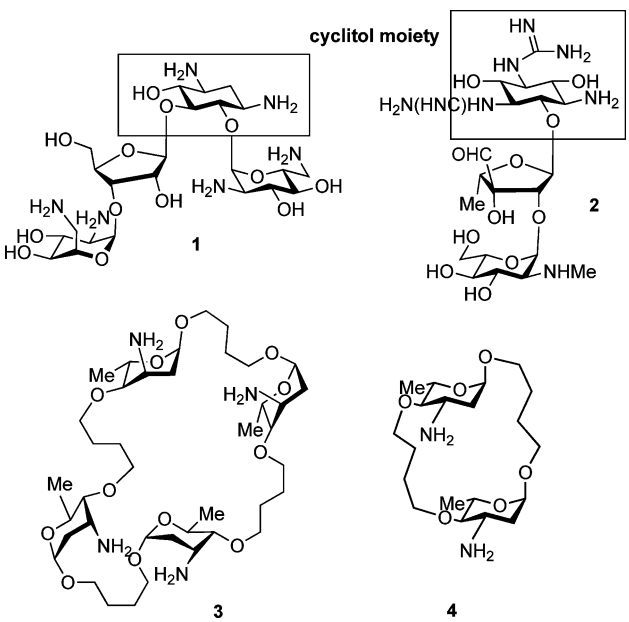

Fig. 1 Structures of neomycin (**1**) and streptomycin (**2**), and macrocyclic neoaminoglycosides **3** and **4**.

Aminoglycoside antibiotics like neomycin (**1**) and streptomycin (**2**) are commonly not only composed of hexoses or pentoses but also contain cylictols such as the 2-deoxystreptamine ring system (**3**). In continuation of our recent work, we now disclose detailed synthetic and conformational studies on aminocyclitols embedded in a macrocyclic environment, as depicted in the general structures **5** and **6** (Fig. 2). Compared to pyranoses the cyclohexane ring shows a larger conformational flexibility,[10] which in the present case should have an effect on the outcome of the RCM and the conformational dynamics of the macrocycles formed. In this

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† Electronic supplementary information (ESI) available: Additional experimental information; determination of *E*/*Z* ratios; discussion of compounds **29a,b**, **33** and **37**; crystal structure data. See DOI: 10.1039/b716347a

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report, we provide detailed synthetic studies and conformational analyses on two out of four macrocycles of type **5** and **6** that can also be of relevance for macrocyclic natural products containing six-membered rings within a macrocycle.

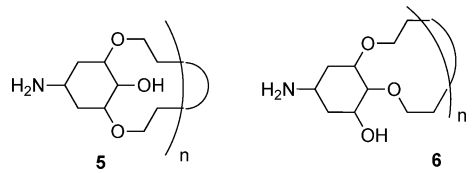


Fig. 2 General formulae of macrocyclic aminocyclitols **5** and **6**.

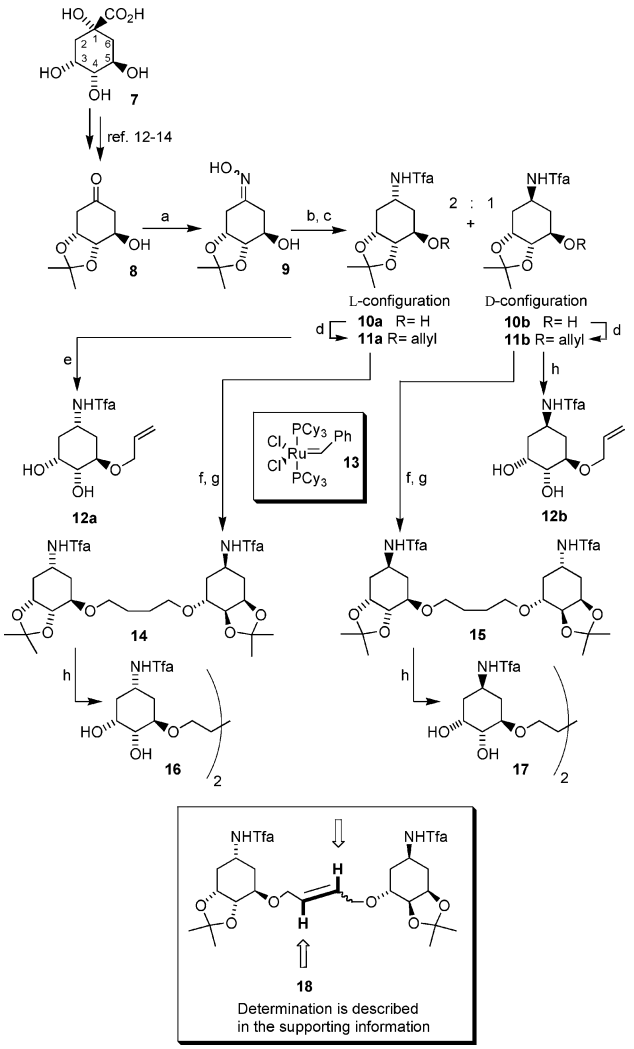
Results and discussion

Synthesis of macrocycles

The syntheses of macrocyclic cyclitols utilised D-quinic acid **7** as the starting building block (Scheme 1).[11] It readily provides four stereogenic centres of which three can be conserved for the target products. Quinic acid **7** was converted *via* known sequences into ketone **8**,[12–14] which was then transformed into the corresponding oxime **9**. Reduction to the corresponding amine was achieved with sodium borohydride in the presence of a catalytic amount of nickel(II) acetate, a rather uncommon reagent system, but in our hands the best we tested for this transformation.[15] After protection as trifluoroacetamide and formation of diastereoisomers **10a** and **10b** followed by *O*-allylation at C-5, two cyclitol derivatives **11a** and **11b** (2 : 1) were obtained and separated. However, we encountered distortion of the cyclohexane ring by the annelated acetonide, which hampered determination of the configuration at the amido-substituted stereogenic center at C-1. Removal of the this protection yielded diols **12a** and **12b**, at which point structure elucidation of both diastereoisomers became possible. Diastereoisomer **10a** and all products derived therefrom have the L-configuration, while **10b** was determined as having the D-configuration.[16]

In the following transformations, the allyl moiety served as a functional group for metathesis olefinations. Thus, independent treatment of allyl ethers **11a** and **11b** with the Grubbs I catalyst **13**[17] yielded homodimers (E/Z = 10 : 1, configurational assignment was conducted with compound **18** which is discussed in detail in the ESI†).[18] However, the transformation was incomplete, and so the starting material was re-isolated and re-employed in order to achieve almost quantitative yield.

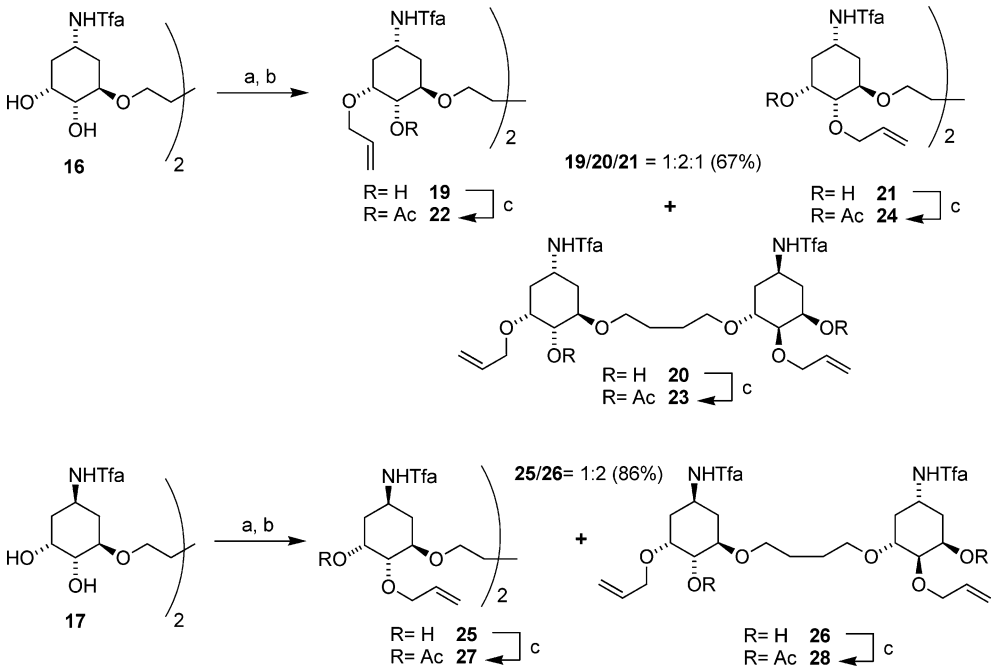
The double bonds were then hydrogenated (to furnish homodimers **14** and **15**) and the acetal groups were hydrolysed to yield tetrols **16** and **17** (Scheme 1). At this stage, we chemically distinguished both hydroxy groups on each cyclohexane ring by stannylidene formation and ring opening using allyl iodide as an electrophile, which yielded allyl ethers **19–21**, **25** and **26** (Scheme 2).[19] Usually, this method is very selective in distinguishing *syn* alcohol groups.[20] Nevertheless, we encountered a total absence of selectivity in the case of the L-diastereoisomer **16** (1 : 1 allylation at O-3 and O-4) and only a slight preference at O-4 for the D-diastereoisomer **17** (1.7 : 1 in favour of O-4 allylation). As shown in the second part of this report, most of these oligosubstituted amino cyclohexanes are conformationally flexible, which affects



Scheme 1 Preparation of homodimers **16** and **17**. *Reagents and conditions*: a) $HONH_3Cl$, NaOAc, MeOH, rt, 24 h (95%); b) $NaBH_4$, cat. $Ni(OAc)_2$, MeOH, rt, 3 h; c) CF_3CO_2Et, Et_3N, MeOH, rt, 24 h (93% over two steps); d) allyl iodide, Ag_2O, MeCN, 45 °C, 24 h (75–85%); e) conc. $HCl_{(aq)}$, MeOH–H_2O (10 : 1), 1 h, quantitative yield for **12a** and **12b**; f) **13**, CH_2Cl_2, 37 °C, 52 h, 77% from **11a** (23% recovered **11a**) and 46% from **11b** (50% recovered **11b**); g) PtO_2, H_2, EtOAc–CH_2Cl_2–MeOH (16 : 8 : 1), 16 h; h) conc. $HCl_{(aq)}$, MeOH–H_2O (10 : 1), 1 h (86% of **16** for two steps and 69% of **17** for two steps); Tfa = trifluoroacetyl, Cy = cyclohexyl.

the outcome of reactions like the present protection protocol. Separation of positional isomers was achieved after formation of the corresponding acetates **22–24**, **27** and **28**.

With these dimeric bis-*O*-allylated 1,4-butanediol-linked cyclitols in hand, we conducted macrocyclisations under RCM conditions, again employing the Grubbs I catalyst **13**. In our earlier work with *O*-allylated glycosides we found that the mode of macrocyclisation depends on several factors, one of them being the relative configuration of all substituents at the pyran ring. Thus, starting from a diene precursor, direct macrocyclisation (*e.g.* formation of macrocycle **4** with an *arabino* configuration around the pyranose ring) or dimerisation and trimerisation (*e.g.* formation of macrocycle **3** with a *lyxo* configuration around the pyranose ring)[8c] can occur, making the outcome of the RCM difficult to predict.



Scheme 2 *Reagents and conditions*: a) Bu_2SnO, toluene, Δ, 2 h; b) allyl bromide, CsF, DMF, 60 °C to rt, 18 h (from **16**: 67% for two steps; from **17**: 86% for two steps); c) Ac_2O, DMAP, Et_3N, 30 min; quantitative yields.

In the present cases (acetates **22–24**, **27** and **28**) RCM yielded only direct ring-closing products irrespective of the stereochemistry associated with the amido group, as was confirmed by mass spectrometric analysis. Formation of larger macrocycles could not be detected by TLC and MS after sampling the crude RCM products. The free alcohols **19–21**, **25** and **26** could also be employed but RCM afforded lower yields. The RCM products are again *E*/*Z* mixtures of C_2-symmetric alkenes that can be analysed by the NMR method described in the ESI†.[18c] After hydrogenation of the newly formed olefinic double bond we obtained macrocycles **29**, **31**, **33**, **35** and **37** (Scheme 3).

To our surprise each metathesis reaction yielded two or three products with distinctly different TLC R_f values. However, in most cases the compounds could not be separated by flash column chromatography. The mixtures clearly revealed only one mass in the mass spectra, while the NMR spectrum distinctly showed the presence of different compounds or very broad signals, which hampered detailed assignment. Careful investigations of these products indicate the presence of conformational isomers, which will be discussed in detail below. After having worked out this behaviour, we terminated the sequence by deprotection under standard conditions to yield the target macrocycles **30**, **32**, **34**, **36** and **38**. As for many other aminoalcohols of rather complex structure, the NMR spectra of these products were difficult to fully solve and interpret. Therefore, we first focused on the precursors and protected aminoalcohols **29**, **31**, **33**, **35** and **37**.

Analytical and conformational considerations

Prior to discussing conformational aspects in detail, we wish to define conformations $^1C_4$ and $^4C_1$ for clarity, in analogy to the IUPAC rules for carbohydrates (Fig. 3).[21] In this context we regard the carbon C-6 as the pseudo ring oxygen atom. The numbering is consistent with the labelling in all schemes in this paper, which is based on the original labelling of the starting D-quinic acid **7**. In order to differentiate the cyclohexane rings with acetyl groups at O-3 from those acetylated at O-4 we shall label the cyclohexanes to be *endo* when the acetate group is at C-4 while *exo*-acetate groups are at C-3 irrespective of whether acyclic RCM precursors or macrocycles are being discussed. In fact, in macrocycles the C-3 position is located outside the macrocycle while the C-4 position lies inside.

The most important tool used to determine the cyclohexane ring conformation is the analysis of the ^3J scalar coupling constants according to the Karplus equation which can straightforwardly can be adopted to cyclohexanes in ideal chair conformations.[22] In the present cases, however, we often encountered broadened signals in the ^{1}H as well as ^{13}C NMR spectra at room temperature, which can be taken as an indication of a fast equilibrium relative to the NMR timescale. If necessary, we also used NOE contacts to determine the arrangement of atoms in space and thus elucidate the cyclohexane chair conformation.

Acyclic precursors

We first conducted conformational studies on the cyclohexane rings in precursor building blocks as well as on acyclic homodimers. These analyses turned out to be important for understanding conformational peculiarities found in the macrocycles, which are strongly influenced by the conformations of the individual cyclohexane moieties present (*vide supra*) (Table 1).

In chloroform the cyclohexane ring in **12a** adopts a $^1C_4$ chair conformation and the amido group is oriented in an axial position. An intramolecular H-bond is possible and would stabilise the $^1C_4$ conformation. The chemical shift of the NH proton in chloroform at 295 K can be regarded as an indicator of intramolecular H-bonding. NH chemical shifts higher than 7.4 ppm are always a diagnostic tool for an intramolecular H-bond to an oxygen atom

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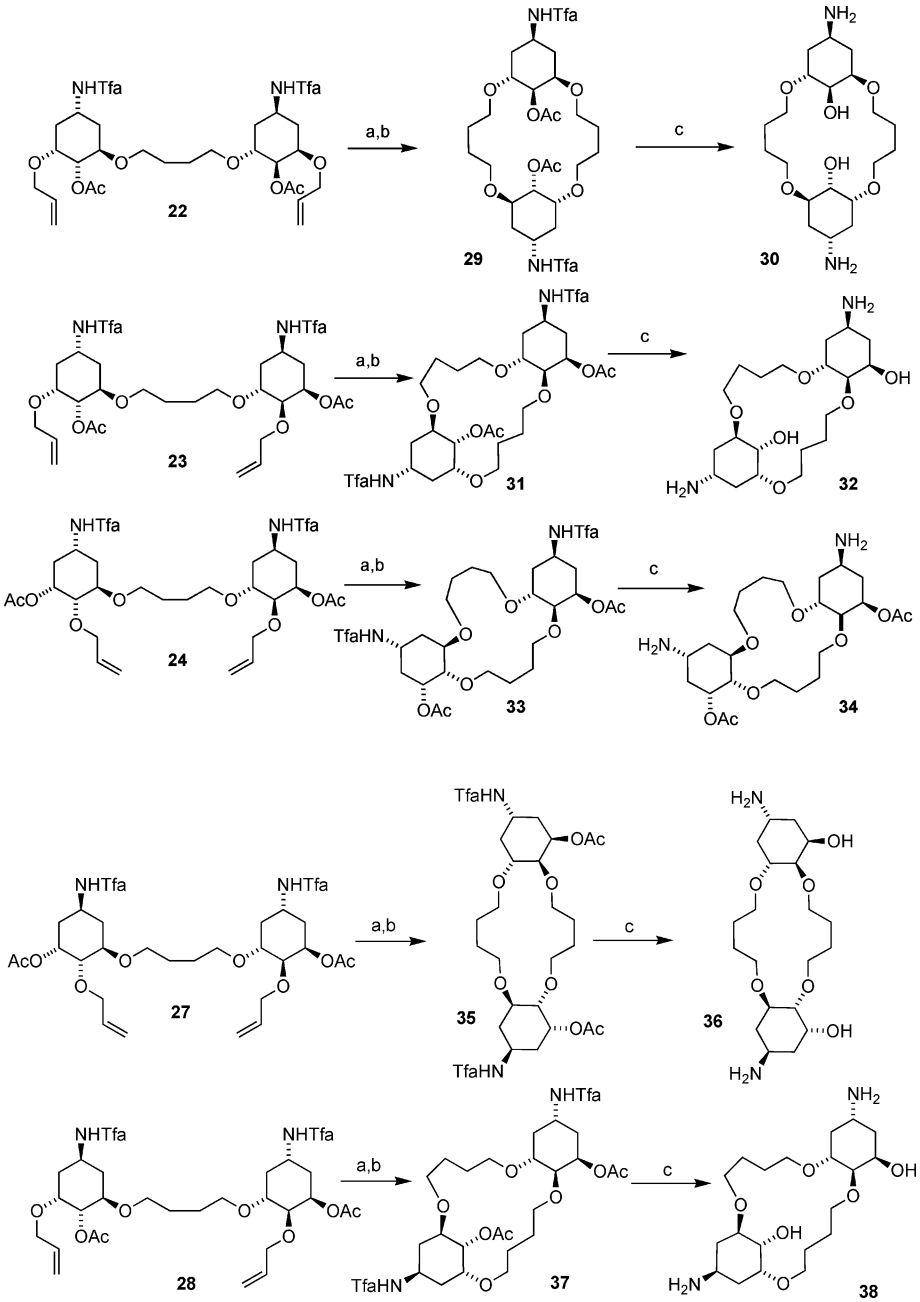


Scheme 3 RCM of dienes **22**, **23**, **24**, **27** and **28**. *Reagents and conditions*: a) **13** (10 mol%), CH_2Cl_2, 37 °C; b) PtO_2, H_2, CH_2Cl_2–ethyl acetate–MeOH (**29**: 43%; **31**: 66%; **33**: 53%; **35**: 53%; **37**: 39% for two steps); c) NaOH, H_2O–MeOH (**30**: 67%; **32**: 81%; **34**: 83%; **36**: 61%; **38**: 86%).

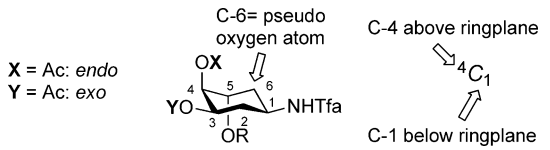


Fig. 3 Definition of the prefixes "*endo*" and "*exo*" and $^1C_4$ and $^4C_1$ in the present context.

in a 1,3-diaxial relationship. The NH signal of the NHTfa group of **12a** in chloroform is located at 8.11 ppm and indicates an intramolecular H-bond. On the other hand, in methanol, which is a polar H-bond competing solvent, the cyclohexane ring of **12a** adopts a $^4C_1$ chair conformation with the amido group oriented in an equatorial position for which no intramolecular H-bond is possible.

NMR analyses of the more polar compounds **12b**, **16** and **17** had to be conducted in CD_3OD instead of $CDCl_3$. Consequently the amido group occupies an equatorial position and no intramolecular H-bond is formed.

RCM products

Conformational analysis was carried out with *N*-acylated macrocycles **29**, **31**, **33**, **35** and **37** and with the fully deprotected derivatives **30**, **32**, **34**, **36** and **38**. The NMR spectra of the latter

macrocycles commonly revealed poor resolution. In part, the results collected for the protected macrocycles could be used for the analysis of the latter ones. Among the five acylated macrocycles only the conformations of the two macrocycles **31** and **35** could be analysed in great detail. They showed remarkably different behaviour (*vide supra*). Analysis of the other three macrocycles **29**, **33** and **37** can be found in the ESI†. In essence, they show similar conformational effects.

RCM products 31a,b

The diene precursor **23** is composed of an *endo*- and an *exo*-acetate cyclohexane ring. For better recognition, the labels of the *exo*-acetate cyclohexane rings are marked with a prime (′) and are always placed on the right-hand side. In $CDCl_3$ both cyclohexane rings adopt a $^1C_4$ conformation. The amido groups at C-1 and at C-1′ are placed in an axial position and can form a stabilizing hydrogen bond with O-3 and O-3′. NMR investigations in $CDCl_3$ of the macrocycles **31a** and **31b** prepared from **23** (coupling constants *J*, selective TOCSY and selective NOESY NMR experiments) showed that both compounds are identical with respect to their stereo- and regiochemistry. Further proof for these considerations was collected when both conformers **31a** and **31b** separately as well as a mixture of both conformers were independently deacetylated to yield macrocycle **32** as a single product.

It is important to note that in the macrocycles **31a** and **31b** the *exo*-acetate rings did not give sharp NMR signals even at low temperatures (210 K), which created difficulties in fully interpreting all data. The coupling constants listed in Table 2 of the remaining sharp signals of the *exo*-acetate cyclohexane ring of **31a** and **31b** cannot unequivocally be attributed to a certain chair conformation. The cyclohexane ring that holds the *endo*-acetate group gives sharp NMR signals in both conformers of **31**. From the coupling constants it can be concluded that the *endo*-acetate ring adopts a $^4C_1$ conformation in **31a** and a $^1C_4$ conformation in **31b**. The chair conformations of the *endo*-acetate cyclohexane rings ($^4C_1$ in **31a** and $^1C_4$ in **31b**) cannot invert into each other due to steric hindrance between the acetyl group and the backbone of the macrocycle. The two conformers **31a** and **31b** are stable for months in solution at room temperature. Even in refluxing toluene (1 h) inversion of conformation was not observed. Further structural proof was collected from X-ray analysis of crystalline **31b** (Fig. 4).[23] In the crystal the cyclohexane ring with the *endo*-acetyl group clearly adopts a $^1C_4$-conformation, while the cyclohexane ring with the *exo*-acetyl group shows a $^4C_1$ conformation.

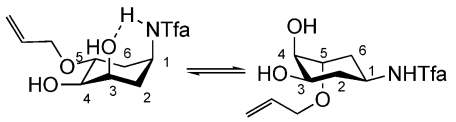
Free aminoalcohol **32** was independently prepared by deprotection of **31a** or **31b**, respectively. As is evident from the coupling constants in Table 2, the whole ring systems appears to be highly flexible, as only the amino group adopts an equatorial position, whereas for the other ring protons no defined coupling constants could be determined. This observation clearly reveals a change of conformation with respect to the NMR timescale.

RCM products 35a,b

Diene **27** is the C-1 epimer of diene **24** with D-configured cyclohexane rings and two *exo*-acetate groups. As for **28**, the cyclohexane rings of diene **27** adopt an axial-rich $^4C_1$ conformation that is stabilised by an intramolecular H-bond from NH to O-5 (see NH chemical shift in Table 3). Macrocycle **35** has two *exo*-acetate

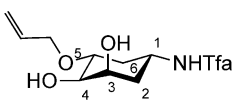
Table 1 Conformations of cyclohexanes **12a** and **12b** as well as dimers **16** and **17** obtained from NMR analysis

L-configured series

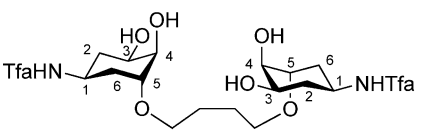


12a ($^1C_4$, in $CDCl_3$) **12a** ($^4C_1$, in CD_3OD)

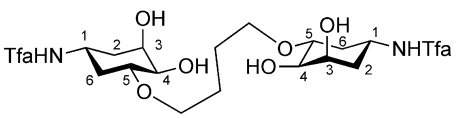
D-configured series



12b ($^1C_4$, in CD_3OD)



16 ($^4C_1$ in CD_3OD)



17 ($^1C_4$ in CD_3OD)

		^3J/Hz [a]								δ/ppm [b]
Compound	Solvent	1-H	2_{ax}-H	2_{eq}-H	3-H	4-H	5-H	6_{ax}-H	6_{eq}-H	*H*NTfa
12a	$CDCl_3$	4.1, 3.6, 3.6, 3.5	4.1, 2.9	3.6, 3.0, 2.9	3.0, 3.0, 2.9	9.1, 3.0	11.2, 9.1, 3.9	11.2, 3.5	3.9, 3.6	8.11
12a	CD_3OD	m	m	m	10.7, 4.5, 3.2	3.5, 3.2	3.7, 3.7, 3.5	m	m	n.d.
12b	CD_3OD	11.5, 11.2, 3.9, 3.9	11.5, 3.5	4.5, 4.0	m	m	10.5, 9.1, 4.9	11.2, 10.5	4.9, 3.9	n.d.
16	CD_3OD	10.9, 10.9, 4.6, 4.6	m	m	10.5, 4.8, 3.0	3.8, 3.0	3.8, 3.6, 3.6	m	m	n.d.
17	CD_3OD	10.9, 10.8, 4.2, 4.1	10.8, 2.6	5.1, 4.2	5.1, 2.8, 2.6	8.3, 2.8	m	10.9, 10.9	6.3, 4.1	n.d.

[a] Coupling constants between 1-H and NH (around 8.0 Hz) not listed; large geminal ^2J couplings at positions 2 and 6 (around 12 Hz) not listed; m = multiplet, caused by overlapping of signals, higher order signals or broad signals. [b] Determined at 295 K; n.d. = not detectable because of use of CD_3OD as solvent.

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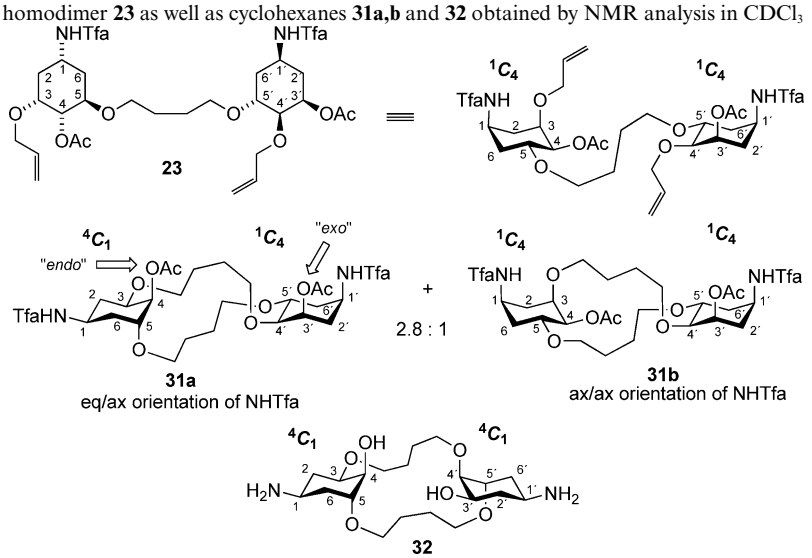
Table 2 Conformations of homodimer **23** as well as cyclohexanes **31a,b** and **32** obtained by NMR analysis in $CDCl_3$



		^3J/Hz [a]								δ/ppm [b]
Compound	Solvent	1-H	2_{ax}-H	2_{eq}-H	3-H	4-H	5-H	6_{ax}-H	6_{eq}-H	*H*NTfa
23 (*endo*)	$CDCl_3$	5.4, 5.3, 5.2, 5.0	m	m	4.1, 4.1, 3.0	7.8, 3.0	8.0, 7.8, 4.0	m	m	7.55
23 (*exo*)	$CDCl_3$	5.0, 4.8, 4.6, 4.5	m	m	m	m	m	m	m	6.58
31a (*endo*)	$CDCl_3$	12.4, 12.4, 4.2, 3.9	4.2, 2.4	3.9, 3.8	11.9, 3.6, 2.9	2.9, 2.7	m	m	m	6.50
31a (*exo*)	$CDCl_3$	4.6, 4.6, 4.5, 4.3	m	m	br s	7.3, 2.5	br dd 9.0, 5.4	m	m	7.19
31b (*endo*)	$CDCl_3$	m	4.4, 2.4	5.6, 2.6	br dd 5.6, 2.7	10.3, 2.7	11.2, 10.3, 4.2	m	br d	8.24
31b (*exo*)	$CDCl_3$	m	m	m	br s	6.8, 3.0	m	m	m	6.90
32 (*endo*)	CD_3OD	11.2, 11.2, 3.9, 3.9	m	m	m	br d 2.7	m	m	m	n.d.
32 (*exo*)	CD_3OD	9.5, 9.5, 3.9, 3.9	m	m	10.0, 3.5, 2.7	m	m	m	m	n.d.

[a] Coupling constants between 1-H and NH (around 8.0 Hz) not listed; large geminal ^2J couplings at positions 2 and 6 (around 12 Hz) not listed; m = multiplet, caused by overlapping of signals, higher order signals or broad signals. [b] Determined at 295 K; n.d. = not detectable because of use of CD_3OD as solvent.

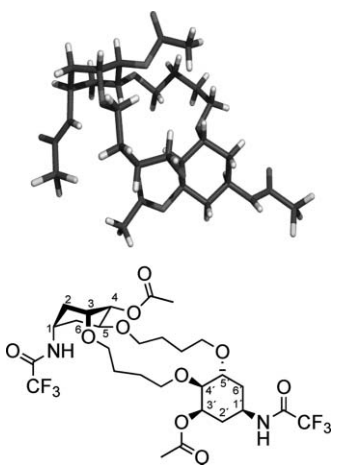


Fig. 4 X-Ray analysis of macrocycle **31b**.[24]

groups and derives from diene **27**. In CD_3OD, only one conformation is present with a single set of sharp signals for both cyclohexane rings. This indicates that the molecule has a C_2-symmetry in methanol. The analysis of the coupling constants indicates that both cyclohexane rings adopt an equatorial-rich $^1C_4$ conformation.

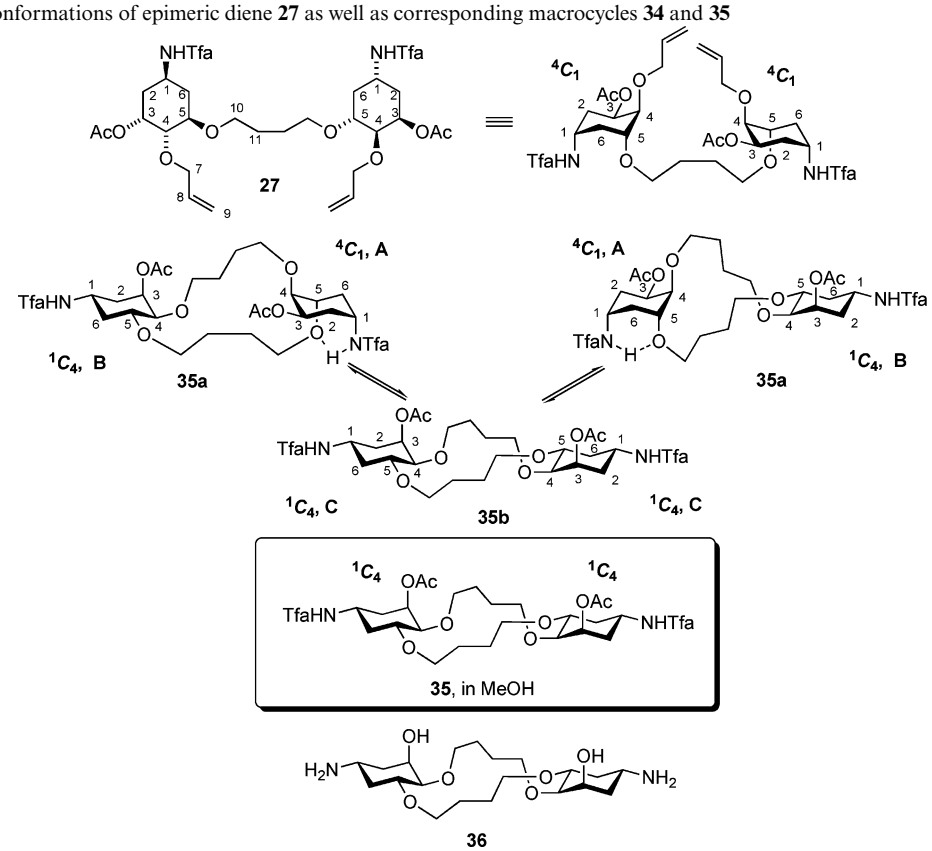
Deprotected aminoalcohol **36** adopts also a $^1C_4$ conformation, as does **35** in methanol. With three substituents in equatorial positions in the cyclohexane ring, the conformation is rather more defined than in **32**, where only two substituents can adopt the same orientation. Nevertheless, this configuration still enables the ring system to be very flexible, as can be judged from the behaviour of **35** in $CDCl_3$ (Fig. 5).

These sets of signals belong to two interconverting conformations (see equilibrium in Fig. 6). ROESY spectra recorded at 220 K in $CDCl_3$ clearly reveal exchange cross-peaks between the two sets of signals. One set of NMR signals belongs to an unsymmetrical conformation (94% for **35a**) whereas the other set belongs to a C_2-symmetrical conformation (6% of **35b**) (Fig. 6).

In macrocycle **35a** the two cyclohexane rings adopt different conformations: an equatorial-rich $^1C_4$ conformation (denoted **B**) and an axial-rich $^4C_1$ conformation (denoted **A**).[25] Consequently, the ^{1}H-NMR chemical shifts of the two cyclohexanes differ. The coupling constants at 3-H in conformation **A** (singlet, line width = 10 Hz) and at 3-H in the conformation **B** (dd, J = 11.6, 5.5 Hz) indicate correspondingly an equatorial-rich $^1C_4$ and an axial-rich $^4C_1$ cyclohexane ring conformation.

The axial-rich conformer is presumably stabilised by an intramolecular hydrogen bond between NH and O-5. Additional support for this conformation was collected from the ROESY spectra recorded at 220 K. Characteristic ROE connectivities found for the two chair conformations are depicted in Fig. 7.

Table 3 Preferred conformations of epimeric diene **27** as well as corresponding macrocycles **34** and **35**



Compound	Solvent	^3J/Hz [a]								δ/ppm [b]
		1-H	2_{ax}-H	2_{eq}-H	3-H	4-H	5-H	6_{ax}-H	6_{eq}-H	*H*NTfa
27	$CDCl_3$	3.9, 3.9, 3.9, 3.9	12.5, 3.9	br d 3.9	12.5, 4.0, 3.0	4.0, 3.8	4.1, 3.8, 3.7	br dd 4.1, 3.9	br d 3.9	7.83
35a (**A**)	$CDCl_3$	m	m	m	11.6, 5.5	m	m	m	m	8.28[c]
35a (**B**)	$CDCl_3$	m	m	m	br s	m	m	m	m	7.00–7.08[c]
35b (**C**)	$CDCl_3$	m	m	m	br s	m	m	m	m	8.02[c]
35	CD_3OD	12.1, 12.0, 4.1, 3.9	m	3.9, 3.5	3.5, 3.2, 3.1	9.4, 3.2	11.4, 9.4, 4.4	12.0, 11.4	4.5, 4.4	n.d.
36	CD_3OD	11.6, 11.5, 4.0, 3.9	11.5, 2.6	6.5, 3.5	3.5, 3.1, 2.6	9.2, 3.0	m	11.8, 11.6	7.1, 4.0	n.d.

[a] Coupling constants between 1-H and NH (around 8.0 Hz) not listed; large geminal ^2J couplings at positions 2 and 6 (around 12 Hz) not listed; m = multiplet, caused by overlapping of signals, higher order signals or broad signals. [b] Determined at 295 K; n.d. = not detectable because of use of CD_3OD as solvent. [c] Determined at 220 K.

For the minor conformer only one set of signals could be detected. This is a clear indication that **35b** has a C_2-symmetry with two cyclohexane rings populating the same chair conformation. The ^{1}H NMR chemical shifts of the cyclohexane protons in **35b** resemble the chemical shifts of the equatorial-rich $^1C_4$ (**B**) conformation in **35a**. This indicates that in **35b** both cyclohexane rings presumably adopt an equatorial-rich $^1C_4$ conformation.

Line-shape analysis of the ^{1}H NMR spectra of **35** provided cyclohexane chair flipping rates (k).[26] Computer-generated line shapes for the 3-H resonances at temperatures between 300 K and 220 K and the determined rate constants are listed alongside the experimental spectra in Fig. 8.

By plotting $\ln(k/T)$ *vs.* $1/T$ and fitting these results to the Eyring equation, one is able to determine the enthalpy of activation for the cyclohexane ring flip. The activation energy amounts to 38 kJ mol^{-1}, which is about 7 kJ mol^{-1} lower than the activation energy for the ring flip of the unsubstituted cyclohexane ring.[27] It should be noted that in CD_3OD only one conformation can be detected in which both cyclohexane rings adopt the equatorial-rich $^1C_4$ chair conformations.

Conclusions

In conclusion, we were able to synthesise several cyclohexane-based macrocyclic aminoalcohols **30**, **32**, **34**, **36** and **38** with potential nucleic acid binding properties.[8,9,28] Each of these macrocycles contains two tetrasubstituted cyclohexane rings linked though two butanediol units. Unlike sugar-derived pyrans, these individual tetrasubstituted cyclohexane moieties show high conformational flexibility. On being incorporated into a macrocyclic system as in **29**, **31**, **33**, **35** and **37**, diverse static as well as dynamic conformational phenomena occurred. The relative configuration and the nature of substituents around the cyclohexane moieties influence not only the overall conformation of the macrocycle, but

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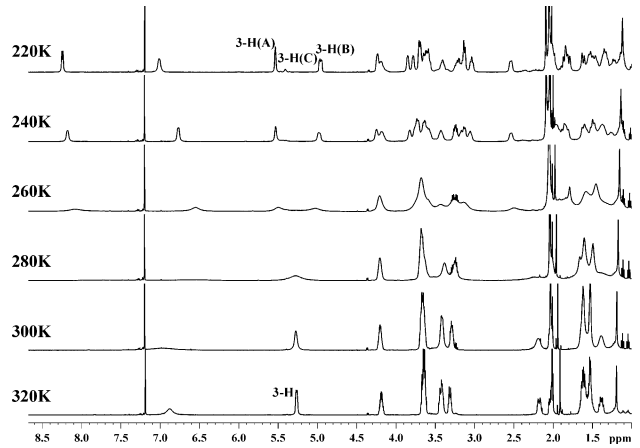

Fig. 5 Temperature dependence of the ^{1}H NMR spectra of macrocycle **35**. The signal splitting at 220 K is exemplified for 3-H.

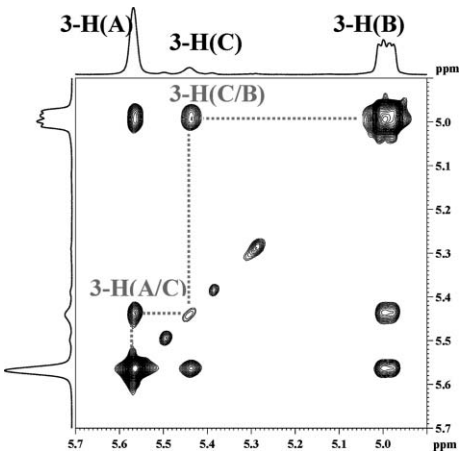

Fig. 6 Exchange cross-peaks in the ROESY spectra of **35** at 220 K; the chemical exchange between 3-H in **35a** (conformation **A** and **B**) and **35b** (conformation **C**) is shown (dotted line).

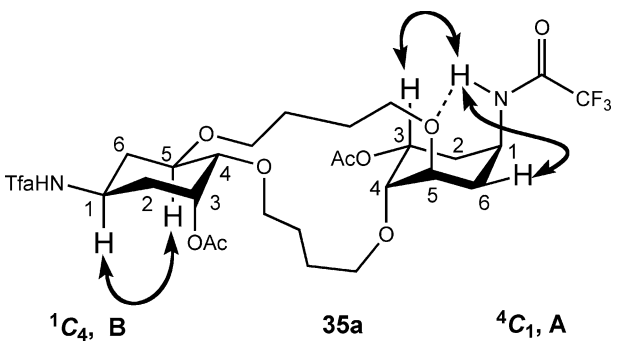

Fig. 7 Significant NOE connectivities found for **35a** which support the two chair conformations **A** and **B**.

also the interaction between the two cyclohexane rings through the linking chains. In macrocycle **31** we observed the existence of two distinct stable conformations that do not interconvert and thus can be separated. On the other hand, compound **34** contains cyclohexane rings that rapidly switch from one conformation to the other at room temperature. The energy barrier for the ring flip was calculated and determined to be significantly lower than in unsubstituted cyclohexane rings. In all cases, the conformational

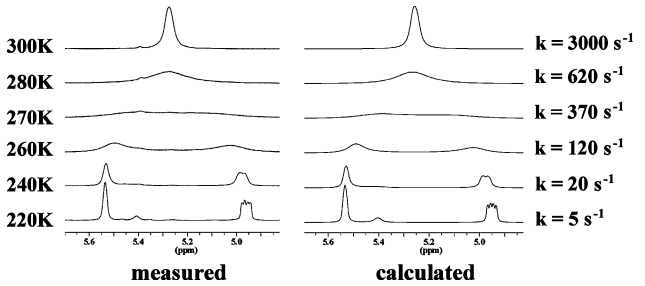

Fig. 8 Experimental *vs.* calculated line shapes for the ^{1}H NMR resonances of 3-H in **35** at different temperatures.

studies strongly suggest that the intramolecular H-bonding from an amido H-atom to an alcohol or ether functionality exerts a decisive contribution to the overall stabilisation of the cyclohexane chair conformation, thus overcoming increased steric energy when switching from an equatorial-rich to an axial-rich arrangement of substituents. Thus, oligosubstituted cyclohexane moieties embedded in macrocycles behave very differently to analogous pyran rings.[8] It needs to be noted that the conformational switch occurs in non-polar solvents like chloroform and not in a protic medium like methanol, the latter more closely resembling a biological system. However, biomacromolecules induce active conformations upon small ligands. Therefore, the present study is of importance as it clearly reveals that cyclohexane-based ligands are conformationally more flexible than the corresponding pyranyl analogues. The enhanced flexibility of both acyclic as well as embedded cyclohexanes also has an impact on the chemical behaviour; for example, protection protocols based on stannylidene intermediates derived from **16** and **17** proceeded with poor regioselectivity compared to pyran-based carbohydrates. RCM always gave the small macrocycles, an observation which is in contrast to the corresponding sugar-based precursors.[8,29] Finally, we are certain that our conformational studies should be of relevance to related macrocyclic natural products in general because such conformational flexibility may enable molecules of this kind to bind to different substrate structures. Investigations on that subject are underway in our laboratories.

Experimental

General remarks and starting materials

NMR spectra were recorded on Bruker Avance DPX spectrometers at 200 and 400 MHz and on a Bruker Avance DRX spectrometer at 500 MHz, using tetramethylsilane as the internal standard, if not otherwise mentioned. ^{1}H multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CDCl_3$ (77 ppm) or CD_3OD (49 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. ^{13}C multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbon), d = doublet (methine), q = quartet (methyl), t = triplet (methylene). The atom labelling is consistent with the numbering used in the respective schemes. Mass spectra were recorded on a

LCT spectrometer (Micromass) with a lock-spray unit for ESI or on a VG Autospec spectrometer (Micromass). Ion mass (m/z) signals are reported as values in atomic mass units, followed in parentheses by the peak intensities relative to the base peak (100%). Optical rotations [a] were collected on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F_{254} (E. Merck, Darmstadt), and spots were detected either by UV-absorption or by charring with $KMnO_4$/NaOH in water. Amines were detected using a ninhydrin solution in propanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt). Quinic acid **7** was purchased from Fluka in >98% purity. All compounds starting from quinic acid **7** to yield ketone **8** were prepared according to the literature.[12–14] The preparation of compounds **9**, **10a,b**, **11a,b**, **12a,b**, **14**, **15** and macrocycles **29**, **33**, **37** as well as aminoalcohols **30**, **34** and **38** are described in the ESI†. Compound purities were assessed by NMR analysis.

1′,4′-*O*-(5)-Di-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (16). The butanediol-linked dimer **14** (416 mg, 0.670 mmol) was dissolved in 25 ml of MeOH–H_2O (5 : 1) and treated with Amberlyst 15 (230 mg). The solution was shaken for 18 h. After filtration and evaporation of the solvent, product **16** (342 mg, 0.633 mmol; 94% yield) was isolated as a colourless solid. Likewise, the HCl procedure described for compound **17** works equally well.

$R_f = 0.39$ (CH_2Cl_2–MeOH = 9 : 1); $[a]_D^{20} = -3.5$ ($c = 1$, MeOH); ^{1}H NMR (400 MHz, CD_3OD, TMS = 0 ppm): $\delta = 1.64$ (m, 4 H, 8-H), 1.70–1.88 (m, 8 H, 2-H, 6-H), 3.48 (ddd, $J = 11.5$, 5.6, 3.4 Hz, 2 H, 7_b-H), 3.59 (ddd, $J = 11.5$, 5.6, 3.4 Hz, 2 H, 7_a-H), 3.63 (ddd, $J = 3.8$, 3.6, 3.6 Hz, 2 H, 5-H), 3.81 (dd, $J = 3.8$, 3.0 Hz, 2 H, 4-H), 3.88 (ddd, $J = 10.5$, 4.8, 3.0 Hz, 2 H, 3-H), 4.31 (dddd, $J = 10.9$, 10.9, 4.6, 4.6 Hz, 2 H, 1-H) ppm; ^{13}C NMR (100 MHz, CD_3OD, CD_3OD = 49 ppm): $\delta = 27.9$ (t, C-8), 30.8 (t, C-6), 34.3 (t, C-2), 45.2 (d, C-1), 68.7 (d, C-3), 70.1 (t, C-7), 71.0 (d, C-4), 78.5 (d, C-5), 117.5 (s, CF_3, $^1J_{C,F} = 286.4$ Hz), 158.0 (s, $COCF_3$, $^2J_{C,F} = 36.8$ Hz) ppm; HRMS (ESI): m/z for positive ions; calculated: 563.1804 (M + Na^+); found: 563.1804.

1′,4′-*O*-(5)-Di-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*S*)-(trifluoroacetamido)-1,4-butane (17). The butanediol-linked dimer **15** (959 mg, 1.545 mmol) was dissolved in 33 ml MeOH–H_2O (10 : 1) and 0.5 ml concentrated $HCl_{(aq)}$. This solution was stirred for 1 h at RT. The solvents were evaporated in vacuum to yield the product **17** (838 mg, 1.551 mmol) in quantitative yield as a colourless solid. The Amberlyst 15 procedure described for compound **16** works equally well. The product is not very soluble in methanol or chloroform.

$R_f = 0.15$ (CH_2Cl_2–MeOH = 9 : 1); m.p. = 155–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD, TMS = 0 ppm): $\delta = 1.35$ (ddd, $J = 12.2$, 10.9, 10.9 Hz, 2 H, 6_{ax}-H), 1.62 (ddd, $J = 13.3$, 10.8, 2.6 Hz, 2 H, 2_{ax}-H), 1.66 (m, 4 H, 8-H), 1.97 (ddd, $J = 13.3$, 5.1, 4.2 Hz, 2 H, 2_{eq}-H), 2.22 (ddd, $J = 12.2$, 6.3, 4.1 Hz, 2 H, 6_{eq}-H), 3.46 (dd, $J = 8.3$, 2.8 Hz, 2 H, 4-H), 3.55–3.67 (m, 6 H, 5-H, 7-H), 4.01 (ddd, $J = 5.1$, 2.8, 2.6 Hz, 2 H, 3-H), 4.22 (dddd, $J = 10.9$, 10.8, 4.2, 4.1 Hz, 2 H, 1-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, CD_3OD = 49 ppm): $\delta = 27.8$ (t, 8-C), 35.1 (t, 6-C), 36.7 (t, 2-C), 44.9 (d, 1-C), 69.4 (d, 3-C), 70.9 (t, 7-C), 75.2 (d, 4-C), 78.3 (d, 5-C), 117.5 (s, CF_3, $^1J_{C,F} = 286.8$ Hz), 158.0 (s, $COCF_3$, $^2J_{C,F} = 36.9$ Hz) ppm; HRMS (ESI): m/z for negative ions; calculated: 539.1834 (M − H^+); found: 539.1846.

1′,4′-*O*-(5)-Di-3-allyl-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1-(*R*)-(trifluoroacetamido)-1,4-butane (19), 1′,4′-*O*-(5)-(3-Allyl)-(4′-allyl)-di-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (20) and 1′,4′-*O*-(5)-di-4-allyl-(3(*R*),4(*S*),5-(*R*)-trihydroxy-cyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (21). Tetrol **16** (674 mg, 1.248 mmol) and Bu_2SnO (776 mg, 3.12 mmol) were dissolved in 20 ml toluene and heated under reflux for 2 h until the solution has become homogeneous. The solvent was removed *in vacuo* and the residue was dissolved in 20 ml anhydrous DMF under an argon atmosphere and cooled to −15 °C. Allyl bromide (1.43 ml, 6.24 mmol) was added and the solution stirred for 10 min. Afterwards CsF (947 mg, 6.24 mmol) was added to the mixture and stirring was continued for 1 h. After removal of the icebath the reaction mixture was stirred for additional 20 h at RT. After dilution with 70 ml CH_2Cl_2, the organic layer was washed three times with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude oil was purified by column chromatography over silica gel (petroleum ether–ethyl acetate = 3 : 1) to afford a colourless oil (517 mg, 0.834 mmol; 67% yield) consisting of three regioisomers which were separated in the following step. For analytical reasons only a small amount was separated and characterised at this stage.

19: $R_f = 0.40$ (CH_2Cl_2–MeOH = 9 : 1); $[a]_D^{20} = -76.3$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta = 1.51$–1.58 (m, 2 H, 6_{ax}-H), 1.65 (m, 4 H, 11-H), 1.79 (ddd, $J = 14.0$, 4.5, 3.9 Hz, 2 H, 2_{ax}-H), 1.94 (ddd, $J = 14.0$, 5.4, 4.7 Hz, 2 H, 2_{eq}-H), 2.18 (br d, $J = 13.6$ Hz, 2 H, 6_{eq}-H), 3.26 (br s, 2 H, OH), 3.45 (ddd, $J = 12.0$, 5.8, 3.0 Hz, 2 H, 10_b-H), 3.61 (ddd, $J = 12.0$, 8.0, 4.0 Hz, 2 H, 10_a-H), 3.58–3.67 (m, 4 H, 5-H, 4-H), 3.93 (ddd, $J = 5.4$, 3.9, 3.0 Hz, 2 H, 3-H), 4.12 (ddt, $J = 12.5$, 6.0, 1.4 Hz, 1 H, 7_b-H), 4.14 (ddt, $J = 8.8$, 5.7, 1.3 Hz, 1 H, 7_b′-H), 4.25 (ddt, $J = 12.5$, 5.7, 1.3 Hz, 2 H, 7_a-H), 4.30 (ddddd, $J = 8.7$, 4.7, 4.4, 4.4, 3.9 Hz, 2 H, 1-H), 5.22 (ddd, $J = 10.3$, 2.7, 1.3 Hz, 2 H, 9_b-H), 5.29 (ddd, $J = 17.2$, 3.1, 1.3 Hz, 2 H, 9_a-H), 5.91 (ddt, $J = 17.2$, 10.3, 5.7 Hz, 2 H, 8-H), 7.70 (br s, 2 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta = 26.7$ (t, C-11), 31.4 (t, C-2), 32.6 (broad signal, t, C-6), 45.0 (d, C-1), 69.3 (t, C-10), 72.1 (t, C-7), 73.3 (broad signal, d, C-4), 75.4 (d, C-5), 77.2 (d, C-3), 115.8 (s, CF_3, $^1J_{C,F} = 287.9$ Hz), 117.7 (t, C-9), 134.1 (d, C-8), 156.0 (s, $COCF_3$, $^2J_{C,F} = 36.9$ Hz) ppm; HRMS (ESI): m/z for positive ions; calculated: 643.2430 (M + Na^+); found: 643.2430.

20: $R_f = 0.67$ (CH_2Cl_2–MeOH = 9 : 1); $[a]_D^{20} = -77.3$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta_H = 1.54$ (m, 2 H, 2′-H), 1.63 (m, 4 H, 11-H), 1.78 (m, 2 H, 6′-H), 1.96 (m, 2 H, 6-H), 2.19 (m, 2 H, 2-H), 2.83 (s, 1 H, OH), 3.06 (s, 1 H, OH), 3.31 (dd, $J = 8.4$, 2.9 Hz, 1 H, 4-H), 3.40–3.47 (m, 1 H, 10′-H), 3.49–3.55 (m, 1 H, 10′-H), 3.55–3.67 (m, 4 H, 4′-H, 5-H, 10-H), 3.92 (ddd, $J = 5.6$, 2.7, 2.7 Hz, 1 H, 3′-H), 4.12 (ddt, $J = 12.7$, 6.0, 1.3 Hz, 1 H, 7_a′-H), 4.18 (ddt, $J = 12.7$, 6.9, 1.3 Hz, 1 H, 7_b′-H), 4.21–4.26 (m, 4 H, 3-H, 5′-H, 7_a-H, 7_b-H), 4.26–4.34 (m, 2 H, 1-H, 1′-H), 5.21 (ddd, $J = 10.2$, 6.3, 2.3 Hz, 2 H, 9′-H), 5.30 (ddd, $J = 17.2$, 6.2, 3.2 Hz, 2 H, 9-H), 5.89 (ddd, $J = 10.2$, 5.8, 4.1 Hz, 1 H, 8-H), 5.95 (ddd, $J = 10.2$, 6.9, 4.1 Hz, 1 H, 8′-H), 7.69 (br s, 1 H, NH′), 7.95 (br s, 1 H, NH) ppm; ^{13}C-NMR

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(100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ = 26.7 (t, C-11′), 26.8 (t, C-11), 31.4 (t, C-6′), 32.6 (t, C-6), 32.6 (t, C-2′), 33.6 (t, C-2), 45.0 (d, C-1), 45.0 (C-1′), 69.1 (d, C-5), 69.2 (t, C-10′), 70.0 (t, C-10), 71.9 (t, C-7), 74.2 (d, C-3′), 75,3 (broad signal, d, C-4′), 76,8 (d, C-3), 81.2 (broad signal, d, C-4), 115.8 (s, CF_3, $^1J_{C,F}$ = 287.9 Hz), 117.2 (t, C-9′),117.6 (t, C-9), 134.0 (d, C-8′), 134.6 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 643.2430 (M + Na^+); found: 643.2430.

21: R_f = 0.70 (CH_2Cl_2–MeOH = 9 : 1); $[\alpha]_D^{20}$ = −84.2 (*c* = 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ = 1.52 (ddd, *J* = 13.6, 10.4, 3.7 Hz, 2 H, 6_{ax}-H), 1.61 (m, 4 H, 11-H), 1.75 (ddd, *J* = 14.4, 3.4, 2.9 Hz, 2 H, 2_{ax}-H), 1.99 (m, 2 H, 2_{eq}-H), 2.21 (br d, *J* = 12.9 Hz, 2 H, 6_{eq}-H), 3.03 (s, 2 H, OH), 3.30 (dd, *J* = 8.2, 3.1 Hz, 2 H, 4-H), 3.51 (ddd, *J* = 6.0, 5.8, 2.7 Hz, 2 H, 10′-H), 3.56 (ddd, *J* = 6.0, 5.8, 2.7 Hz, 2 H, 10-H), 3.62 (ddd, *J* = 10.4, 8.2, 4.3 Hz, 2 H, 5-H), 4.16 (ddt, *J* = 12.7, 5.6, 1.4 Hz, 2 H, 7_b-H), 4.24–4.19 (m, 2 H, 3-H), 4.23 (ddt, *J* = 12.7, 5.6, 1.4 Hz, 2 H, 7_a-H), 4.28 (ddddd, *J* = 7.9, 3.9, 3.9, 3.7, 3.4 Hz, 2 H, 1-H), 5.20 (ddd, *J* = 10.5, 3.0, 1.4 Hz, 2 H, 9_b-H), 5.29 (ddd, *J* = 17.2, 3.0, 1.4 Hz, 2 H, 9_a-H), 5.92 (dddd, *J* = 17.2, 10.5, 5.6, 5.6 Hz, 2 H, 8-H), 7.93 (br s, 2 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ = 26.8 (t, C-11), 32.6 (t, C-6), 33.6 (t, C-2), 45.0 (d, C-1), 69.1 (d, C-5), 70.0 (t, C-10), 71.9 (t, C-7), 74.2 (d, C-3), 81.2 (d, C-4), 115.8 (s, CF_3, $^1J_{C,F}$ = 287.5 Hz), 117.2 (t, C-9), 134.6 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.5 Hz) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 643.2430 (M + Na^+); found: 643.2430.

Compounds **25** and **26** were not isolated and were immediately employed in the next step for the preparation of dimers **27** and **28**.

1′,4′-*O*-(5)-Di-3-allyl-di-4-aceto-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (22), 1′,4′-*O*-(5)-(3-Allyl)-(4-aceto)-(3′-aceto)-(4′-allyl)-di-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (23) and 1′,4′-*O*-(5)-Di-4-allyl-di-3-aceto-[3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-trifluoroacetamido]-1,4-butane (24). To the mixture of regioisomers **19**, **20** and **21** (451 mg, 0.727 mmol) in 20 ml CH_2Cl_2 were added Et_3N (0.30 ml, 2.181 mmol), Ac_2O (0.27 ml, 2.908 mmol) and DMAP (40 mg, 0.327 mmol). This mixture was stirred for 2 h at RT. After removal of the solvent under reduced pressure the crude material was purified by flash column chromatography over silica gel (petroleum ether–ethyl acetate = 3 : 1) to yield the products **22** (63 mg, 0.089 mmol; 12%), **23** (253 mg, 0.359 mmol; 49%) and **24** (124 mg, 0.176 mmol; 24%) all as colourless oils.

22: R_f = 0.38 (petroleum ether–ethyl acetate = 1 : 1); $[\alpha]_D^{20}$ = −55.3 (*c* = 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ = 1.55 (m, 4 H, 11-H), 1.65–1.74 (m, 2 H, 6_b-H), 1.85–1.91 (m, 4 H, 2-H), 2.04–2.09 (m, 2 H, 6_a-H), 2.10 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, $COCH_3$), 3.42 (ddd, *J* = 11.7, 5.7, 3.1 Hz, 2 H, 10_b-H), 3.54 (ddd, *J* = 11.7, 5.7, 3.2 Hz, 2 H, 10_a-H), 3.69 (ddd, *J* = 8.3, 8.1, 4.0 Hz, 2 H, 5-H), 3.93 (ddd, *J* = 4.4, 4.3, 3.2 Hz, 2 H, 3-H), 4.01 (ddt, *J* = 12.5, 5.8, 1.2 Hz, 2 H, 7_b-H), 4.12 (ddt, *J* = 12.4, 5.8, 1.4 Hz, 2 H, 7_a-H), 4.24 (ddddd, *J* = 8.3, 4.8, 4.8, 4.6, 4.5 Hz, 2 H, 1-H), 4.93 (dd, *J* = 8.1, 2.4 Hz, 2 H, 4-H), 5.21 (ddd, *J* = 10.4, 2.7, 1.2 Hz, 2 H, 9_b-H), 5.26 (ddd, *J* = 17.2, 3.0, 1.6 Hz, 2 H, 9_a-H), 5.86 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 2 H, 8-H), 7.54 (br s, 2 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ = 21.0 (q, $COCH_3$), 26.7 (t, C-11), 31.9 (t, C-2), 33.5 (broad signal, t, C-6), 44.7 (d, C-1), 69.8 (t, C-10), 71.9 (t, C-7), 72.8 (d, C-5), 74.6 (broad signal, d, C-4), 75.3 (broad signal, d, C-3), 115.8 (s, CF_3, $^1J_{C,F}$ = 287.5 Hz), 118.0 (t, C-9), 133.8 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 170.2 (s, $COCH_3$) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 727.2641 (M + Na^+); found: 727.2626.

23: R_f = 0.44 (petroleum ether–ethyl acetate = 1 : 1); $[\alpha]_D^{20}$ = −33.8 (*c* = 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ = 1.61 (m, 4 H, 11-H), 1.70–2.05 (m, 8 H, 6-H, 2-H), 2.08 (s, 3 H, $COCH_3$′), 2.12 (s, 3 H, $COCH_3$), 3.43–3.61 (m, 4 H, 10-H), 3.64–3.68 (m, 2 H, 4′-H, 5′-H), 3.72 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1 H, 5-H), 3.94 (ddd, *J*= 4.1, 4.1, 3.9 Hz, 1 H, 3-H), 4.00–4.10 (m, 2 H, 7-H), 4.11–4.17 (m, 2 H, 7-H), 4.21 (ddddd, *J* = 9.3, 5.0, 4.8, 4.6, 4.5 Hz, 1 H, 1′-H), 4.30 (ddddd, *J*= 7.2, 5.4, 5.3, 5.2, 5.0 Hz, 1 H, 1-H), 4.97 (dd, *J*= 7.5, 2.1 Hz, 1 H, 4-H), 5.17 (m, 1 H, 3′-H), 5.18 (ddd, *J*= 10.4, 3.0, 1.3 Hz, 1 H, 9-H), 5.22 (ddd, *J* = 10.4, 2.8, 1.3 Hz, 1 H, 9-H), 5.24–5.31 (m, 2 H, 9-H), 5.87 (dddd, *J* = 16.0, 8.9, 5.7, 1.3 Hz, 1 H, 8′H), 5.89 (dddd, *J* = 16.1, 11.5, 5.7, 1.1 Hz, 1 H, 8-H), 6.58 (br d, *J* = 7.3 Hz, 1 H, NH′), 7.55 (br s, 1 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ = 21.0 (q, $COCH_3$), 26.6 (t, C-11′), 26.7 (t, C-11), 31.2 and 31.9 (t, C-2, C-6), 43.8 (d, C-1′), 44.6 (d, C-1), 69.3 (t, C-10′), 69.7 (t, C-10), 70.0 (d, C-3′), 72.0 (broad signal, t, C-7′), 72.1 (t, C-7), 72.9 (broad signal, d, C-5), 72.9 (broad signal, d, C-4), 74.8 (d, C-5′), 75.1 (broad signal, d, C-4′), 75.2 (broad signal, d, C-3), 115.8 (s, CF_3′, *J* = 288.2 Hz), 115.8 (s, CF_3, $^1J_{C,F}$ = 288.2 Hz), 116.9 (t, C-9′), 117.9 (t, C-9), 133.8 (d, C-8), 134.7 (d, C-8′), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 169.8 (s, $COCH_3$′), 170.2 (s, $COCH_3$) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 727.2641 (M + Na^+); found: 727.2626.

24: R_f = 0.54 (petroleum ether–ethyl acetate = 1 : 1); $[\alpha]_D^{20}$ = −3.1 (*c* = 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ_H = 1.64 (m, 4 H, 11-H), 1.77 (ddd, *J* = 13.1, 10.2, 2.4 Hz, 2 H, 6_{ax}-H), 1.82 (ddd, *J* = 11.7, 10.7, 10.5 Hz, 2 H, 2_{ax}-H), 1.90–2.08 (m, 4 H, 6_{eq}-H, 2_{eq}-H), 2.10 (s, *J* = 1.0 Hz, 3 H, $COCH_3$), 2.11 (s, *J* = 1.0 Hz, 3 H, $COCH_3$), 3.49 (ddd, *J* = 8.6, 5.8, 3.0 Hz, 2 H, 10_b-H), 3.54 (ddd, *J* = 8.6, 5.6, 3.2 Hz, 2 H, 10_a-H), 3.65–3.70 (m, 4 H, 4-H, 5-H), 4.01 (ddt, *J* = 13.0, 5.6, 1.4 Hz, 2 H, 7_b-H), 4.14 (ddt, *J* = 13.0, 5.6, 1.5 Hz, 2 H, 7_a-H), 4.21 (ddddd, *J* = 10.5, 10.2, 8.6, 4.7, 4.7 Hz, 2 H, 1-H), 5.15–5.22 (m, 4 H, 9_b-H, 3-H), 5.29 (ddd, *J* = 17.2, 3.3, 1.7 Hz, 2 H, 9_a-H), 5.89 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 2 H, 8-H), 6.48 (br d, *J* = 8.6 Hz, 2 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ_C = 21.1 (q, $COCH_3$), 26.6 (t, C-11), 31.2 (t, C-6, C-2), 43.8 (d, C-1), 69.3 (t, C-10), 70.0 (d, C-3), 72.1 (t, C-7), 74.8 (d, C-4), 75.3 (d, C-5), 115.7 (s, CF_3, $^1J_{C,F}$ = 288.1 Hz), 117.0 (t, C-9), 134.8 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.9 Hz), 169.8 (s, $COCH_3$) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 727.2641 (M + Na^+); found: 727.2647.

1′,4′-*O*-(5)-Di-4-allyl-di-3-aceto-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*S*)-(trifluoroacetamido)-1,4-butane (27) and 1′,4′-*O*-(5)-(3-Allyl)-(4-aceto)-(3′-aceto)-(4′-allyl)-di-(3(*R*),4(*S*),5(*R*)-trihydroxycyclohexane)-1(*R*)-(trifluoroacetamido)-1,4-butane (28). In analogy to the procedure described for the synthesis of compounds **19**, **20** and **21**, tetrol **17** (490 mg, 0.907 mmol) was dissolved in 25 ml toluene and Bu_2SnO (564 mg, 2.268 mmol) was added. For the second step CsF (689 mg, 4.535 mmol) and allyl bromide (0.38 ml, 4.535 mmol) in 25 ml DMF were employed. The resulting products were filtered through a pad of silica gel (ethyl acetate–petroleum ether = 3 : 1) to yield the mixture

of two regioisomers **25** and **26** (661 mg, 1.066 mmol), which were employed in the next step without further separation or purification. According to the procedure for compounds **22–24**, the residue was dissolved in 20 ml CH_2Cl_2 and treated with Et_3N (0.34 ml, 3.192 mmol), Ac_2O (0.40 ml, 4.256 mmol) and DMAP (12.5 mg, 0.105 mmol). The crude material was purified by column chromatography over silica gel (petroleum ether–ethyl acetate = 2.5 : 1) to yield bisallyl ethers **27** (411 mg, 0.584 mmol; 64% for two steps) and **28** (101 mg, 0.143 mmol, 16%).

27: $R_f = 0.44$ (petroleum ether–ethyl acetate = 1 : 1); $[\alpha]_D^{20} = -36$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta =$ 1.65–1.71 (m, 4 H, 11-H), 1.74 (br dd, $J = 4.1$, 3.9 Hz, 2 H, 6_b-H), 1.90 (ddd, $J = 12.5$, 4.0, 3.9 Hz, 2 H, 2_b-H), 2.07 (s, 6 H, $COCH_3$), 2.08 (br dd, $J = 12.1$, 3.9 Hz, 2 H, 6_a-H), 2.11 (br dd, $J = 7.3$, 3.9 Hz, 2 H, 2_a-H), 3.52 (ddd, $J = 11.1$, 5.5, 3.1 Hz, 2 H, 10′-H), 3.69 (ddd, $J = 11.8$, 5.6, 2.9 Hz, 2 H, 10-H), 3.79 (ddd, $J = 4.1$, 3.8, 3.7 Hz, 2 H, 5-H), 3.89 (dd, $J = 4.0$, 3.8 Hz, 2 H, 4-H), 4.04 (ddt, $J = 12.9$, 5.6, 1.4 Hz, 2 H, 7′-H), 4.14 (ddt, $J = 12.9$, 5.6, 1.4 Hz, 2 H, 7-H), 4.34 (ddddd, $J = 7.6$, 3.9, 3.9, 3.9, 3.9 Hz, 2 H, 1-H), 5.15 (ddd, $J = 12.5$, 4.0, 3.0 Hz, 2 H, 3-H), 5.19 (ddd, $J = 10.4$, 2.9, 1.3 Hz, 2 H, 9′-H), 5.27 (ddd, $J = 17.2$, 3.2, 1.6 Hz, 2 H, 9-H), 5.87 (ddt, $J = 17.2$, 10.4, 5.6 Hz, 2 H, 8-H), 7.83 (br s, 2 H, NH) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3 = 77$ ppm): $\delta = 21.1$ (q, $COCH_3$), 26.7 (t, C-11), 29.0 (broad signal, t, C-6), 29.9 (broad signal, t, C-2), 45.3 (d, C-1), 67.9 (d, C-3), 69.9 (t, C-10), 72.4 (t, C-7), 73.0 (broad signal, d, C-4), 77.6 (d, C-5), 115.9 (s, CF_3, $^1J_{C,F} = 288.1$ Hz), 117.2 (t, C-9), 134.6 (d, C-8), 156.1 (s, $COCF_3$, $^2J_{C,F} = 36.7$ Hz), 170.3 (s, $COCH_3$) ppm. HRMS (ESI): m/z for positive ions; calculated: 727.2641 ($M + Na^+$); found: 727.2650.

28: Not every signal could be unequivocally assigned to each of the two cyclohexane rings. $R_f = 0.39$ (petroleum ether–ethyl acetate = 1 : 1); $[\alpha]_D^{20} = -46.2$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta =$ 1.60–1.79 (m, 7 H, 11-H, CH_2), 1.86–2.08 (m, 4 H, 2_b′-H, CH_2), 2.08 (s, 3 H, $COCH_3$′), 2.11 (s, 3 H, $COCH_3$), 2.14 (dddm, $J = 8.1$, 4.1, 0.9 Hz, 1 H, 2_a′-H), 3.51 (ddd, $J = 8.8$, 5.7, 5.7 Hz, 1 H, 10-H), 3.58 (ddd, $J = 9.0$, 5.8, 5.8 Hz, 1 H, 10′H), 3.68 (ddd, $J = 11.8$, 6.5, 2.4 Hz, 2 H, 10-H), 3.75–3.82 (m, 3 H, 3-H, 5′-H, 5-H), 3.88 (br s, 1 H, 4′-H), 3.99 (ddt, $J = 12.6$, 5.8, 1.3 Hz, 1 H, 7_b-H), 4.03 (ddt, $J = 5.8$, 4.5, 1.3 Hz, 1 H, 7_a-H), 4.06 (ddt, $J = 5.6$, 4.4, 1.4 Hz, 1 H, 7_b′-H), 4.14 (ddt, $J = 12.9$, 5.6, 1.4 Hz, 1 H, 7_a′-H), 4.35 (ddddd, $J = 8.0$, 4.0, 4.0, 4.0, 4.0 Hz, 2 H, 1′-H, 1-H), 5.14 (ddd, $J = 11.6$, 4.1, 2.6 Hz, 1 H, 3′-H), 5.18 (ddd, $J = 5.7$, 3.0, 1.3 Hz, 1 H, 9_b-H), 5.20 (ddd, $J = 5.7$, 3.0, 1.3 Hz, 1 H, 9_a-H), 5.24 (ddd, $J = 7.5$, 3.2, 1.6 Hz, 1 H, 9_b′-H), 5.29 (ddd, $J = 7.4$, 3.2, 1.6 Hz, 1 H, 9_a′-H), 5.33 (br s, 1 H, 4-H), 5.85 (dddd, $J = 11.3$, 10.4, 5.8, 3.3 Hz, 1 H, 8-H), 5.88 (dddd, $J = 11.4$, 10.4, 5.8, 3.3 Hz, 1 H, 8-H), 7.68 (br s, 1 H, NH), 7.77 (br s, 1 H, NH′) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3 = 77$ ppm): $\delta = 21.0$ (q, $COCH_3$), 21.1 (q, $COCH_3$), 26.6 (t, C-11), 26.7 (t, C-11), 29.2 (broad signal, t), 29.9 (broad signal, t), 30.0 (broad signal, t), 31.1 (broad signal, t), 45.3 (d, C-1′), 45.3 (d, C-1), 67.9 (d, C-3′), 69.9 (broad signal, d, C-4), 70.0 (t, C-10), 70.3 (t, C-7), 72.4 (t, C-7′), 74.0 (broad signal, d, C-4′), 76.3 (broad signal, d, C-3), 77.2 (d, C-5), 77.6 (d, C-5), 115.9 (s, CF_3, $^1J_{C,F} = 287.5$ Hz), 117.2 (t, C-9′), 117.4 (t, C-9), 134.4 (d, C-8), 134.6 (d, C-8), 156.0 (s, $COCF_3$, $^2J_{C,F} = 36.5$ Hz), 156.0 (s, $COCF_3$, $^2J_{C,F} = 36.6$ Hz), 170.2 (s, $COCH_3$), 170.3 (s, $COCH_3$) ppm. HRMS (ESI): m/z for positive ions; calculated: 727.2641 ($M + Na^+$); found: 727.2653.

Macrocycles 31a and 31b. According to the procedure described for the preparation of macrocycle **29**, bisallylether **23** (328 mg, 466 mmol) and Grubbs catalyst **13** (38 mg, 0.047 mmol) were dissolved in 50 ml degassed benzene under an argon atmosphere and heated at 40 °C for 36 h. After 6 h an additional portion of catalyst **13** (19 mg, 0.023 mmol) was added. Then, all volatile compounds were removed under reduced pressure and the residue was filtered through silica gel (petroleum ether–ethyl acetate = 2 : 1) to yield a colourless oil (236 mg, 0.349 mmol; 75% yield). The product was immediately employed in the next step.

A portion of this crude material (180 mg, 0.266 mmol) was dissolved in ethyl acetate–CH_2Cl_2–MeOH (16 : 8 : 1; 12.5 ml), Pt_2O (24.2 mg, 0.106 mmol) was added and the reaction mixture was kept under hydrogen atmosphere for 14 h. The resulting mixture of products **31a** and **31b** were separated by flash column chromatography over silica gel (petroleum ether–ethyl acetate = 2 : 1) to yield macrocycle **31a** (77.5 mg, 0.114 mmol; 42%) as a colourless oil. Besides a mixed fraction (27.4 mg, 0.040 mmol; 15%), macrocycle **31b** was collected in a minor fraction (15.9 mg, 0.023 mmol; 9%).

31a: m.p.: 230–232 °C; $R_f = 0.60$ (CH_2Cl_2–MeOH = 9 : 1); $[\alpha]_D^{20} = -42.4$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$, TMS = 0 ppm): $\delta =$ 1.43–1.54 (m, 4 H, 6_b-H, CH_2), 1.55–1.76 (m, 12 H, 6_b′-H, CH_2), 1.79 (ddd, $J = 14.0$, 4.2, 2.4 Hz, 1 H, 2_b-H), 1.87–1.97 (m, 2 H, 2_a′-H, 2_b′-H), 2.02 (ddd, $J = 14.0$, 3.9, 3.8 Hz, 1 H, 2_a-H), 2.09–2.12 (m, 1 H, 6_a′-H), 2.11 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, $COCH_3$), 2.14–2.21 (m, 1 H, 6_a-H), 3.38 (ddd, $J = 9.5$, 8.6, 3.6 Hz, 1 H, 7_b′-H), 3.41 (dd, $J = 7.3$, 2.5 Hz, 1 H, 4′-H), 3.50 (ddd, $J =$ 8.6. 8.6, 3.7 Hz, 1 H, 10_b-H), 3.54–3.64 (m, 5 H, 5-H, CH_2), 3.65 (ddm, $J = 9.0$, 5.4 Hz, 1 H, 5′-H), 3.68 (ddd, $J = 9.5$, 4.7, 4.6 Hz, 1 H, 10_a-H), 3.78 (ddd, $J = 10.1$, 4.9, 4.9 Hz, 1 H, 7_a′-H), 3.82 (ddd, J= 11.9, 3.6, 2.9 Hz, 1 H, 3-H), 4.20 (ddddd, $J = 12.4$, 12.4, 8.0, 4.2, 3.9 Hz, 1 H, 1-H), 4.35 (ddddd, $J = 8.1$, 4.6, 4.6, 4.5, 4.3 Hz, 1 H, 1′-H), 5.29 (dd, $J = 2.9$, 2.7 Hz, 1 H, 4-H), 5.50 (br s, 3′-H), 6.50 (br d, $J = 8.0$ Hz, 1 H, NH), 7.19 (br d, $J = 8.1$ Hz, 1 H, NH′) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$, $CDCl_3 = 77$ ppm): $\delta = 20.9$ (t, $COCH_3$), 21.1 (t, $COCH_3$), 25.2 (t, C-8′, C-11′), 26.2 (t, C-8), 27.0 (t, C-11), 31.3 (t, C-2), 31.5 (t, C-2′), 32.4 (t, C-6), 33.3 (t, C-6′), 43.7 (d, C-1′), 44.6 (d, C-1), 67.8 (d, C-4), 68.1 (t, C-10′), 69.4 (d, C-3′), 69.7 (t, C-7′), 69.9 (t, C-7), 70.3 (t, C-10), 71.0 (d, C-3), 73.6 (d, C-5′), 74.2 (d, C-5), 78.7 (broad signal, d, C-4′), 115.7 (s, CF_3, $^1J_{C,F} = 288.0$ Hz), 115.8 (s, CF_3, $^1J_{C,F} = 287.9$ Hz), 155.2 (s, $COCF_3$, $^2J_{C,F} = 36.8$ Hz), 156.4 (s, $COCF_3$, $^2J_{C,F} = 37.0$ Hz), 169.3 (q, $COCH_3$), 170.0 (q, $COCH_3$) ppm; HRMS (ESI): m/z for positive ions: calculated: 701.2485 ($M + Na^+$), found: 701.2490.

31b: m.p.: 205–208 °C; $R_f = 0.67$ (CH_2Cl_2–MeOH = 9 : 1); $[\alpha]_D^{20} = -63.8$ ($c = 1$, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$, TMS = 0 ppm): $\delta =$ 1.43–1.54 (m, 4 H, 6_b-H, CH_2), 1.55–1.76 (m, 12 H, 6_b′-H, CH_2), 1.79 (ddd, $J = 15.0$, 4.4, 2.4 Hz, 1 H, 2_b-H), 1.87–1.97 (m, 2 H, 2_a′-H, 2_b′-H), 2.02 (ddd, $J = 15.1$, 5.7, 2.6 Hz, 1 H, 2_a-H), 2.11 (s, 3 H, $COCH_3$), 2.09–2.12 (m, 1 H, 6_a′-H), 2.13 (s, 3 H, $COCH_3$), 2.42 (br d, $J = 13.7$ Hz, 1 H, 6_a-H), 3.37 (dd, $J = 6.8$, 3.0 Hz, 1 H, 4′-H), 3.43–3.50 (m, 4 H, CH_2), 3.50–3.56 (m, 2 H, CH_2), 3.57–3.63 (m, 2 H, CH_2), 3.63–3.70 (m, 4 H, CH_2, 5′-H), 3.83 (dd, $J = 8.3$, 4.0 Hz, 1 H, CH_2), 3.89 (ddd, $J = 11.2$, 10.5, 4.2 Hz, 1 H, 5-H), 4.00 (br dd, $J = 5.4$, 2.7 Hz, 2 H, 3-H), 4.29–4.34 (m, 1 H, 1′-H), 4.35–4.40 (m, 1 H, 1-H), 4.77 (dd, $J = 10.1$, 2.7 Hz, 1 H, 4-H), 5.45 (br s, 3′-H), 6.90 (br s, 1 H, NH′), 8.24 (br d, $J = 7.8$ Hz, 1 H, NH) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$, $CDCl_3 = 77$ ppm):

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δ= 20.9 (t, $COCH_3$), 21.1 (t, $COCH_3$), 25.2 (t), 26.2 (t), 27.4 (t), 32.2 (t, C-2, C-6′), 34.4 (t, C-6), 45.4 (d, C-1′), 45.4 (d, C-1), 68.4 (t, C-10, C-10′), 68.9 (t), 69.5 (d, C-3′), 70.0 (d, C-5), 70.7 (t), 72.9 (t, C-7, C-7′), 73.1 (d, C-5′), 77.1 (d, C-4), 77.8 (d, C-3), 78.5 (broad signal, d, C-4′), 115.8 (s, CF_3, $^1J_{C,F}$ = 288.1 Hz), 116.0 (s, CF_3, $^1J_{C,F}$ = 288.6 Hz), 155.7 (s, $COCF_3$, $^2J_{C,F}$ = 36.5 Hz), 156.0 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 169.2 (q, $COCH_3$), 170.1 (q, $COCH_3$) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 701.2485 ($M + Na^+$); found: 701.2452. HRMS (ESI): *m/z* for negative ions: calculated: 677.2509 ($M - H^+$); found: 677.2493.

Aminoalcohol 32. Based on the procedure described for the preparation of aminoalcohol **30**, a mixture of the protected aminoalcohols **31a** and **31b** (27.4 mg, 0.040 mmol) were dissolved in a mixture of water and methanol (1 : 1; 4 ml) and were treated with NaOH (19.4 mg, 0.485 mmol). The solution was stirred for 2 h at RT and was then neutralised with dry ice. After evaporation of all volatile compounds the residue was purified by reverse-phase chromatography (RP18; $H_2O \rightarrow H_2O$–MeOH = 4 : 1 → 3 : 2 → 1 : 1) to furnish product **32** (12.9 mg, 0.032 mmol; 81%) as a colourless sticky solid.

$[\alpha]_D^{20} = -11.1$ (*c* = 1, MeOH); ^{1}H NMR (400 MHz, CD_3OD, CD_3OH = 3.31 ppm): δ = 1.46–1.80 (m, 14 H), 1.81–1.91 (m, 2 H, 2-H, 6-H), 2.90 (dddd, *J* = 11.2, 11.2, 3.9, 3.9 Hz, 1 H, 1-H), 2.96 (dddd, *J* = 9.5, 9.5, 3.9, 3.9 Hz, 1 H, 1′-H), 3.40–3.47 (m, 2 H, 4′-H, CH_2), 3.52–3.63 (m, 5 H, 5-H, CH_2), 3.63–3.70 (m, 3 H, 5-H, 2 × CH_2), 3.72–3.79 (m, 2 H, 5′-H, CH_2), 3.88 (ddd, *J* = 10.0, 3.5, 2.7 Hz, 1 H, 3′-H), 3.94 (br d, *J* = 2.7 Hz, 1 H, 4-H) ppm; ^{13}C NMR (100 MHz, CD_3OD, CD_3OD = 49 ppm): δ 26.7 (t), 27.1 (t), 27.2 (t), 28.3 (t), 34.9 (t, C-2), 35.6 (t, C-6), 36.3 (t), 38.6 (t), 45.7 and 45.9 (d, C-1, C-1′), 68.6 (t), 69.1 (d, C-4, C-3′), 70.2 (t), 70.8 (t), 71.4 (t), 76.1 (d, C-5, C-5′), 79.2 (d, C-3), 80.0 (d, C-4′) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 425.2628 ($M + Na^+$); found: 425.2636.

Macrocycle 35. According to the procedure described for the preparation of macrocycle **29**, bisallylether **27** (361 mg, 0.512 mmol) and Grubbs catalyst **13** (31 mg, 0.010 mmol) were dissolved in 170 ml degassed CH_2Cl_2. The resulting crude product was purified by column chromatography over silica gel (ethyl acetate–petroleum ether = 3 : 1) to yield the unsaturated macrocycle (230 mg, 0.340 mmol; 66%) as a colourless oil as well as the starting material **27** (43.2 mg, 0.061 mmol; 12%). The macrocycle (230 mg, 0.340 mmol) was dissolved in 5 ml of ethyl acetate–CH_2Cl_2–MeOH and treated with Pt_2O (31 mg, 0.136 mmol) under a hydrogen atmosphere to furnish macrocycle **35** (187 mg, 0.276 mmol; 81%) as a colourless oil.

R_f = 0.48 (CH_2Cl_2–MeOH = 9 : 1); $[\alpha]_D^{20} = -48.2$ (*c* = 1, $CHCl_3$); room temperature NMR spectra with $CDCl_3$ as solvent showed broadened signals: ^{1}H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ = 1.31–1.45 (m, 2 H, 6_b-H), 1.46–1.71 (m, 10 H, 2_b-H, 8-H and 11-H), 1.98–2.09 (m, 8 H, Ac, 2_a-H), 2.11–2.29 (m, 2 H, 6_a-H), 3.21–3.33 (m, 2 H, CH_2), 3.35–3.48 (m, 4 H, 4-H, CH_2), 3.57–3.74 (m, 6 H, 5-H, CH_2), 4.12–4.26 (m, 2 H, 1-H), 5.18–5.35 (br s, 2 H, 3-H), 6.64–7.11 (br m, 2 H, NH) ppm; at 220 K signals sharpened considerably and three ring conformations (labelled A, B, C) became visible: ^{1}H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): δ_H = 1.11–1.21 (m, 3 H, $6_{B,ax}$-H), 1.21–1.30 (m, 1 H), 1.31–1.43 (m, 3 H), 1.45–1.61 (m, 4 H), 1.62–1.69 (m, 1 H, $6_{A,eq}$-H), 1.79–1.94 (m, 3 H, $6_{A,ax}$-H), 2.00–2.06 (m, 3 H), 2.08 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$), 2.53–2.61 (m, 1 H, $6_{B,eq}$-H), 3.02–3.10 (m, 1 H, 7_B′-H), 3.12–3.19 (m, 2 H, 4_B-H, 10_B′-H), 3.20–3.31 (m, 1 H, 7_A′-H), 3.33–3.53 (m, 1 H + *2 H*, 5_C-H, 10_A′-H, 10_C′-H), 3.57–3.69 (m, 3 H, 5_B-H, 10_A-H, 7_A-H), 3.70–3.77 (m, 2 H, 4_A-H, 5_A-H), 3.78–3.84 (m, 1 H, 10_B-H), 3.85–3.92 (m, 1 H, 7_B-H), 4.13–4.24 (m, 1 H, 1_B-H), 4.24–4.30 (m, 1 H, 1_A-H), 4.99 (dd, *J* = 11.6, 5.5 Hz, 3_A-H), 5.44 (br t, *1 H*, 3_c-H), 5.53–5.59 (br s, 1 H, 3_B-H), 7.00–7.08 (br s, 1 H, NH_B), 8.28 (br d, *J* = 7.4 Hz, 1 H, NH_A) ppm; at room temperature with CD_3OD as solvent the signals also sharpened: ^{1}H NMR (400 MHz, CD_3OD, TMS = 0 ppm): δ = 1.37 (ddd, *J* = 12.1, 12.0, 11.4 Hz, 2 H, 6_b-H), 1.50–1.77 (m, 10 H, 2_b-H, 8-H, 11-H), 2.00 (ddd, *J* = 13.8, 3.9, 3.5 Hz, 2 H, 2_a-H), 2.09 (s, 6 H, $COCH_3$), 2.27 (ddd, *J* = 12.1, 4.5, 4.4 Hz, 2 H, 6_a-H), 3.22 (dd, *J* = 9.4, 3.2 Hz, 2 H, 4-H), 3.44–3.51 (m, 2 H, CH_2), 3.52–3.61 (m, 2 H, CH_2), 3.53 (ddd, *J* = 11.4, 9.4, 4.4 Hz, 2 H, 5-H), 3.65–3.73 (m, 4 H, CH_2), 4.10 (dddd, *J* = 12.1, 12.0, 4.1, 3.9 Hz, 2 H, 1-H), 5.49 (ddd, *J* = 3.5, 3.2, 3.1 Hz, 2 H, 3-H) ppm; at room temperature with $CDCl_3$ as solvent the signals showed broadened signals; C-4 not detectable: ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): δ= 21.1 (t, $COCH_3$), 26.0 and 26.3 (t, C-8, C-11), 32.2 (t, broad signal), 44.4 (d, C-1), 67.2 (d, C-3), 69.2 (t), 70.3 (t, broad signal), 75.6 (d, C-5), no signal for C-4, 115.7 (s, CF_3, $^1J_{C,F}$ = 288.1 Hz), 156.4 (s, $COCF_3$, $^2J_{C,F}$ = 36.9 Hz), 170.2 (s, $COCH_3$) ppm; room temperature in CD_3OD: ^{13}C NMR (125 MHz, CD_3OD, CD_3OD = 49 ppm): δ= 21.0 (t, $COCH_3$), 27.8 and 28.2 (t, C-8, C-11), 34.7 (t, C-2), 36.6 (t, C-6), 44.6 (d, C-1), 69.3 (d, C-3), 71.6 and 71.7 (t, C-7, C-10), 77.2 (d, C-5), 82.7 (d, C-4), 117.4 (s, CF_3, $^1J_{C,F}$ = 286.7 Hz), 158.2 (s, $COCF_3$, $^2J_{C,F}$ = 37.0 Hz), 171.9 (s, $COCH_3$) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 701.2485 ($M + Na^+$); found: 701.2482.

Aminoalcohol 36. Based on the procedure described for the preparation of aminoalcohol **30**, the protected aminoalcohol **35** (77.6 mg, 0.114 mmol) and NaOH (91.5 mg, 2.288 mmol) were dissolved in a mixture of water and methanol (1 : 1; 4 ml). The resulting residue was purified by reverse-phase chromatography (RP18; $H_2O \rightarrow H_2O$–MeOH = 4 : 1 → 3 : 2 → 1 : 1) to isolate aminoalcohol **36** (28 mg, 0.070 mmol; 61%) as a colourless syrup.

$[\alpha]_D^{20} = -93.4$ (*c* = 1, MeOH); ^{1}H NMR (400 MHz, CD_3OD, CD_3OH = 3.31 ppm): δ = 1.11 (ddd, *J* = 11.8, 11.8, 11.6 Hz, 2 H, 6_b-H), 1.29 (ddd, *J* = 13.5, 11.5, 2.6, 2 H, 2_b-H), 1.68 (m, 4 H, 11-H), 1.75 (m, 4 H, 8-H), 2.02 (ddd, *J* = 13.5, 6.5, 3.5 Hz, 2 H, 2_a-H), 2.21 (ddd, *J* = 11.8, 7.1, 4.0 Hz, 2 H, 6_a-H), 3.08 (dddd, *J* = 11.6, 11.5, 4.0, 3.9 Hz, 2 H, 1-H), 3.11 (dd, *J* = 9.2, 3.0 Hz, 2 H, 4-H), 3.47 (dt, *J* = 4.5, 5.2 Hz, 2 H, 7_b-H), 3.52–3.66 (m, 4 H, 5-H, 10_b-H), 3.67 (ddd, *J* = 8.9, 6.0, 5.6 Hz, 2 H, 10_a-H), 3.75 (dt, *J* = 8.7, 5.4 Hz, 2 H, 7_a-H), 4.14 (ddd, *J* = 3.1, 3.5, 2.6 Hz, 2 H, 3-H) ppm; ^{13}C NMR (100 MHz, CD_3OD, CD_3OD = 49 ppm): δ = 28.0 and 28.1 (t, C-8, C-11), 41.0 (t, C-2, C-6), 44.5 (d, C-1), 67.5 (d, C-3), 71.3 (t, C-7, C-10), 77.5 (d, C-5), 85.0 (d, C-4) ppm; HRMS (ESI): *m/z* for positive ions: calculated: 403.2808 ($M + H^+$); found: 403.2819.

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