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Synthesis of Cyclic γ-Amino Acids for Foldamers and Peptide Nanotubes

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Cyclic γ-amino acids are molecular building blocks of great interest in peptide and foldamer chemistry, as they allow the preparation of new structures that are not found in Nature. In this paper, we describe the synthesis of cyclic γ-amino acids that have a *cis* relationship between the amino and the carboxylic acid groups. This arrangement, in most cases, induces the resulting peptides to adopt a flat conformation, which makes them appropriate for the design of foldamers that adopt β-sheet-type structures.

Introduction

Peptides and proteins are essential components of living organisms and are responsible for, amongst other things, catalytic activity and structural or mechanical functions. In order to carry out these functions, they fold into specific and characteristic three-dimensional structures.[1] These structures and functions arise mainly from the combination of the 20 proteinogenic amino acids (Aas). The synthesis of non-natural amino acids has attracted interest from chemists and materials scientists, due to the envisaged large number of possible applications.[2,3] In addition, in recent years, chemists have started to develop oligomeric structures made from non-natural monomers, called foldamers,[4] in the search for new molecules that can adopt special and unique structures with new properties for materials or therapeutical sciences.[5] The search for new monomers that can be used in the synthesis of foldamers is still of great interest. In addition to β-amino acids,[6] γ-amino acids are powerful building blocks due to their unique structural properties derived from the additional carbon atoms between the carbonyl and amino groups.[7] The preparation of a large variety of derivatives of these compounds is possible, because a range of side-chains can be introduced at the α-, β- and/or γ-positions.[8] Cyclic amino acids are of particular interest in foldamer synthesis, due to their conformational restrictions, and the particular orientation of the carbonyl and amino groups.[9] Finally, γ-amino acids have been prepared and studied because of their biological applications as GABA mimics or antiviral agents.[10]

In the last few years, we have focussed on the design and synthesis of supramolecular structures derived from cyclic peptides (CPs) that contain γ-aminocycloalkanecarboxylic acids (γ-Acas).[11,12] We have shown that peptides of α- and γ-amino acids, and more recently, peptides of all γ-amino acids,[13] of alternating chirality can adopt a flat conformation that allows stacking to form dimers or nanotubes. The main characteristic of these CPs is the projection of the β-carbon of each γ-amino acid towards the cavity, a situation that modifies the properties of the ensemble. In this paper, we present our results on the preparation of a variety of γ-Acas that may be of interest for the design not only of nanotubes but also of foldamers. A common feature of the compounds is the *cis*-relationship between the carboxylic acid and amino groups, which would make then particularly appropriate for β-strand conformations (Figure 1). The strand, because of the rigidity of the cyclic ring, would be bent by an angle ϕ that would depend on the ring size (n = 0, 1, 2, etc.). Such a structure would give rise to coiled

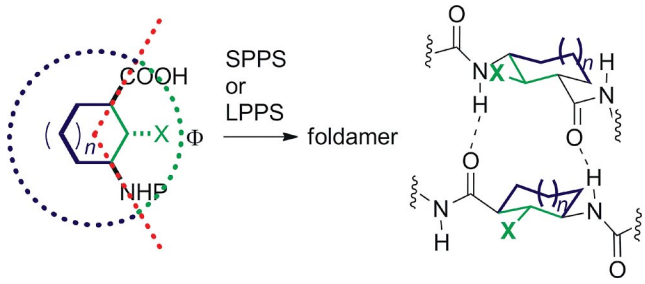

Figure 1. General structure of cyclic γ-amino acids (γ-Aca) for use in foldamer synthesis described in this article, and proposed properties of the oligomer β-strand derived from the γ-Aca (SPPS = solid-phase peptide synthesis, LPPS = liquid-phase peptide synthesis).

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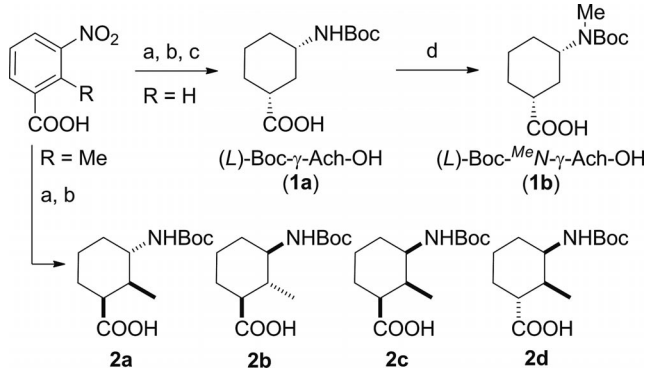
strands in which the properties of the major arc would depend on the properties of the longer chain (C-4, C-5 and so on) of the cyclic moiety, while the internal part, i.e., the minor arc, would depend on the properties of the β-carbon (C-2) and its functionalization (X ≠ H).

Results and Discussion

The first γ-Aca prepared in this study was 3-aminocyclohexanecarboxylic acid (γ-Ach-OH), which was obtained in three steps from 3-nitrobenzoic acid (Scheme 1).[11a] The first step was the simultaneous reduction of the nitro group and aromatic ring with Raney Nickel under hydrogen pressure (100 bar) at 150 °C. These conditions gave the *cis* isomer of the 3-aminocyclohexanecarboxylic acid.[11,14] The resulting amino acid was treated with Boc anhydride, and the racemic Boc-γ-Ach-OH (Boc = *tert*-butoxycarbonyl) was resolved by crystallization in the presence of (+)-1-phenylethanamine, an inexpensive commercial chiral amine (both enantiomers are available at similar prices). This amine has proved to be very useful, and most of the chiral Boc-protected γ-Acas that we have prepared were resolved in a similar manner. In general, the *R* isomer, (+)-1-phenylethanamine, crystallized together with the 1*R*,3*S* enantiomer (L-Boc-γ-Ach-OH, **1a**), while the *S* enantiomer provided the 1*S*,3*R*-configured amino acid (D-Boc-γ-Ach-OH).[15] At least two co-crystallizations were generally required to obtain the Boc-Aca with an enantiomeric excess higher than 97%.



Scheme 1. *Reagents and conditions:* (a) H_2 (100 atm), Raney Ni, NaOH, H_2O, 150 °C, 80%; (b) $(Boc)_2O$, DIEA (diisopropylethylamine), H_2O/dioxane, 80%; (c) (*R*)-phenylethanamine, $CHCl_3$/hexanes; (d) NaH, MeI, THF, 88%.

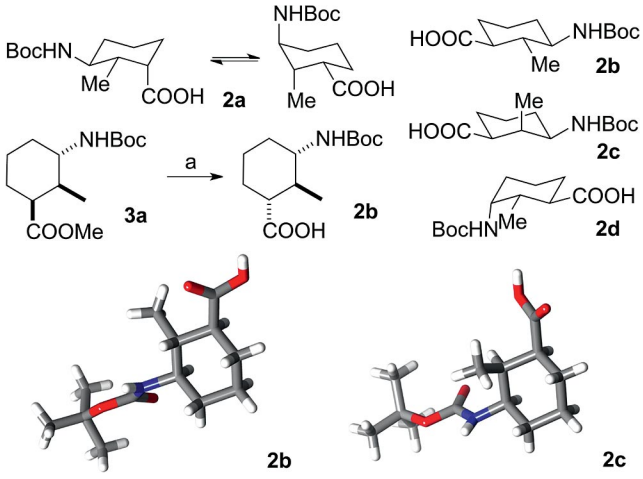
The Boc-protected amino acid can be transformed into other derivatives, such as *N*-alkylated compounds. *N*-Methyl amino acids are known to increase membrane permeability and enhance other biologically relevant properties.[16] In addition, the self-assembling properties of cyclic peptides have been studied in organic solvents by selective homochiral *N*-alkylation.[11,12,17] Thus, the *N*-methylated derivative (**1b**) was prepared by treatment of Boc-Ach-OH with NaH in the presence of iodomethane. The use of these amino acids in cyclic peptides of alternating α- and γ-Aas confirmed that the resulting peptides adopt the flat conformation and self-assemble into dimers that resemble the characteristic β-sheet structure present in nanotubes.[11,12]

The partially hydrophobic character of the cavity of the ensemble provided by the γ-Ach residue led us to study the preparation of the β-methylated derivative using a similar procedure. Thus, the 2-methyl-3-nitrobenzoic acid was treated under similar conditions to give a mixture of the four possible diastereomers in a 3:3:3:1 ratio. Unfortunately, these compounds could not be separated by flash chromatography, but selective washes of the Boc-protected amino acids with dichloromethane allowed the separation of the most soluble fractions, i.e., *trans*,*trans* isomer **2b** and minor isomer **2d**, while the insoluble solid was enriched in **2a** and **2c**. Crystallization of this solid mixture from methanol gave pure **2c**, while the mother liquors contained mainly diastereomer **2a** (9:1 ratio). Crystallization of the dichloromethane-soluble fraction from chloroform/hexane gave pure isomer **2b**. Interestingly, sometimes under these conditions, crystals with a different form, which corresponded to the minor stereoisomer (i.e., **2d**), were observed, which allowed the purification and characterization of this compound. The initial structural assignment was carried out by NMR spectroscopy, particularly ^{13}C NMR spectroscopy, and the structure was later confirmed by X-ray crystallography. In the ^{13}C NMR spectra, we considered that an axial orientation of a substituent would induce an upfield shift of the carbon bearing the axial substituent (see Table 1).[18] We reasoned that only one of the four diastereomers would have the most stable conformation in which all of the substituents would be equatorially orientated (**2b**), and that the other three would each have only one axially orientated group (Scheme 2): the carboxylic acid in **2a**, whose Cα appears at δ = 42.9 ppm, the methyl group in isomer **2c**, in which the Cβ signal is at δ = 33.7 ppm, and the amino group in **2d**, with the Cγ at δ = 49.1 ppm. The axial orientation of the methyl group in compound **2c** can also be inferred from its own upfield shift (δ = 8.2 ppm). On the other hand, the downfield shift observed for each of the three methine ring-carbons in compound **2b** also confirms the expected all-equatorial orientation.

Table 1. ^{13}C NMR chemical shifts of Cα, Cβ, and Cγ, and of the methyl group corresponding to the cyclohexanecarboxylic acid derivatives (in **1** and **2a**–**d**), which were used to assign their relative configurations. The lowest values for each carbon are shown in bold and the highest are in italics.

	δ (Cα)	δ (Cβ)	δ (Cγ)	δ (Me)
1	43.5		50.2	
2a	**42.9**	36.4	49.9	14.7
2b	*50.0*	*39.4*	*54.0*	16.5
2c	45.8	**33.7**	51.9	**8.2**
2d	44.2	36.0	**49.1**	15.9

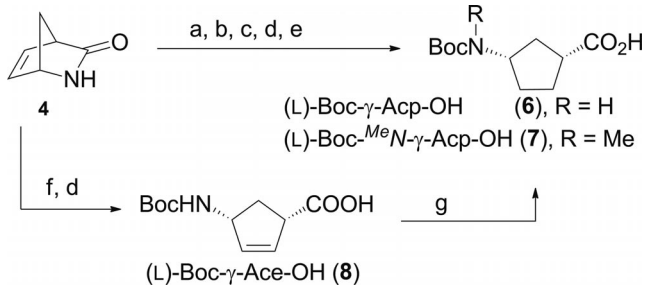
The structures of the most relevant isomers (**2b** and **2c**) were confirmed by X-ray crystallography (Scheme 2). We also resolved **2b** by co-crystallization in the presence of *S*-phenylethanamine to give the dextrorotatory isomer with 98% *ee*. Although the hydrogenation gave rise to a complex mixture of the four diastereomers, the two most interesting



Scheme 2. *Reagents and conditions:* (a) NaOMe, MeOH, Δ. The most stable chair conformations of the 2-methyl derivatives. The proposed equilibrium between chair conformations is represented for **2a**. The isomerization of methyl ester **3a** with sodium methoxide in methanol provided a mixture enriched in isomer **2b**. Bottom, single-crystal X-ray structures of compounds **2b** and **2c**.[19]

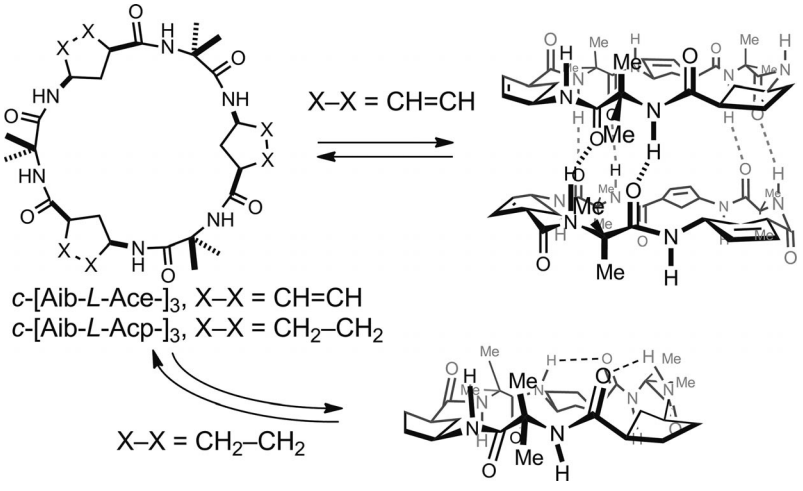
isomers (i.e., **2b** and **2c**) could be obtained by isomerization of the methyl esters of the other two isomers. For example, a mixture enriched in the thermodynamically more stable isomer **2b** (3:1) was obtained on heating **3a** (9:1 mixture with **3b**) in methanol in the presence of sodium methoxide, in a reaction in which isomerization and hydrolysis took place simultaneously.

The next targets were the cyclopentyl derivatives. The simplest example, 3-aminocyclopentanecarboxylic acid (γ-Acp-OH), was obtained from the commercially available Vince lactam (**4**). Hydrogenation, followed by hydrolysis with HCl, and reaction with Boc anhydride gave Boc-γ-Acp-OH (Scheme 3). The resulting protected γ-amino acid was also resolved by co-crystallization with *S*-phenylethanamine to give the 1*S*,3*R* enantiomer (D-Boc-γ-Acp-OH, **6**).[15,20] L-Boc-γ-Acp-OH was obtained from the mother liquors and by using the other enantiomer of the chiral amine. Finally, the *N*-methyl derivative (i.e., **7**) was obtained by alkylation of **6** with sodium hydride and iodomethane in THF.



Scheme 3. *Reagents and conditions:* (a) H_2, Pd/C, MeOH, 98%; (b) HCl (10%), 90%; (c) $(Boc)_2O$, DIEA, H_2O/dioxane, 89%; (d) (*R*)-phenylethylamine, $CHCl_3$/hexanes; (e) NaH, MeI, THF, 88%; (f) i) 10% HCl, Δ; ii) Boc_2O, DIEA, H_2O/dioxane (80% over two steps); (g) H_2, Pd/C, EtOH, 98%.

The unsaturated derivative, 4-aminocyclopent-2-enecarboxylic acid (γ-Ace-OH), was also prepared by simple hydrolysis under acidic conditions, and this was followed by amine protection with Boc anhydride. Once again, the resolution was carried out with phenylethanamine to provide the enantiopure form of the Ace. Once more, the levorotatory enantiomer (*R*) of the phenylethanamine gave rise to the 1*S*,4*R*-configured stereoisomer, L-Boc-γ-Ace-OH (**8**), while the *S* isomer provided the D form (1*R*,4*S*). This resolution could be carried out on a multi-gram scale and in a more reproducible manner than for the saturated derivative. In this way, an improved synthesis of Boc-γ-Acp-OH can be carried out by simply hydrogenating the corresponding enantiomers of Boc-γ-Ace-OH. The potential applications of the γ-Ace residue in foldamer chemistry were studied with the dimer-forming cyclic peptide *c*-[Aib-L-γ-Ace-]$_3$ (Scheme 4).[12b] The Aib residue was introduced to examine the steric effect on the self-assembling properties of the CP ring when a methyl substituent is axially orientated at the α-position of every second residue. This peptide did self-

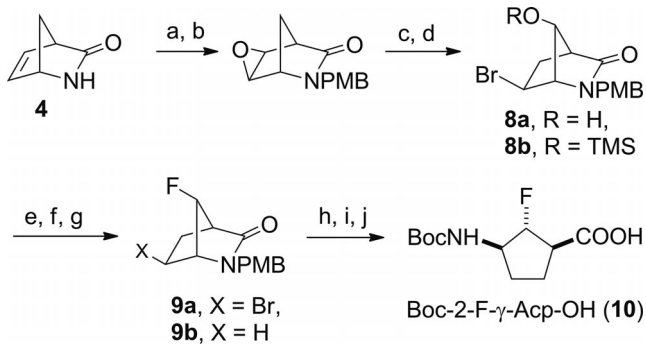


Scheme 4. Representation of the self-assembling properties of cyclic peptides containing Acp and Ace residues alternated with Aib, showing their different tendencies to adopt the flat conformation.

assemble into dimers with a β-sheet-type interaction, but the reduced analogue (i.e., *c*-[Aib-L-γ-Acp-]$_3$) was folded as a consequence of the steric interactions between the axially orientated α-methyl and carbonyl groups of the γ-Acp. This difference between the two cyclic peptides must be related to the higher degree of flexibility of the 1,3-cyclopentylene moiety of γ-Acp compared to the 1,4-cyclopent-2-enylene ring, which might prevent the CP from adopting the flat conformation required for dimerization in the β-strand form. Unfortunately, the Ace was configurationally unstable and, under the typical basic or acidic conditions used in peptide synthesis, epimerization or isomerization took place, thus making its implementation in foldamer chemistry difficult.

Interestingly, Vince lactam (**4**) can also be used for the preparation of other γ-amino acids with functional groups in other positions.[10] Some work has already been carried out in this area, but it focussed on the synthesis of GABA analogues. As mentioned above, we were interested in the introduction of functional groups at C-2, but *trans*-orientated with respect to the amino and carboxylic acid groups. Such a configuration would not interfere with the folding and assembling properties of the resulting peptide. Our initial target was the *N*-Boc-protected 2-fluoro derivative (i.e., Boc-2-F-γ-Acp-OH, **10**), which would then be used in peptide synthesis. We followed a similar strategy to that previously described for the preparation of (1*r*,2*s*,3*s*,4*s*)-3-amino-4-bromo-2-fluorocyclopentanecarboxylic acid, although this approach was reported to give the *cis*,*cis* isomer.[21] Thus, treatment of the *p*-methoxybenzyl-protected Vince lactam with *m*-CPBA (*m*-chloroperbenzoic acid) provided the epoxide. This was transformed into **8b** by reaction with hydrogen bromide followed by treatment of the crude mixture with trimethylsilyl triflate (TMSOTf; Scheme 5). TMS protection facilitated separation of the 7-hydroxy derivative (**8a**) from its regioisomer [6-bromo-5-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one],[21] which was also generated under these conditions in 12% yield. Radical debromination carried out with tributyltin hydride in the presence of initiator 2,2′-azobis(isobutyronitrile) (AIBN) was followed by TMS deprotection with tetrabutylamonium fluoride and treatment of the resulting alcohol with one equivalent of (diethylamino)sulfur trifluoride (DAST) in dichloromethane at –78 °C. This sequence gave bicyclic fluoride **9b** in 60% yield. It has been reported that this transformation takes place by an S_N2 mechanism,[21] but two-dimensional NMR experiments showed that the fluoride substitution took place with retention of configuration. The cross-peak in the HOESY (heteronuclear NOESY)[22] spectra between the fluoride and the lactam protons at C-5 and C-6 suggests a *cis* orientation (Figure 2).

Some additional experiments were carried out to study the fluorination reaction. DAST treatment was also carried out on bromide derivative **8a** to ascertain whether the retention of configuration was due to steric congestion. Treatment of this lactam with DAST again provided the corresponding fluoride derivative with retention of configuration (**9a**). NOe experiments revealed a cross-peak between the



Scheme 5. *Reagents and conditions:* (a) NaH, PMBCl, TBAI (tetrabutylammonium iodide), DMF, 91%; (b) *m*-CPBA, $CHCl_3$, 91%; (c) HBr (45%), CH_3CN; (d) TMSOTf, Pyridine, DMAP (4-dimethylaminopyridine), CH_2Cl_2, Δ, 75% (two steps); (e) Bu_3SnH, AIBN, benzene, Δ, 97%; (f) TBAF (tetrabutylammonium fluoride), THF, 88%; (g) DAST, CH_2Cl_2, –78 °C – room temp., 60%; (h) CAN, CH_3CN; (i) HCl (4 M)/AcOH; (j) $(Boc)_2O$, DIEA, H_2O/dioxane (1:1), 53% (three steps).

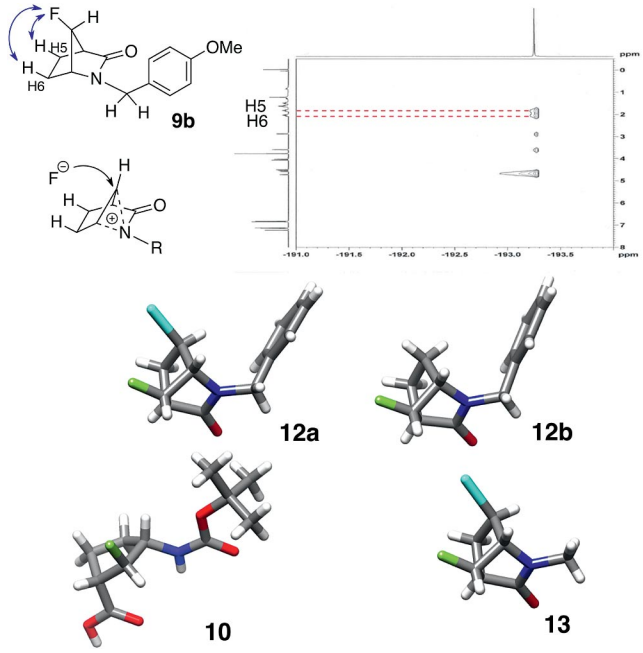
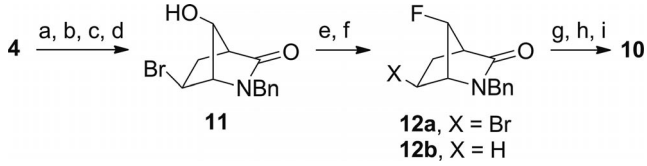


Figure 2. Top, HOESY spectra of fluoride derivative **9b**, in which the cross-peaks are between fluoride and protons H-5 and H-6.[22] Bottom, single-crystal X-ray structures of compounds **10**, **12a**, **12b**, and **13**.[19]

apical proton and the methylene protons of the PMB (*para*-methoxybenzyl) group, which confirmed their spatial proximity. Replacement of the PMB group by benzyl protection (**11**) did not change the stereochemistry of the fluoride substituent, and lactam **12b** was formed in 60% yield with retention of configuration (Scheme 6). The relative configuration of lactams **12a** and **12b**, and of the final amino acid (i.e., **10**) was confirmed by X-ray diffraction, as shown in Figure 2. The retention of configuration can be explained in terms of an amide-assisted intermediate (Figure 2) in which the nitrogen stabilizes the carbocation generated upon activation of the hydroxy group by DAST. The

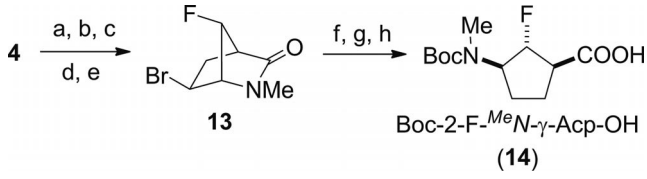
fluoride ion would react with the apical carbon to regenerate the five-membered lactam instead of the β-lactam, and so provide the fluoride derivative with retention of configuration.



Scheme 6. Reagents and conditions: (a) KOH, BnBr, TBAI, DMSO, 96%; (b) *m*-CPBA, $CHCl_3$, 88%; (c) i) 45% HBr, CH_3CN; ii) TMSOTf, Py, DMAP, CH_2Cl_2, Δ, 53% (two steps); (d) TBAF, THF, 93%; (e) DAST, CH_2Cl_2, –78 °C – room temp., 62%; (f) Bu_3SnH, AIBN, benzene, Δ, 88%; (g) Na/NH_3, *t*BuOH, –78 °C, 78%; (h) HCl (4 M)/AcOH; (i) $(Boc)_2O$, DIEA, H_2O/dioxane (1:1), 93% (two steps).

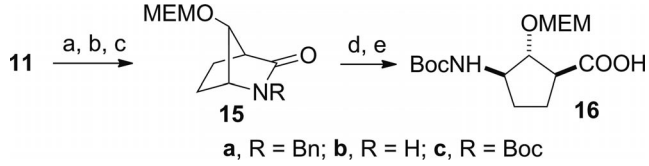
The synthesis of the amino acid was completed by both approaches. Fluoride **9b** was treated with ceric ammonium nitrate (CAN) to remove the protecting group. The lactam was then hydrolysed by treatment with HCl, and the resulting amino acid was protected as its *tert*-butylcarbamate by reaction with Boc anhydride. Similarly, compound **12a** was treated with tributyltin hydride in the presence of AIBN to remove the bromide, and the resulting lactam was treated with sodium in liquid ammonia to remove the benzyl protecting group. The resulting fluoride-substituted lactam was treated as before to provide compound **10**.

Alkylation of the resulting lactam did not give rise to *N*-methyl-substituted amino acid **14** (Boc-2-F-^{Me}*N*-γ-Acp-OH). Under typical basic conditions (NaH) we only observed decomposition of the starting material. For this reason, compound **14** was prepared following a strategy (see Scheme 7) similar to that described for **10**, starting from lactam **4**. Perhaps the main differences are the lower yields observed in the fluoride-substitution reaction (only 40% yield) and in the lactam hydrolysis and protection of the secondary amide (only 36% yield for both steps). Once again, the fluorination reaction took place with retention of configuration, as inferred from the X-ray diffraction pattern of a crystal of compound **13** (Figure 2).



Scheme 7. *Reagents and conditions:* (a) NaH, MeI, THF, 87%; (b) *m*-CPBA, CH_2Cl_2, 75%; (c) i) 45% HBr, CH_3CN; ii) TMSOTf, Py, DMAP, CH_2Cl_2, Δ, 52% (two steps); (d) TBAF, THF, 98%; (e) DAST, CH_2Cl_2, –78 °C – room temp., 40%; (f) Bu_3SnH, AIBN, benzene, Δ, 93%; (g) HCl (4 M)/AcOH; (h) $(Boc)_2O$, DIEA, H_2O/dioxane (1:1), 36% (two steps).

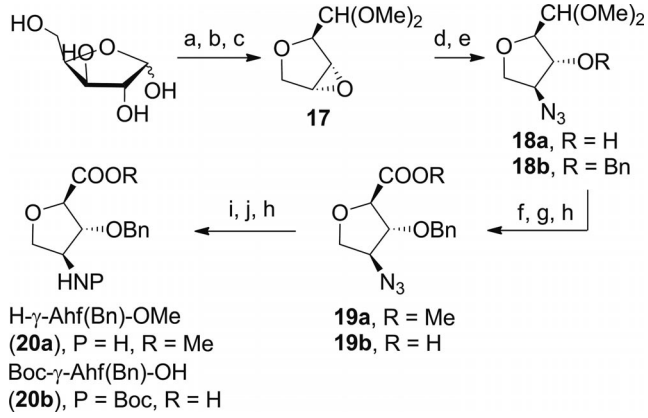
Finally, 2-hydroxy derivative **16** was also prepared by a similar strategy (Scheme 8). The starting material was intermediate **11**, which was transformed into MEM-protected compound **15a** by treatment with methoxyethoxymethyl chloride (MEMCl) in the presence of diisopropylethylamine, followed by radical debromination with tributyltin hydride and AIBN. Debenzylation of **15a** was carried out with sodium and liquid ammonia in THF at –78 °C, and the lactam was hydrolysed under basic conditions. For this purpose, the resulting lactam (i.e., **15b**) was treated with Boc anhydride in the presence of DMAP, and the resulting *tert*-butylcarbamate (i.e., **15c**) was stirred in a mixture of methanol and water (3:1) in the presence of potassium carbonate to give **16** in 78% yield.



Scheme 8. *Reagents and conditions:* (a) MEMCl, DIEA, CH_2Cl_2, 80%; (b) Bu_3SnH, AIBN, benzene, Δ, 85%; (c) Na, NH_3, THF, –78 °C, 74%; (d) $(Boc)_2O$, DMAP, CH_2Cl_2, 91%; (e) K_2CO_3, $MeOH/H_2O$ (3:1), 78%.

The efficiency of the processes presented are remarkable. Most of the reactions could be carried out on a multigram scale, and the transformations took place in good to excellent yields. However, final resolution steps were still required, as all of the methods described above provided the corresponding *N*-Boc protected amino acids as racemic mixtures. In an effort to overcome this drawback, we evaluated other synthetic strategies using the chiral pool. With this idea in mind, the preparation of a 3-substituted tetrahydrofuran [γ-Ahf(Bn)-OH] starting from D-xylose was attempted (Scheme 9).[23] Although we have previously described the synthesis of several such derivatives, some of the key steps have been improved recently.[24] Xylose was dissolved in a mixture of sulfuric acid in acetone under controlled conditions followed by neutralization with sodium hydrogen carbonate. The resulting 1,2-monoacetonide was treated with excess methanesulfonyl chloride to provide the bismesylate, the isopropylidene protecting group was removed by treatment with trifluoroacetic acid (TFA), and then epoxide **17** was formed by reaction with potassium carbonate. Epoxide **17** was ring-opened with sodium azide, and the resulting alcohol was protected by treatment with benzyl bromide. In this step, a variety of substituents can be introduced at this position by using different alkylating electrophiles. Compound **18b** was transformed into methyl ester **19a** by a sequence of hydrolysis of the dimethyl acetal with TFA/water, followed by oxidation of the resulting aldehyde with *N*-bromosuccinide (NBS) in the presence of potassium carbonate. This fully protected amino acid can be used in the synthesis of any kind of peptide using orthogonal or *N*-deprotection conditions. Treatment of the ester with lithium hydroxide produced the corresponding acid (**19b**), while reduction with triphenylphosphane in THF or hydrogenation with 10% palladium on carbon provided the free amine derivative **20a**. Compound **19b** could be obtained in one pot from acetal **18a** by hydrolysis with TFA and subsequent oxidation with chromium trioxide in a mix-

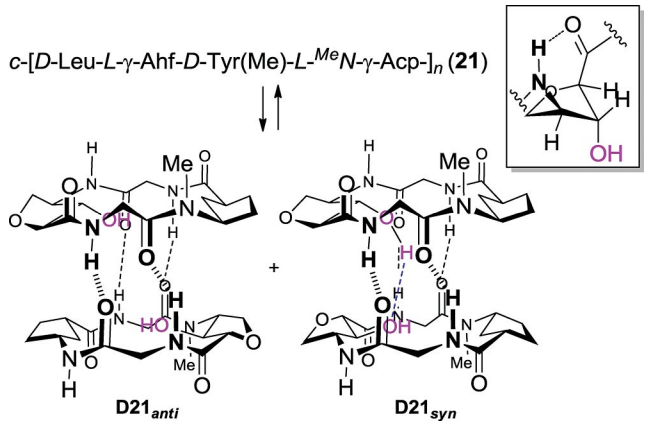
ture of THF and water in the presence of acetone. Although the yield was slightly lower than that of the previously described method (67 vs. 80%), the process is simpler, and the acid (i.e., **19b**) was sufficiently pure to be used without chromatographic purification. The Boc-protected amino acid (i.e., **20b**) for use in solid phase synthesis could be obtained by the reaction of **20a** with *tert*-butoxycarbonyl anhydride in dichloromethane, followed by hydrolysis with lithium hydroxide in a water/methanol mixture.



Scheme 9. *Reagents and conditions:* (a) i) H_2SO_4/acetone, room temp., 30 min; ii) H_2SO_4 (0.15 M), iii) $NaHCO_3$, acetone/H_2O, room temp., 95%; (b) MsCl, Et_3N, CH_2Cl_2, 96%; (c) i) TFA/MeOH; ii) K_2CO_3, 93%; (d) NaN_3, NH_4Cl, H_2O, EtOH, 83%; (e) NaH, BnBr, NBu_4I, THF, 87%; (f) TFA/H_2O (4:1), 95%; (g) NBS, K_2CO_3, MeOH, CH_3CN, 90%; (h) LiOH, MeOH/H_2O, 94%; (i) Ph_3P, THF, 77%; (j) Boc_2O, DIEA, CH_2Cl_2, 85%.

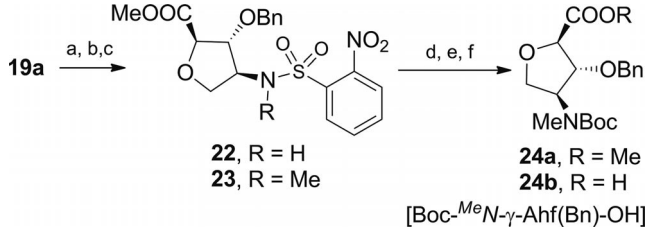
It has been shown previously that this amino acid tends to adopt a conformation in which the three substituents are in pseudoaxial orientations, due to the stereoelectronic influence of the hydroxy substituent and the furan oxygen, assisted by a hydrogen bond between the NH and carbonyl moieties (Scheme 10).[25] As a result, this amino acid adopts a γ-turn-type conformation. More recent work in our group has shown that the use of this compound in a conformationally restricted cyclic peptide, such as tetrapeptide **21**, led the amino acid to adopt a β-strand-like conformation that allowed the peptide to self-assemble into the corresponding dimer with a large association constant.[24] It should be mentioned that the presence of the hydroxy group projecting towards the cavity of the dimer is responsible not only for the large association constant, but also for discrimination in dimer formation. CP **21** can form two non-equivalent dimers ($D\mathbf{21}_{syn}$ and $D\mathbf{21}_{anti}$), but computational calculations suggest that the presence of the hydroxy group shifts the equilibrium towards the one in which both of the hydroxy groups participate in hydrogen-bonding interactions ($D\mathbf{21}_{syn}$).

Finally, attempts to obtain *N*-methylated amino acid **24b** [Boc-^{Me}*N*-γ-Ahf(Bn)-OH] by alkylation of **20a** or its methyl ester with NaH and methyl iodide were unsuccessful. Under all the conditions we tested, we observed decomposition of the starting material. As an alternative, we decided to use Fukuyama's method (Scheme 11)[26] and, after the reduction of the azide group of **19a**, the resulting amine was



Scheme 10. A cyclic peptide containing Ahf that forms a dimer with large association constant. In the dimer, the hydroxy groups participate in an inter-peptide hydrogen bond that favours the formation of only one dimer, instead of the previously reported γ-turn.[25]

treated with *o*-nosyl chloride (NsCl, *o*-nitrobenzene-1-sulfonyl chloride) to give compound **22**. Sulfonamide **22** was treated with potassium carbonate in the presence of methyl iodide to give the *N*-methylated derivative (i.e., **23**) in 77% yield. This fully protected amino acid can be used directly in solid phase or solution synthesis by orthogonal deprotection of the carboxylic acid (LiOH in methanol) or the amino group (thiophenol/potassium carbonate), or it could simply be transformed into the more conventional Boc derivative (i.e., **24b**). Thus, the reaction of **23** with PhSH and K_2CO_3 in DMF, followed by reaction with *tert*-butyloxycarbonyl anhydride gave Boc-protected amino acid **24a**, which was treated with lithium hydroxide in methanol to provide **24b** in 60% yield over the three steps.



Scheme 11. *Reagents and conditions:* (a) H_2, 10% Pd/C, CH_2Cl_2, 96%; (b) NsCl, DIEA, CH_2Cl_2, 73%; (c) MeI, K_2CO_3, DMF, 77%; (d) C_6H_5SH, K_2CO_3, DMF, 72%; (e) Boc_2O, DIEA, CH_2Cl_2, 90%; (f) LiOH, MeOH/H_2O, 94%.

Conclusions

The synthesis of various protected cyclic γ-amino acids suitable for use in peptide synthesis is described. A common feature of all of these amino acids is the *cis*-orientation of the substituents, which makes them especially suitable for the formation of β-strand conformations in non-natural oligomers. In addition, in some derivatives, the β-carbon substituent is in a *trans* disposition with respect to the carbonyl and amino groups. This configuration allows the compounds to modify the properties of internal part, i.e., the

minor arc, of the coiled peptide structure, induced by the rigidity of the cycloalkyl moiety. The DAST induced fluoride-substitution reaction of [2.2.1] bicyclic lactams at the apical carbon took place with retention of configuration, probably via a carbocation stabilized by the amide group.

Experimental Section

General: D-(+)-Xylose >98% was acquired from Lancaster. All reagents obtained from commercial suppliers were used without further purification unless otherwise noted. CH_2Cl_2, DIEA, and *tert*-butyl alcohol to be used as reaction solvents were distilled from CaH_2 under argon immediately before use. Tetrahydrofuran (THF) was dried and distilled from sodium/benzophenone.[27] Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds that were not UV-active were visualized by dipping the plates into a ninhydrin solution and heating. Silica gel flash chromatography was performed using E. Merck silica gel (type 60SDS, 230–400 mesh). Solvent mixtures for chromatography are reported as v/v ratios. ^{1}H NMR spectra were recorded with Varian Inova 500 MHz, Varian Inova 400 MHz, Varian Mercury 300 MHz, or Bruker DPX 250 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and were calibrated to tetramethylsilane (δ = 0.00 ppm) or to the residual solvent signals. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint). First-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Varian Inova 500 MHz, Varian Inova 400 MHz, Varian Mercury 300 MHz or Bruker DPX 250 MHz spectrometers. Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with a phase-angle of 135°. ^{19}F NMR spectra were recorded with a Varian Mercury 300 MHz spectrometer. Fast Atom Bombardement (FAB^+) and Chemical Ionization (CI^+) mass spectra were recorded with a Micromass Autospec mass spectrometer. Electrospray (ESI) mass spectra were recorded with a Bruker BIOTOF II mass spectrometer. FTIR measurements were made with a JASCO FTIR-400 spectrophotometer with the sample placed on a CaF_2 pellet.

***cis*-3-Aminocyclohexanecarboxylic Acid Hydrochloride (HCl·H-γ-Ach-OH):** Raney Ni (7.0 g) was added to a solution of 3-nitrobenzoic acid (11.3 g, 67.61 mmol) and NaOH (3.3 g, 82.50 mmol) in H_2O (200 mL) in a pressure bottle. The resulting mixture was hydrogenated (90–100 atm) at 150 °C for 12 h in a Parr apparatus. The mixture was filtered through Celite, and the catalyst was washed with H_2O. The resulting solution was acidified to pH = 2 with HCl (10% aq.) and then concentrated under vacuum. The residue was desalted by passing through a Dowex AG50W-X4 column (1 M pyridine) to provide γ-Ach-OH (9.73 g, 80%) as a white solid.[11b] R_f = 0.48 (MeOH). ^{1}H NMR (250 MHz, D_2O, 25 °C): δ = 3.04 (m, 1 H, 3-H), 2.20–1.70 (m, 5 H), 1.30–0.90 (m, 4 H) ppm.

(1*R*,3*S*)-3-[(*tert*-Butyloxycarbonyl)amino]cyclohexanecarboxylic Acid (L-Boc-γ-Ach-OH, 1a): Boc_2O (7.0 g, 32.06 mmol) and DIEA (14.7 mL, 84.19 mmol) were added to a solution of *cis*-3-aminocyclohexanecarboxylic acid (4.0 g, 27.93 mmol) in water (25 mL) and dioxane (25 mL). The mixture was stirred at room temp. for 3 h and acidified to pH = 2. The product was extracted with CH_2Cl_2. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated, and the resulting oil was crystallized from CH_2Cl_2/hexane (2:1) to give the product [3.4 g, and 2.1 g from a second crystallization, 80%, R_f = 0.85 (MeOH), m.p. 136–138 °C]. The resulting racemic Boc-γ-Ach-OH was resolved by crystallization from $CHCl_3$/hexane (2:1) in the presence of (+)-1-phenylethanamine (1 equiv.). The resulting white crystals were washed with $CHCl_3$/hexane (2:1), poured into a separating funnel, dissolved in CH_2Cl_2 (500 mL), and washed with citric acid (10% aq.; 3× 150 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated, and the resulting oil was crystallized from CH_2Cl_2/hexane (2:1).[11b] ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 5.56 (m, 1 H, NH), 4.47 (m, 1 H, 3-H), 3.44 (m, 1 H, 1-H), 1.42 (s, 9 H, Boc) ppm.

(1*R*,3*S*)-3-[(*tert*-Butyloxycarbonyl)methylamino]cyclohexanecarboxylic Acid (L-Boc-^{Me}*N*-γ-Ach-OH, 1b): A solution of L-Boc-γ-Ach-OH (1.38 g, 5.68 mmol) in dry THF (50 mL) was treated with NaH (60% in mineral oil; 680 mg, 28.33 mmol). The resulting mixture was stirred at 0 °C for 30 min, and then methyl iodide (1.06 mL, 17.03 mmol) was added. The mixture was stirred overnight at room temp., and an additional 3 equiv. NaH (680 mg, 28.33 mmol) and methyl iodide (1.06 mL, 17.03 mmol) were added at 0 °C (as starting material was detected by TLC), and the resulting mixture was stirred for a further 3 h at room temp. After quenching with water, the solution was concentrated to remove the THF. The resulting aqueous solution was washed with diethyl ether, acidified to pH = 3 by addition of HCl (10% aq.), and finally extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was crystallized from CH_2Cl_2/hexane to give L-Boc-^{Me}*N*-γ-Ach-OH (**1b**; 1.29 g, 88%) as a white solid.[11b] R_f = 0.58 (10% MeOH/CH_2Cl_2). m.p. 141–143 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.01 and 3.77 (m, 1 H, 3-H), 2.69 (s, 3 H, MeN), 2.42 (m, 1 H, 1-H), 1.42 (s, 9 H, Boc) ppm. $[\alpha]_D^{20}$ = –47.2 (c = 0.80 in MeOH).

3-[(*tert*-Butyloxycarbonyl)amino]-2-methylcyclohexanecarboxylic Acids 2a–d: A mixture of 2-methyl-3-nitrobenzoic acid (10 g, 0.055 mol), NaOH (3.0 g, 0.075 mol), and Raney Ni (6.5 g) in water (150 mL) was placed in a Parr reactor (0.5 L capacity). The mixture was stirred at 150 °C for 12 h under hydrogen (100 atm). After cooling and releasing the pressure, the mixture was filtered through Celite, acidified to pH = 2 with HCl (10% aq.), and then concentrated. The mixture was passed through an ion-exchange column, and the salts were removed with Dowex 50 WX 8 to yield the hydrochloride mixture (8.0 g, 75%). R_f = 0.60 (MeOH).

The resulting mixture (2.0 g, 0.010 mol) was treated with Boc_2O (2.62 g, 0.012 mol) and DIEA (5.5 mL, 0.031 mol) in H_2O/dioxane (1:1, 25 mL). The mixture was stirred for 3 h at room temp. The the mixture was acidified to pH = 2 with HCl (10% aq.) and extracted with CH_2Cl_2 (4× 20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give *N*-Boc-3-amino-2-methylcyclohexanecarboxylic acid (2.2 g, 80%) as a mixture of four diastereomers whose NMR spectra showed a **2a**:**2b**:**2c**:**2d** ratio of 3:3:3:1. R_f = 0.35 (MeOH). The product was washed with CH_2Cl_2 (2 mL) and filtered. The mother liquors were enriched in **2b** and **2d**, while the solid portion was enriched in isomers **2a** and **2c**. A portion of the filtrate fraction (50 mg) was dissolved in CH_2Cl_2 (20 mL) and equilibrated by vapour-phase diffusion in hexane to give crystals of isomer **2b**. Also, a portion of the solid fraction (50 mg), which contained mainly **2a** and **2c**, was dissolved in methanol and equilibrated by vapour-phase diffusion in a hexane atmosphere to give crystals of **2c**.

Data for **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.01 (br., 1 H, COOH), 4.55 (m, 1 H, NH), 3.77 (m, 1 H, 3-H), 2.71 (m, 1 H, 1-

H), 1.97 (m, 1 H, 2-H), 1.48 (s, 9 H, Boc), 1.03 (d, J = 6.8 Hz, 3 H, Me) ppm. ^{13}C NMR (125.7 MHz, DMSO): δ = 175.5 (CO), 155.0 (CO), 77.2 (C), 50.0 (CH), 43.0 (CH), 36.4 (CH), 29.3 (CH_2), 28.2 (Boc), 25.4 (CH_2), 20.2 (CH_2), 14.7 (CH_3) ppm. MS (ESI): m/z (%) = 280 (100) [M + Na]$^+$, 258 (1) [M + H]$^+$, 222 (55) [M + Na – tBu]$^+$, 202 (8) [M + H – tBu]$^+$. HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_4$ 280.1519; found 280.1516.

Data for **2c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.67 (d, J = 6.3 Hz, 1 H, NH), 3.66 (br. s, 1 H, 3-H), 2.55 (m, 2 H, 2-H, 1-H), 1.44 (s, 9 H, Boc), 0.84 (d, J = 6.9 Hz, 3 H, Me) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 179.9 (CO), 155.3 (CO), 79.4 (C), 52.1 (CH), 45.9 (CH), 33.8 (CH), 28.5 (Boc), 26.6 (CH_2), 23.4 (CH_2), 21.3 (CH_2), 8.2 (CH_3) ppm. MS (ESI): m/z (%) = 280 (100) [M + Na]$^+$, 258 (5) [M + H]$^+$, 222 (28) [M + Na – tBu]$^+$, 202 (15) [M + H – tBu]$^+$. CCDC-909273.

Data for **2d**: ^{1}H NMR (250 MHz, DMSO): δ = 6.72 (d, J = 9.5 Hz, 1 H, NH), 3.64 (m, 1 H, H-3), 2.32 (td, J = 10.7 and 3.4 Hz, 1 H, H-1), 1.38 (s, 9 H, Boc), 0.76 (d, J = 6.6 Hz, 3 H, Me). ^{13}C NMR (62.9 MHz, DMSO): δ = 176.9 (CO), 155.7 (CO), 77.5 (C), 49.2 (CH), 44.3 (CH), 36.1 (CH), 30.7 (CH_2), 28.5 (CH_2), 28.4 (Boc), 19.2 (CH_2), 15.9 (CH_3). MS (ESI): m/z (%) = 280 (100) [M + Na]$^+$, 258 (3) [M + H]$^+$, 222 (64) [M + Na – tBu]$^+$, 202 (12) [M + H – tBu]$^+$.

(1*S*,2*R*,3*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-2-methylcyclohexanecarboxylic Acid (2b): The racemic mixture of **2b** was resolved by crystallization from $CHCl_3$/hexane (2:1) in the presence of (–)-1-phenylethanamine (1 equiv.). The resulting white crystals were washed with $CHCl_3$/hexane (2:1), poured into a separating funnel, dissolved in CH_2Cl_2, and washed with citric acid (10%). This operation was repeated 2–3 times. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give **2b**. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.6 (br. s, 1 H, COOH), 6.28 (d, J = 7.2 Hz, 1 H, NH), 4.41 (d, J = 9.0 Hz, 1 H, 3-H), 3.19 (m, 1 H, 1-H), 3.00 (m, 1 H, 2-H), 1.42 (s, 9 H, Boc), 0.98 (d, J = 5.4 Hz, 3 H, Me) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 180.8 (CO), 155.8 (CO), 79.4 (C), 54.1 (CH), 50.6 (CH), 39.8 (CH), 33.7 (CH_2), 29.7 (CH_2), 28.5 (Boc), 24.6 (CH_2), 16.7 (CH_3) ppm. MS (ESI-TOF$^+$): m/z (%) = 280 (100) [M + Na]$^+$, 258 (2) [M + H]$^+$, 222 (36) [M + Na – tBu]$^+$, 202 (4) [M + H – tBu]$^+$. HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_4$ 280.1519; found 280.1524. $[\alpha]_D^{20}$ = +20.4 (c = 1.0 in MeOH). CCDC-909272.

Methyl 3-[(*tert*-Butyloxycarbonyl)amino]-2-methylcyclohexanecarboxylate (3a): A solution of **2a** (50 mg, 0.19 mmol) in MeOH (2 mL) was treated with EDC·HCl (93.5 mg, 0.49 mmol), HOBt (65.8 mg, 0.49 mmol), and DMAP (59.4 mg, 0.49 mmol). The resulting mixture was stirred at room temp. for 4 h and the solution was concentrated to remove the MeOH. The resulting oil was dissolved in EtOAc (25 mL) and washed with HCl (5% aq.; 3× 10 mL) and $NaHCO_3$ (satd. aq.; 2× 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane) to give **3a** (40 mg, 76%) as a white solid. R_f = 0.56 (25% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57 (br., 1 H, NH), 3.71 (m, 1 H, 3-H), 3.65 (s, 3 H, OMe), 2.65 (dt, J = 8.2 and 4.3 Hz, 1 H, 1-H), 1.96 (m, 1 H, 2-H), 1.42 (s, 9 H, Boc), 0.93 (d, J = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.3 (CO), 155.5 (CO), 79.2 (C), 51.4 (CH_3), 51.0 (CH), 43.4 (CH), 36.9 (CH), 28.5 (Boc), 28.2 (CH_2), 24.3 (CH_2), 20.6 (CH_2), 14.6 (CH_3) ppm. MS (ESI-TOF$^+$): m/z (%) = 294.2 (18) [M + Na]$^+$, 272.2 (1) [M + H]$^+$, 256.3 (5), 238.1 (15), 216.1 (23) [M + H – tBu]$^+$, 184.1 (9), 156.1 (100) [M + H – Boc – Me]$^+$. HRMS (ESI): calcd. for $C_{14}H_{25}NNaO_4$ 294.1676; found 294.1677.

Methyl 3-[(*tert*-Butyloxycarbonyl)amino]-2-methylcyclohexanecarboxylate (3b): A solution of **2b** (50 mg, 0.19 mmol) in MeOH (2 mL) was treated with EDC·HCl (93.5 mg, 0.49 mmol), HOBt (65.8 mg, 0.49 mmol), and DMAP (59.4 mg, 0.49 mmol). The resulting mixture was stirred at room temp. for 4 h, then the solution was concentrated to remove the MeOH. The resulting oil was dissolved in EtOAc and washed with HCl (5% aq.; 3× 10 mL) and $NaHCO_3$ (satd. aq.; 2× 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane) to give **3b** (45.5 mg, 86%) as a white solid. R_f = 0.56 (25% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39 (d, J = 9.1 Hz, 1 H, 3-H), 3.64 (s, 3 H, OMe), 3.16 (m, 1 H, 1-H), 2.09 (td, J = 11.1 and 3.4 Hz, 1 H, 2-H), 1.94 (m, 1 H), 1.77 (m, 2 H), 1.40 (s, 9 H, Boc), 0.88 (d, J = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.8 (CO), 155.7 (CO), 79.2 (C), 54.2 (CH), 51.6 (CH_3), 50.4 (CH), 40.03 (CH), 3.7 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 24.5 (CH_2), 16.6 (CH_3) ppm. MS (ESI-TOF$^+$): m/z (%) = 294 (18) [M + Na]$^+$, 272 (1) [M + H]$^+$, 256 (5), 238 (10), 216 (36) [M + H – tBu]$^+$, 156 (100) [M + H – Boc – Me]$^+$.

2-Azabicyclo[2.2.1]heptan-3-one: A solution of 2-Azabicyclo[2.2.1]-hept-5-en-3-one (**4**; 25.0 g, 0.23 mol) in EtOAc (1 L) was treated with Pd/C (10%; 7.3 g, 6.88 mmol), and hydrogenated at balloon pressure for 1–2 d. The insoluble material was removed by filtration through Celite, which was rinsed with EtOAc, and the filtrate was concentrated to give 2-azabicyclo[2.2.1]heptan-3-one (25.2 g, 99%) as a white solid.[20a] R_f = 0.20 (EtOAc). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.08 (br., 1 H), 3.72 (m, 1 H, 3-H), 2.53 (m, 1 H, 1-H) ppm.

***cis*-3-Aminocyclopentanecarboxylic Acid Hydrochloride (HCl·H-Acp-OH):** A solution of 2-Azabicyclo[2.2.1]heptan-3-one (10.50 g, 94.60 mmol) in HCl (10% aq.; 500 mL) was stirred for 2 d at room temperature, and then concentrated in vacuo. Addition of acetone to the yellow oil gave a white solid, which was filtered and washed with acetone to give *cis*-3-aminocyclopentanecarboxylic acid hydrochloride (14.61 g, 93%).[20a] R_f = 0.32 (MeOH)]. ^{1}H NMR (D_2O, 250 MHz): δ = 3.70 (m, 1 H, 3-H), 2.95 (quint, J = 8.0 Hz, 1 H, 1-H), 2.35 (m, 1 H, 2-H) ppm.

(1*R*,3*S*)-3-[(*tert*-Butyloxycarbonyl)amino]cyclopentanecarboxylic Acid (L-Boc-γ-Acp-OH, 6): Boc_2O (28.65 g, 131.42 mmol) and DIEA (45.9 mL, 262.84 mmol) were added to a solution of *cis*-3-aminocyclopentanecarboxylic acid hydrochloride (14.50 g, 87.61 mmol) in a mixture of water and dioxane (1:1; 600 mL). After stirring at room temp. for 3 h, the solution was acidified to pH = 3 by the addition of aqueous HCl, and then it was extracted with CH_2Cl_2 (3× 150 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The resulting yellow oil was crystallized from $CHCl_3$/hexanes (1:1) to give racemic *cis*-Boc-3-aminocyclopentanecarboxylic acid (13.38 g, and 3.91 g in a second crystallization). The racemate was resolved by crystallization from $CHCl_3$/hexane (1:1) in the presence of with (+)-1-phenylethanamine (0.7–1 equiv.). The resulting white crystals were washed with $CHCl_3$/hexane (2:1), poured into a separating funnel, dissolved in CH_2Cl_2, and washed with citric acid (5% aq.; 3× 50 mL). This operation was repeated 2–3 times. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated, and the resulting oil was crystallized from $CHCl_3$/hexane (1:1) to give **6** (17.2 g, 86%) as white crystals. R_f = 0.82 (MeOH).[28] ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 6.34 and 5.03 (m, 1 H, NH), 4.15–3.73 (m, 1 H, 3-H), 2.81 (m, 1 H, 1-H), 2.18 (m, 1 H, 3-H), 1.39 (s, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 181.7 (CO_2H), 155.4 (CO), 79.2 (C), 51.9 (CH), 41.7 (CH), 36.0 (CH_2),

33.0 (CH_2), 28.3 (CH_3), 27.9 (CH_2) ppm. MS (CI^+): *m*/*z* (%) = 230 (42) $[M + H]^+$, 174 (89), 156 (66), 130 (100) $[M + H – Boc]^+$, 112 (74), 95 (10), 84 (11). HRMS: calcd. for $C_{11}H_{20}NO_4$ $[M + H]^+$ 230.1392; found 230.1402. $[\alpha]_D^{20}$ = –16.8 (*c* = 1.0 in MeOH).

(1*R*,3*S*)-3-[(*tert*-Butyloxycarbonyl)methylamino]cyclopentanecarboxylic Acid (L-Boc-^{Me}*N*-γ-Acp-OH, 7): A solution of L-Boc-γ-Acp-OH (750 mg, 3.27 mmol) in dry THF (25 mL) was treated with NaH (60% in mineral oil; 390 g, 9.82 mmol), and the mixture was stirred at 0 °C for 30 min. Then, iodomethane (610 μL, 9.82 mmol) was added, and the resulting mixture was stirred overnight at room temp. After quenching with water (50 mL), the solution was concentrated to remove the THF. The resulting aqueous solution was washed with Et_2O (3× 25 mL), then acidified to pH = 3 by the addition of HCl (10% aq.), and finally extracted with CH_2Cl_2 (3× 25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was crystallized from Et_2O/hexanes to give L-Boc-^{Me}*N*-γ-Acp-OH (**7**; 0.78 g, 98%) as colourless crystals. R_f = 0.43 (5% MeOH/CH_2Cl_2).[28] ^1H NMR ($CDCl_3$, 250 MHz): δ = 4.53 (m, 1 H, 3-H), 2.82 (m, 1 H, 1-H), 2.76 (s, 3 H, MeN), 1.46 (s, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 181.2 (CO), 155.8 (CO), 79.6 (C), 55.8 (CH), 41.2 (CH), 31.7 (CH_2), 28.3 (CH_3), 28.2 (CH_3), 27.3 (CH_2), 27.2 (CH_2) ppm. MS (CI^+): *m*/*z* (%) = 244 (3) $[M + H]^+$, 188 (36), 170 (30), 144 (100) $[M + H – Boc]^+$, 126 (85), 112 (9). HRMS: calcd. for $C_{12}H_{22}NO_4$ $[M + H]^+$ 244.1549; found 244.1553. $[\alpha]_D^{20}$ = –23.0 (*c* = 0.80 in MeOH).

***cis*-4-Aminocyclopent-2-enecarboxylic Acid Hydrochloride (HCl·H-Ace-OH):** A solution of 2-azabicyclo[2.2.1]hept-5-en-3-one (25.0 g, 229.08 mmol) in HCl (10% aq.; 1.3 L) was stirred for 24 h at room temperature, and then the mixture was concentrated in vacuo. Addition of acetone to the resulting yellow oil gave a white solid, *cis*-4-aminocyclopent-2-enecarboxylic acid hydrochloride, which was filtered off and washed with acetone to give the product (29.08 g, 100%).[12a] R_f = 0.46 (50% MeOH/CH_2Cl_2). ^1H NMR (D_2O, 250 MHz): δ = 6.18 (d, *J* = 5.6 Hz, 1 H), 6.04–5.79 (m, 1 H), 4.36 (m, 1 H), 3.81–3.60 (m, 1 H), 2.63 (dt, *J* = 14.6 and 8.5 Hz, 1 H), 2.03 (dt, *J* = 14.6 and 4.9 Hz, 1 H) ppm.

(1*S*,4*R*)-4-[(*tert*-Butyloxycarbonyl)amino]cyclopent-2-enecarboxylic Acid (L-Boc-γ-Ace-OH, 8): Boc_2O (74.02 g, 339.55 mmol) and DIEA (118.6 mL, 679.29 mmol) were added to a solution of *cis*-4-aminocyclopent-2-enecarboxylic acid hydrochloride (37.0 g, 163.45 mmol) in water (750 mL) and dioxane (750 mL). After stirring at room temp. for 3 h, the solution was acidified to pH = 3 by the addition of HCl (10%), and then it was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The resulting yellow oil was crystallized from 1:1 $CHCl_3$/hexanes to give Boc-γ-Ace-OH (41.9 g and 11.3 g in successive crystallizations). The racemic product was resolved by crystallization from $CHCl_3$/hexane (1:1) in the presence of (+)-1-phenylethanamine (0.7–1 equiv.). The resulting white crystals were washed with hexane, poured into a separating funnel, dissolved in CH_2Cl_2 (150 mL), and washed with HCl (5% aq.; 3× 100 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated. The resulting oil was crystallized from $CHCl_3$/hexane (1:1) to give **8** (99%) as white crystals].[12a] R_f = 0.60 (10% MeOH/CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz): δ = 10.8 (s, 1 H), 6.30 and 4.98 (s, 1 H), 5.90 (s, 2 H), 4.80–4.51 (m, 1 H), 3.51 (s, 1 H), 2.54 (m, 1 H), 1.94 (m, 1 H), 1.46 (s, 9 H) ppm.

(1*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]cyclopentanecarboxylic Acid (L-Boc-γ-Acp-OH, 6): A solution of L-Boc-γ-Ace-OH (2.58 mg, 11.36 mmol) in EtOH (40 mL) was treated with Pd/C (10%; 121 mg, 1.36 mmol) and hydrogenated at balloon pressure for 12 h. The resulting mixture was filtered through a Celite pad, which was rinsed with EtOH, and the filtrate was concentrated to give L-Boc-γ-Acp-OH (2.60 g, 99%) as a white solid. R_f = 0.60 (10% MeOH/CH_2Cl_2).

(±)-(1*r*,4*s*,7*r*)-2-(4-Methoxybenzyl)-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one: Tributyltin hydride (8.1 mL, 0.030 mol) and AIBN (200 mg, 1.22 mmol) were added to a solution of **8b**[21] (10.0 g, 25.10 mmol) in dry benzene (300 mL). The mixture was heated at reflux for 12 h, and then concentrated under reduced pressure. The residue was purified by flash chromatography (15–30% EtOAc/hexane) to give the desired product (7.8 g, 97%) as a colourless oil. R_f = 0.46 (30% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 4.49 (d, *J* = 14.7 Hz, 1 H, Bn), 4.06 (d, *J* = 14.7 Hz, 1 H, Bn), 3.85 (m, 1 H, 7-H), 3.78 (s, 3 H, MeO), 3.33 (m, 1 H, 1-H), 2.60 (m, 1 H, 4-H), 1.99 (m, 1 H, 5-H), 1.78 (ddd, *J* = 10.3, 7.2, and 4.2 Hz, 1 H, 6-H), 1.48 (ddd, *J* = 11.8, 8.0, and 3.6 Hz, 1 H, 5-H), 1.33 (m, 1 H, 6-H), 0.05 (s, 9 H, TMS) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.2 (CO), 159.2 (C), 129.5 (CH), 129.3 (C), 114.1 (CH), 75.8 (CH), 61.8 (CH), 55.3 (CH_3), 50.6 (CH), 43.8 (CH_2), 25.1 (CH_2), 22.1 (CH_2), 0.03 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 2954, 2910, 2832, 1699, 1613, 1513, 1459, 1416, 1361, 1250, 1173, 1125 cm^{-1}. MS (ESI-TOF$^+$): *m*/*z* (%) = 121.1 (100), 140.1 (17), 212.1 (19), 248.1 (10) $[M + H – TMS]^+$, 270.1 (18) $[M + Na – TMS]^+$, 320 (15) $[M + H]^+$, 342 (9) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{26}NO_3Si$ 320.1676; found 320.1674.

(±)-(1*r*,4*s*,7*r*)-7-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one: TBAF (1 M in THF; 30 mL) was added to a stirred solution of (1*r*,4*s*,7*r*)-2-(4-methoxybenzyl)-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one (7.8 g, 0.024 mol) in THF (210 mL). The mixture was stirred for 30 min, and then the solvent was removed under reduced pressure. The resulting residue was diluted with EtOAc (750 mL), and the solution was washed with HCl (10% aq.; 300 mL), $NaHCO_3$ (satd. aq.; 2× 300 mL), and brine (200 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give the desired product (5.3 g, 88%) as a colourless oil. R_f = 0.48 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.6 Hz, 2 H, Ar), 6.82 (d, *J* = 8.6 Hz, 2 H, Ar-H), 4.48 (d, *J* = 14.7 Hz, 1 H, Bn), 3.98 (d, *J* = 14.7 Hz, 1 H, Bn), 3.92 (m, 1 H, 7-H), 3.88 (br. s, 1 H, OH), 3.77 (s, 3 H, MeO), 3.41 (br. s, 1 H, 1-H), 2.60 (m, 1 H, 4-H), 2.05 (m, 1 H, 5-H), 1.85 (ddd, *J* = 13.6, 5.6, and 2.9 Hz, 1 H, 6-H), 1.41 (m, 2 H, 5-H and 6-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.6 (CO), 159.2 (C), 129.5 (CH), 128.9 (C), 114.2 (CH), 75.3 (CH), 61.5 (CH), 55.3 (CH_3), 50.2 (CH), 43.8 (CH_2), 24.9 (CH_2), 21.9 (CH_2) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 2995, 2951, 2837, 1674, 1513, 1464, 1247, 1176, 1116, 1034 cm^{-1}. MS (ESI-TOF$^+$): *m*/*z* (%) = 270 (8) $[M + Na]^+$, 248 (31) $[M + H]^+$, 245 (100), 149 (81) $[M + H – PMB]^+$. HRMS (ESI): calcd. for $C_{14}H_{17}NO_3Na$ 270.1101; found 270.1102.

(±)-(1*r*,4*s*,7*r*)-7-Fluoro-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (9b): A stirred solution of (±)-(1*r*,4*s*,7*r*)-7-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (2.0 g, 8.08 mmol) in anhydrous CH_2Cl_2 (60 mL) was cooled to –80 °C, and DAST (2.1 mL, 0.016 mol) was added. The resulting mixture was stirred for 2 h at –80 °C, then it was allowed to warm to room temperature, and stirred at that temperature for 12 h. $NaHCO_3$ (satd. aq.; 20 mL) was slowly added, and the mixture was extracted with CH_2Cl_2 (3× 20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under re-

duced pressure. The residue was purified by flash chromatography (30% EtOAc/hexane) to give **9b** (1.2 g, 60%) as a colourless oil. R_f = 0.47 (50% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, J = 8.6 Hz, 2 H, Ar), 6.78 (d, J = 8.6 Hz, 2 H, Ar), 4.60 (d, J = 57.9 Hz, 1 H, 7-H), 4.45 (dd, J = 14.7 and 2.1 Hz, 1 H), 4.02 (d, J = 14.7 Hz, 1 H, Bn), 3.72 (s, 3 H, MeO), 3.56 (br. s, 1 H, 1-H), 2.80 (m, 1 H, 4-H), 1.98 (m, 1 H, 5-H), 1.76 (dddd, J = 16.7, 10.4, 6.5, and 3.8 Hz, 1 H, 6-H), 1.51 (m, 2 H, 5-H and 6-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.3 (d, J = 11.7 Hz, CO), 159.1 (C), 129.3 (CH), 128.5 (C), 114.0 (CH), 91.6 (d, J = 208.3 Hz, CH), 59.3 (d, J = 19.7 Hz, CH), 55.1 (CH_3), 48.5 (d, J = 15.9 Hz, CH), 43.5 (CH_2), 24.7 (CH_2), 21.5 (CH_2) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –193.2 (d, J = 57.9 Hz) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 2991, 2956, 2838, 1707, 1613, 1513, 1413, 1353, 1248, 1176, 1058, 1034 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 273 (17) [M + Na]$^+$, 250 (33) [M + H]$^+$, 245 (100). HRMS (ESI): calcd. for $C_{14}H_{17}FNO_2$ 250.1238; found 250.1238.

(±)-(1*r*,4*r*,7*r*)-7-Fluoro-2-azabicyclo[2.2.1]heptan-3-one: A solution of CAN (3.8 g, 6.93 mmol) in water (5 mL) was added to a stirred solution of **9b** (600 mg, 2.41 mmol) in acetonitrile (20 mL). After stirring for 5 h, the reaction mixture was diluted with EtOAc (200 mL), and the resulting solution was washed with water (4× 10 mL) and brine (30 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material (650 mg) was used in the following transformation without further purification. R_f = 0.41 (50% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (br. s, 1 H, NH), 4.74 (d, J = 57.6 Hz, 1 H, 7-H), 3.80 (m, 1 H, 1-H), 2.77 (m, 1 H, 4-H), 2.01 (m, 2 H, 5-H and 6-H), 1.63 (m, 2 H, 5-H and 6-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.9 (d, J = 11.5 Hz, CO), 92.6 (d, J = 207.6 Hz, CH), 56.3 (d, J = 20.2 Hz, CH), 48.0 (d, J = 16.0 Hz, CH), 27.0 (CH_2), 20.6 (CH_2) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –191.4 (d, J = 57.6 Hz) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3187, 3089, 2924, 2853, 1698, 1462, 1344, 1248, 1120, 1054 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 152 (7) [M + Na]$^+$, 130 (100) [M + H]$^+$. HRMS (ESI): calcd. for C_6H_9FNO: 130.0663; found 130.0665.

(±)-(1*s*,2*s*,3s)-3-[(*tert*-Butyloxycarbonyl)amino]-2-fluorocyclopentanecarboxylic Acid (Boc-2-F-γ-Acp-OH, 10): A solution of (±)-(1*r*,4*r*,7*r*)-7-fluoro-2-azabicyclo[2.2.1]heptan-3-one in acetic acid (12 mL) and HCl (4 N; 12 mL) was stirred at 70 °C for 5 h. After this time, the mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of dioxane and water (1:1; 16 mL), and then treated with DIEA (1.4 mL, 8.02 mmol) and Boc_2O (880 mg, 4.03 mmol). The mixture was stirred at room temperature for 12 h. The resulting aqueous solution was carefully acidified with HCl (5% aq.) to pH = 3. The acidified aqueous solution was extracted with CH_2Cl_2 (2× 100 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (50–100% EtOAc/hexane) to give the desired product (310 mg, 53%) as a white foam. R_f = 0.52 (EtOAc). m.p. 109.4–111.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.64 (br. s, 1 H, NH), 5.20 (d, J = 49.6 Hz, 1 H, 2-H), 4.06 (m, 1 H, 3-H), 3.05 (m, 1 H, 1-H), 2.30–2.00 (m, 3 H, 5-H and 6-H), 1.68 (m, 1 H, 6-H), 1.48 (s, 9 H, Boc) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.9 (d, J = 58.4 Hz, CO), 157.4 (CO), 99.9 (d, J = 181.8 Hz, CH), 81.9 (CH_3), 57.8 (d, J = 30.8 Hz, CH), 49.5 (CH), 29.9 (CH_2), 28.4 (CH_3), 25.9 (CH_2) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3092, 2977, 2937, 2876, 2684, 2525, 1869, 1699, 1663, 1522, 1409, 1369, 1167, 1062 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 148 (100) [M + H – Boc]$^+$, 192 (47) [M + H – *t*Bu]$^+$, 270 (82) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_3$ 270.1112; found 270.1110. CCDC-909274.

(±)-(1*s*,4*r*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one: A solution of KOH (37 g, 0.66 mol) in dry DMSO (200 mL) was added to a solution of **4** (18 g, 0.16 mol) in dry DMSO (100 mL), and the resulting mixture was stirred for 30 min at room temp. TBAI (0.76 g, 2.06 mmol) was added, and the solution was stirred for 15 min. The mixture was cooled to 0 °C, and then benzyl bromide (40 mL, 0.33 mol) was slowly added. The mixture was stirred for 15 min at 0 °C, and then for 5 h at room temp. The resulting mixture was diluted with $CHCl_3$ (400 mL) and washed with NH_4Cl (satd. aq.; 160 mL). The aqueous solution was extracted with $CHCl_3$ (5× 150 mL), and the combined organic extracts were washed with H_2O (150 mL) and brine (150 mL). The combined aqueous phases were extracted with $CHCl_3$ (2× 80 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (60% EtOAc/hexane) to give the desired product (31.6 g, 96%). R_f = 0.46 (50% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (m, 3 H, Ar), 7.20 (m, 2 H, Ar), 6.56 (s, 2 H, 5-H and 6-H), 4.45 (d, J = 14.8 Hz, 1 H, Bn), 4.02 (br. s, 1 H, 1-H), 3.96 (d, J = 14.8 Hz, 1 H, Bn), 3.39 (br. s, 1 H, 4-H), 2.30 (dt, J = 7.7 and 1.6 Hz, 1 H, 7-H), 2.06 (dt, J = 7.7 and 1.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 180.1 (CO), 139.5 (CH), 137.3 (CH), 136.5 (C), 128.6 (CH), 128.3 (CH), 127.5 (CH), 62.6 (CH), 58.3 (CH_2), 53.8 (CH), 48.0 (CH_2) ppm. MS (ESI-TOF$^+$): m/z (%) = 222 (73) [M + Na]$^+$, 200 (86) [M + H]$^+$, 123 (100) [M – Ph]$^+$. HRMS (ESI): calcd. for $C_{13}H_{14}NO$ 200.1070; found 200.1073.

(±)-(1*r*,2*s*,4*r*,5*s*)-6-Benzyl-3-oxa-6-azatricyclo[3.2.1.0^{2,4}]octan-7-one: An excess of *m*-CPBA (70%; 53 g, 0.31 mol) was added to a solution of **(±)-**(1*s*,4*r*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one (30 g, 0.15 mol) in $CHCl_3$ (500 mL), and the resulting solution was heated at reflux for 6 h. After cooling down to room temp., the mixture was diluted with chloroform (1 L), and washed with Na_2SO_3 (satd. aq.; 600 mL) and Na_2CO_3 (2× 500 mL). The combined aqueous phases were extracted with $CHCl_3$ (2× 500 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc/hexane) to give the desired product (29.4 g, 91%). R_f = 0.42 (50% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 3 H, Ar), 7.25 (m, 2 H, Ar), 4.44 (AB, J = 14.8 Hz, 1 H, Bn), 4.33 (AB, J = 14.8 Hz, 1 H, Bn), 3.77 (br. s, 1 H, 1-H), 3.54 (br. s, 1 H, 6-H), 3.26 (br. s, 1 H, 5-H), 3.00 (m, 1 H, 4-H), 1.80 (d, J = 9.7 Hz, 1 H, 7-H), 1.63 (d, J = 9.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.0 (CO), 137.3 (C), 128.8 (CH), 128.3 (CH), 128.0 (CH), 59.6 (CH), 55.3 (CH), 51.7 (CH), 47.2 (CH), 46.0 (CH_2), 30.2 (CH_2) ppm. MS (ESI-TOF$^+$): m/z (%) = 216 (100) [M + H]$^+$, 238 (40) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{14}NO_2$ 216.1019; found 216.1019.

(±)-(1*s*,4*s*,6*s*,7*r*)-2-Benzyl-6-bromo-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one: HBr (48%; 40 mL) was added to a stirred solution of (1*r*,2*s*,4*r*,5*s*)-6-benzyl-3-oxa-6-azatricyclo[3.2.1.0^{2,4}]-octan-7-one (30.0 g, 0.14 mol) in acetonitrile (1.2 L) at 0 °C. After stirring for 2 h at this temperature, the resulting reaction mixture was washed with saturated $NaHCO_3$ (500 mL), and the aqueous layer was extracted with EtOAc (2× 500 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a mixture (32.2 g, 73%). R_f = 0.39 (5% methanol/CH_2Cl_2).

The previously prepared mixture and pyridine (5.3 mL, 65.80 mmol) were dissolved in CH_2Cl_2 (100 mL). The solution was

cooled down to 0 °C, and trimethylsilyl triflate (12 mL, 66.14 mmol) was added. After 10 min, DMAP (800 mg, 6.55 mmol) was added, and the mixture was stirred overnight at reflux. The resulting solution was allowed to cool, diluted with CH_2Cl_2 (200 mL), and washed with HCl (2% aq.; 50 mL). The aqueous solution was extracted with CH_2Cl_2 (2× 100 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane) to provide (±)-(1*s*,4*s*,6*s*,7*r*)-2-benzyl-6-bromo-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one [4.2 g, 52%; R_f = 0.54 (25% EtOAc/hexane)] together with the other regioisomer (±)-(1*s*,4*r*,5*s*,6*s*)-2-benzyl-6-bromo-5-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one [1.0 g, 13%; R_f = 0.26 (25% EtOAc/hexane)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 3 H, Ar), 7.21 (m, 2 H, Ar), 4.58 (d, J = 14.8 Hz, 1 H, Bn), 4.07 (d, J = 14.8 Hz, 1 H, Bn), 4.06 (s, 1 H, 7-H), 3.70 (m, 1 H, 6-H), 3.55 (s, 1 H, 1-H), 2.69 (t, J = 1.9 Hz, 1 H, 4-H), 2.44 (dt, J = 13.4 and 4.2 Hz, 1 H, 5-H), 2.36 (dd, J = 13.4 and 8.0 Hz, 1 H, 5-H), 0.10 (s, 9 H, TMS) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.7 (CO), 136.2 (C), 129.0 (CH), 128.0 (CH), 76.2 (CH), 66.2 (CH), 51.3 (CH), 44.4 (CH_2), 41.5 (CH), 34.0 (CH_2), 0.03 (CH_3) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 392 (5) [M + Na]$^+$, 390 (5) [M + Na]$^+$, 370 (9) [M + H]$^+$, 368 (9) [M + H]$^+$, 320 (34) [M + Na – TMS]$^+$ 328 (35) [M + Na – TMS]$^+$, 298 (89) [M + H – TMS]$^+$, 296 (100) [M + H – TMS]$^+$. HRMS (ESI): calcd. for $C_{16}H_{23}{}^{79}BrNO_2Si$ 368.0676; found 368.0676; calcd. for $C_{16}H_{23}{}^{81}BrNO_2Si$ 370.0657; found 370.0661.

(±)-(1*s*,4*s*,6*s*,7*r*)-2-Benzyl-6-bromo-7-hydroxy-2-azabicyclo[2.2.1]-heptan-3-one (11): TBAF (1 M in THF; 23 mL) was added to a stirred solution of **(±)-**(1*s*,4*s*,6*s*,7*r*)-2-benzyl-6-bromo-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one (5.3 g, 0.014 mol) in dry THF (140 mL). The mixture was stirred for 35 min at room temp., and then the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc) to give the desired product (3.9 g, 93%) R_f = 0.61 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 3 H, Ar), 7.23 (m, 2 H, Ar), 4.61 (d, J = 14.8 Hz, 1 H, Bn), 4.19 (s, 1 H, 7-H), 4.04 (d, J = 14.8 Hz, 1 H, Bn), 3.78 (t, J = 6.0 Hz, 1 H, 1-H), 3.69 (s, 1 H, 6-H), 2.83 (br. s, 1 H, 4-H), 2.48 (m, 2 H, 5-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.6 (CO), 136.0 (C), 129.0 (CH), 128.1 (CH), 128.2 (CH), 76.7 (CH), 65.6 (CH), 50.7 (CH), 44.5 (CH_2), 42.1 (CH), 34.0 (CH_2) ppm.

(±)-(1*s*,4*s*,6*s*,7*r*)-2-Benzyl-6-bromo-7-fluoro-2-azabicyclo[2.2.1]-heptan-3-one (12a): DAST (2.4 mL, 0.018 mol) was added to a stirred solution of (±)-(1*s*,4*s*,6*s*,7*r*)-2-benzyl-6-bromo-7-hydroxy-2-azabicyclo[2.2.1]heptan-3-one (3.7 g, 0.012 mol) in anhydrous CH_2Cl_2 (100 mL) at –78 °C. The resulting mixture was stirred for 2 h at this temperature, and then it was allowed to warm to room temperature and stirred overnight. After this time, $NaHCO_3$ (satd. aq.; 100 mL) was slowly added, and the mixture was extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (50% EtOAc/hexane) to give the desired product (2.2 g, 62%). R_f = 0.65 (50% EtOAc/hexane). This product was crystallized from a solution in EtOAc by vapour-phase equilibration with hexane. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (m, 3 H, Ar), 7.22 (m, 2 H, Ar), 4.85 (d, J = 55.7 Hz, 1 H, 7-H), 4.60 (d, J = 14.8 Hz, 1 H, Bn), 4.11 (d, J = 14.8 Hz, 1 H, Bn), 3.87 (s, 1 H, 1-H), 3.80 (m, 1 H, 6-H), 3.01 (s, 1 H, 4-H), 2.54 (m, 1 H, 5-H), 2.44 (dt, J = 13.8 and 4.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.2 (d, J = 10.1 Hz, CO), 135.7 (C), 129.1 (CH), 128.3 (CH), 128.1 (CH), 91.7 (d, J = 214.9 Hz, CH), 64.6 (d, J = 17.6 Hz, CH), 49.1 (d, J = 17.6 Hz, CH), 44.5 (CH_2), 40.2 (CH), 33.9 (CH_2) ppm. CCDC-909275.

(±)-(1*r*,4*s*,7*r*)-2-Benzyl-7-fluoro-2-azabicyclo[2.2.1]heptan-3-one (12b): Tributyltin hydride (1.6 mL, 5.95 mmol) and AIBN (25 mg, 0.15 mmol) were added to a solution of **12a** (1.3 g, 4.36 mmol) in dry benzene (45 mL), and the resulting stirred solution was heated at reflux overnight. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (50% EtOAc/hexane) to give **12b** (850 mg, 88%). R_f = 0.57 (50% EtOAc/hexane). A crystal for X-Ray diffraction was obtained from a solution of this compound in CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 3 H, Ar), 7.22 (m, 2 H, Ar), 4.71 (d, J = 57.7 Hz, 1 H, 7-H), 4.64 (d, J = 14.8 Hz, 1 H, Bn), 4.09 (d, J = 14.8 Hz, 1 H, Bn), 3.64 (m, 1 H, 1-H), 2.92 (m, 1 H, 4-H), 2.06 (m, 1 H, 5-H), 1.86 (m, 1 H, 6-H), 1.66–1.52 (m, 2 H, 5-H and 6-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.7 (d, J = 12.5 Hz, CO), 136.5 (C), 128.8 (CH), 128.1 (CH), 127.9 (CH), 91.7 (d, J = 208.7 Hz, CH), 59.6 (d, J = 20.1 Hz, CH), 48.6 (d, J = 16.3 Hz, CH), 44.2 (CH_2), 24.7 (CH_2), 21.6 (CH_2) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 258 (1) [M + K]$^+$, 242 (63) [M + Na]$^+$, 220 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{15}FNO$ 220.1132; found 220.1139. CCDC-909276.

(±)-(1*r*,4*s*,7*r*)-7-Fluoro-2-azabicyclo[2.2.1]heptan-3-one: Freshly cut sodium metal (0.32 g, 0.014 mol) was added to a stirred solution of liquid NH_3 (5 mL) and *tert*-butanol (1.5 mL) at –78 °C to form a deep blue solution. Then, a solution of **12b** (440 mg, 1.99 mmol) in THF (6 mL) was added portionwise to the stirred solution at –78 °C. The resulting solution was stirred for 20 min at this temperature, then the mixture was warmed to –30 °C, and stirring was continued for 4 min. The mixture was then cooled back to –78 °C, and solid NH_4Cl (1.1 g, 20.56 mmol) was slowly added. NH_4Cl (satd. aq.; 10 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (75% EtOAc/hexane) to give the desired product (200 mg, 78%). R_f = 0.41 (EtOAc).

(±)-(1*s*,2*s*,3*s*)-3-*tert*-Butoxycarbonylamino-2-fluorocyclopentanecarboxylic Acid (Boc-2-F-γ-Acp-OH, 10): (±)-(1*r*,4*s*,7*r*)-7-Fluoro-2-azabicyclo[2.2.1]heptan-3-one (50 mg, 0.39 mmol) was dissolved in acetic acid (1.5 mL) and HCl (4 N aq.; 1.5 mL). The resulting mixture was stirred at 70 °C for 4.5 h, and then it was concentrated under reduced pressure. The residue was dissolved in a mixture of dioxane and water (1:1; 3 mL), and DIEA (270 μL, 1.55 mmol) and Boc_2O (130 mg, 0.58 mmol) were successively added. The resulting mixture was stirred at room temperature overnight, and then it was carefully acidified with HCl (5% aq.) to pH = 3. The acidified aqueous solution was extracted with CH_2Cl_2 (3× 10 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (0.5% AcOH/EtOAc) to give **10** (93 mg, 97%) as a white foam. R_f = 0.56 (0.5% AcOH/EtOAc).

(±)-(1*s*,4*r*)-2-Methyl-2-azabicyclo[2.2.1]hept-5-en-3-one: A solution of lactam **4** (10 g, 0.092 mol) in dry THF (350 mL) was cooled to 0 °C and then treated with NaH (60% dispersion in mineral oil; 20 g, 0.46 mol). The reaction mixture was stirred at 0 °C for 30 min, and then methyl iodide (28.6 mL, 0.46 mol) was slowly added. The mixture was stirred for 3 d at room temperature under Ar. Then the mixture was cooled to 0 °C and quenched with water. The THF was removed under reduced pressure. The residue was passed though a silica gel pad eluting with methanol/chloroform (10%). The filtrate was dried with anhydrous Na_2SO_4, filtered, and con-

centrated under reduced pressure. The residue was purified by flash chromatography (75% EtOAc/hexane) to give the desired product (9.8 g, 87%). R_f = 0.45 (65% EtOAc/hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.62 (m, 1 H, 6-H), 6.40 (m, 1 H, 5-H), 3.89 (m, 1 H, 1-H), 3.08 (m, 1 H, 4-H), 2.45 (s, 3 H, MeN), 2.13 (m, 1 H, 7-H), 1.91 (d, J = 7.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 181.0 (CO), 138.9 (CH), 137.9 (CH), 65.0 (CH), 58.0 (CH), 53.4 (CH_3), 31.3 (CH_2) ppm. HRMS (CI^+): calcd. for $C_7H_{10}NO$ 124.0762; found 124.0763.

(±)-(1*r*,2*s*,4*r*,5*s*)-6-Methyl-3-oxa-6-azatricyclo[3.2.1.0^{2,4}]octan-7-one: A solution of (1*s*,4*r*)-2-methyl-2-azabicyclo[2.2.1]hept-5-en-3-one (9.8 g, 0.080 mol) in CH_2Cl_2 (1 L) was treated with $NaHCO_3$ (10 g, 0.12 mol). After 15 min, *m*-CPBA (70%; 42 g, 0.24 mol) was added, and the mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (50% EtOAc/hexane) to give the desired product (8.3 g, 75%). R_f = 0.43 (EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.58 (m, 1 H, 1-H), 3.51 (m, 1 H, 6-H), 3.32 (m, 1 H, 2-H), 2.72 (m, 1 H, 5-H), 2.60 (s, 3 H, MeN), 1.58 (d, J = 9.4 Hz, 1 H, 8-H), 1.40 (d, J = 9.4 Hz, 8-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 177.7 (CO), 61.4 (CH), 54.9 (CH), 51.7 (CH), 47.0 (CH), 29.7 (CH_3), 28.9 (CH_2) ppm. HRMS (ESI): calcd. for $C_7H_{10}NO_2$ 140.0706; found 140.0702.

(±)-(1*s*,4*s*,6*s*,7*r*)-6-Bromo-2-methyl-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one: HBr (48%; 1.5 mL) was added to a stirred solution of (1*r*,2*s*,4*r*,5*s*)-6-methyl-3-oxa-6-azatricyclo[3.2.1.0^{2,4}]-octan-7-one (1.0 g, 7.19 mmol) in acetonitrile (50 mL) at 0 °C. After stirring for 2 h at this temperature, the reaction mixture was diluted with EtOAc (150 mL) and washed with $NaHCO_3$ (satd. aq.; 100 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a mixture (1.2 g, 76%). R_f = 0.30 (3% methanol/CH_2Cl_2).

A stirred solution of the previously prepared mixture in CH_2Cl_2 (50 mL) was succesively treated with pyridine (880 µL, 10.92 mmol), trimethylsilyl triflate (2.0 mL, 11.02 mmol), and DMAP (150 mg, 1.23 mmol). After stirring overnight at reflux, the resulting solution was cooled, diluted with CH_2Cl_2 (100 mL), and washed with H_2O (2× 50 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% EtOAc/hexane) to give (±)-(1*s*,4*s*,6*s*,7*r*)-6-bromo-2-methyl-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one [610 mg, 52%; R_f = 0.63 (50% EtOAc/hexane)], and the other regioisomer (±)-(1*s*,4*r*,5*s*,6*s*)-6-bromo-2-methyl-5-(trimethylsilyloxy)-2-azabicyclo-[2.2.1]heptan-3-one [120 mg, 10%; R_f = 0.38 (50% EtOAc/hexane)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.13 (s, 1 H, 7-H), 3.86 (m, 1 H, 6-H), 3.59 (s, 1 H, 1-H), 2.77 (s, 3 H, MeN), 2.63 (s, 1 H, 4-H), 2.47 (m, 1 H, 5-H), 2.36 (dd, J = 13.4 and 8.4 Hz, 1 H, 5-H), 0.17 (s, 9 H, TMS) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.3 (CO), 75.7 (CH), 68.5 (CH), 51.1 (CH), 40.9 (CH), 34.0 (CH_2), 27.5 (CH_3), –0.16 (CH_3) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 292 (100) [M + H]$^+$, 294 (84) [M + H]$^+$.

(±)-(1*s*,4*s*,6*s*,7*r*)-6-Bromo-7-hydroxy-2-methyl-2-azabicyclo[2.2.1]-heptan-3-one: TBAF (1 M in THF; 2 mL) was added to a stirred solution of (1*s*,4*s*,6*s*,7*r*)-6-bromo-2-methyl-7-(trimethylsilyloxy)-2-azabicyclo[2.2.1]heptan-3-one (1.1 g, 3.76 mmol) in dry THF (30 mL). The mixture was stirred for 10 min, and then the solvent was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (50% EtOAc/hexane) to give the desired product (870 mg, 98%). R_f = 0.40 (70% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (m, 1 H, 7-H), 3.91 (m, 1 H, 6-H), 3.71 (s, 1 H, 1-H), 2.84 (d, J = 5.2 Hz, 1 H, 4-H), 2.74 (br. s, 1 H, OH), 2.76 (s, 3 H, MeN), 2.45 (m, 2 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.3 (CO), 76.2 (CH), 68.1 (CH), 50.5 (CH), 41.4 (CH), 34.0 (CH_2), 27.7 (CH_3) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 245 (100), 222 (14) [M + H]$^+$, 220 (13) [M + H]$^+$. HRMS (ESI): calcd. for $C_7H_{11}{}^{79}BrNO_2$ 219.9968; found 219.9965; calcd. for $C_7H_{11}{}^{81}BrNO_2$ 221.9948; found 221.9946.

(±)-(1*s*,4*s*,6*s*,7*r*)-6-Bromo-7-fluoro-2-methyl-2-azabicyclo[2.2.1]-heptan-3-one (13): DAST (1.2 mL, 9.08 mmol) was added to a stirred solution of (1*s*,4*s*,6*s*,7*r*)-6-bromo-7-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (1.0 g, 4.55 mmol) in anhydrous CH_2Cl_2 (35 mL) at –80 °C. The resulting mixture was stirred for 2 h at that temperature, and then it was allowed to warm to room temperature. After stirring for 14 h, $NaHCO_3$ (satd. aq.; 15 mL) was slowly added, and the mixture was extracted with CH_2Cl_2 (2× 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (70% EtOAc/hexane) to give the desired product (440 mg, 40%). R_f = 0.36 (50% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.92 (d, J = 55.7 Hz, 1 H, 7-H), 3.96 (m, 1 H, 6-H), 3.90 (s, 1 H, 1-H), 2.94 (br. s, 1 H, 4-H), 2.81 (s, 3 H, MeN), 2.53 (dd, J = 14.5 and 7.8 Hz, 1 H, 5-H), 2.45 (dt, J = 13.9 and 4.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.8 (d, J = 10.1 Hz, CO), 91.4 (d, J = 214.1 Hz, CH), 66.9 (d, J = 17.1 Hz, CH), 48.8 (d, J = 16.6 Hz, CH), 39.6 (CH), 33.9 (CH_2), 27.6 (CH_3) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –188.1 (d, J = 57.6 Hz) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 245 (100), 223 (23) [M + H]$^+$, 221 (25) [M + H]$^+$. HRMS (ESI): calcd. for $C_7H_{10}{}^{79}BrFNO$ 221.9924; found 221.9923; calcd. for $C_7H_{10}{}^{81}BrFNO$ 223.9904; found 223.9903. CCDC-909277.

(±)-(1*r*,4*s*,7*r*)-7-Fluoro-2-methyl-2-azabicyclo[2.2.1]heptan-3-one: Tributyltin hydride (450 µL, 1.67 mmol) and AIBN (10 mg, 0.061 mmol) were added to a solution of **13** (310 mg, 1.38 mmol) in dry benzene (10 mL). The resulting solution was heated at reflux with stirring overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (50% EtOAc/hexane) to give the desired product (190 mg, 93%). R_f = 0.37 (60% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (d, J = 57.9 Hz, 1 H, 7-H), 3.66 (s, 1 H, 1-H), 2.83 (m, 1 H, 4-H), 2.78 (s, 3 H, MeN), 2.05 (m, 1 H, 5-H), 1.92 (m, 1 H, 6-H), 1.72 (m, 1 H, 5-H), 1.64 (m, 1 H, 6-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.2 (d, J = 11.3 Hz, CO), 91.4 (d, J = 207.3 Hz, CH), 62.0 (d, J = 19.9 Hz, CH), 48.4 (d, J = 15.9 Hz, CH), 27.3 (CH_3), 24.2 (CH_2), 21.6 (CH_2) ppm. MS (ESI-TOF$^+$): *m*/*z* (%) = 144 (100) [M + H]$^+$.

(±)-(1*s*,2*s*,3*s*)-3-[(*tert*-Butyloxycarbonyl)methylamino]-2-fluorocyclopentanecarboxylic Acid (Boc-2-F-^{Me}*N*-γ-Acp-OH, 14): (±)-(1*r*,4*s*,7*r*)-7-Fluoro-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (80 mg, 0.60 mmol) was dissolved in acetic acid (1.5 mL) and HCl (4 N aq.; 1.5 mL). The resulting mixture was stirred at 70 °C for 8 h, and then it was concentrated under reduced pressure. The residue was dissolved in a mixture of dioxane and water (1:1; 4 mL) and treated with DIEA (490 µL, 2.81 mmol) and Boc_2O (170 mg, 0.78 mmol). The resulting mixture was stirred at room temperature for 12 h, after which it was acidified carefully with HCl (5% aq.) to pH = 3. The acidified aqueous solution was extracted with CH_2Cl_2 (3× 10 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (70% EtOAc/hexane) to give **14** (54 mg, 36%). R_f = 0.38 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.23 (dt, J = 54.0 and 7.2 Hz, 1 H, 2-H), 4.49 (m, 1 H, 3-H), 3.01 (m, 1 H, 1-H), 2.82 (s, 3 H, MeN), 2.22–1.64 (m, 4 H, 4-H and 5-H), 1.44 (s, 9 H, Boc) ppm. ^{13}C

NMR (75.4 MHz, $CDCl_3$): δ = 176.9 (CO), 155.9 (C=O), 91.6 (d, J = 186.5 Hz, CH), 80.5 (C), 61.7 (CH), 47.2 (d, J = 21.5 Hz, CH), 30.5 (CH_3), 28.5 (CH_3), 24.2 (CH_2), 24.1 (CH_2) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –186.3 (d, J = 52.3 Hz) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3480, 2976, 2932, 2884, 1693, 1671, 1482, 1368, 1251, 1160, 1011 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 284 (35) $[M + Na]^+$, 245 (100) $[M + H – OH]^+$, 162 (13) $[M + H – Boc]^+$. HRMS (ESI): calcd. for $C_{12}H_{20}FNO_4Na$ 284.1269; found 284.1263.

(±)-(1*s*,4*s*,6*s*,7*r*)-2-Benzyl-6-bromo-7-[(2-methoxyethoxy)methoxy]-2-azabicyclo[2.2.1]heptan-3-one: A solution of **11** (500 mg, 1.69 mmol) in dry CH_2Cl_2 (17 mL) was succesively treated with DIEA (3.0 mL, 0.017 mol) and methoxyethoxymethyl chloride (1.0 mL, 8.76 mmol). The resulting mixture was stirred overnight at room temp. Then CH_2Cl_2 (50 mL) was added, and the solution was washed with NH_4Cl (satd. aq.; 50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% EtOAc/hexane) to give the desired product (620 mg, 80%). R_f = 0.50 (EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (m, 3 H, Ar), 7.21 (m, 2 H, Ar), 4.82 (s, 2 H, MEM), 4.75 (d, J = 7.0 Hz, MEM), 4.69 (d, J = 7.0 Hz, MEM), 4.56 (d, J = 14.9 Hz, 1 H, Bn), 4.14 (q, J = 1.5 Hz, 1 H, 6-H), 4.10 (d, J = 14.9 Hz, 1 H, Bn), 3.78 (m, 1 H, 7-H), 3.72 (m, 3 H, 1-H and MEM), 3.56 (m, 2 H, MEM), 3.36 (s, 3 H, MEM), 2.86 (m, 1 H, 4-H), 2.43 (m, 2 H, 5-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.3 (CO), 136.0 (C), 129.0 (CH), 128.1 (CH), 94.0 (CH_2), 79.4 (CH), 71.7 (CH_2), 67.6 (CH_2), 64.5 (CH), 59.0 (CH_3), 49.5 (CH), 44.5 (CH_2), 41.5 (CH), 34.3 (CH_2) ppm.

(±)-(1*r*,4*s*,7*r*)-7-[(2-Methoxyethoxy)methoxy]-2-azabicyclo[2.2.1]heptan-3-one (15b): Tributyltin hydride (840 μL, 3.12 mmol) and AIBN (13 mg, 0.079 mmol) were successively added to a solution of (±)-(1*s*,4*s*,6*s*,7*r*)-2-benzyl-6-bromo-7–2-methoxyethoxymethoxy-2-azabicyclo[2.2.1]heptan-3-one (870 mg, 2.26 mmol) in dry benzene (24 mL). The resulting solution was heated at reflux and stirred overnight under argon. The mixture was then allowed to cool, and concentrated under reduced pressure, and the residue was purified by flash chromatography (50% EtOAc/hexane) to give **15a** (590 mg, 85%), which was used immediately in the next step.

Freshly cut sodium metal (350 mg, 0.015 mol) was added to a stirred solution of liquid NH_3 (25 mL) at –78 °C to form a deep blue solution. Then a solution of previously prepared lactam **15a** (590 mg, 1.93 mmol) in THF (30 mL) was added portionwise to the stirred reaction mixture at –78 °C. The resulting solution was stirred for 30 min at –78 °C, then solid NH_4Cl (1.9 g, 35.51 mmol) was slowly added. NH_4Cl (satd. aq.; 60 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (75% EtOAc/hexane) to give **15b** (320 mg, 74%). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.02 (br. s, 1 H, NH), 4.78 (s, 2 H, MEM), 3.99 (m, 1 H, 1-H), 3.80 (m, 1 H, 7-H), 3.70 (m, 2 H, MEM), 3.60 (m, 2 H, MEM), 3.42 (s, 3 H, MEM), 2.72 (m, 1 H, 4-H), 2.03 (m, 2 H, 5-H and 6-H), 1.60 (m, 2 H, 5-H and 6-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.2 (CO), 94.7 (CH_2), 81.3 (CH), 71.6 (CH_2), 67.5 (CH_2), 59.1 (CH_3), 56.8 (CH), 48.0 (CH), 27.6 (CH_2), 21.2 (CH_2) ppm. MS (ESI-TOF$^+$): m/z (%) = 238 (100) $[M + Na]^+$, 216 (7) $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{17}NO_4Na$ 238.1050; found 238.1046.

(±)-(1*r*,4*s*,7*r*)-2-[(*tert*-Butyloxycarbonyl)amino]-7-[(2-methoxyethoxy)methoxy]-2-azabicyclo[2.2.1]heptan-3-one (15c): A solution of **15b** (34 mg, 0.16 mmol) in dry CH_2Cl_2 (1.5 mL) was treated with Boc_2O (130 mg, 0.58 mmol) and DMAP (7.7 mg, 0.63 mmol), and the mixture was stirred at room temperature for 20 h. The resulting solution was diluted with CH_2Cl_2 (5 mL), and washed with HCl (5% aq.; 5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (75% EtOAc/hexane) to give **15c** (50 mg, 91%) as a white foam. R_f = 0.50 (75% EtOAc/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.78 (s, 2 H, MEM), 4.42 (m, 1 H, 1-H), 4.01 (m, 1 H, 7-H), 3.70 (m, 2 H, MEM), 3.59 (m, 2 H, MEM), 3.41 (s, 3 H, MEM), 2.81 (m, 1 H, 4-H), 2.05 (m, 2 H, 5-H and 6-H), 1.75 (m, 2 H, 5-H and 6-H), 1.48 (s, 9 H, Boc) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.5 (CO), 148.9 (CO), 94.6 (CH_2), 83.1 (CH_3), 78.4 (CH), 71.6 (CH_2), 67.6 (CH_2), 60.0 (CH_3), 59.1 (CH), 50.0 (CH), 28.0 (CH_3), 25.9 (CH_2), 21.5 (CH_2) ppm. MS (ESI-TOF$^+$): m/z (%) = 338 (21) $[M + Na]^+$, 316 (1) $[M + H]^+$, 238 (100) $[M + Na – Boc]^+$, 216 (2) $[M + H – Boc]^+$. HRMS (ESI): calcd. for $C_{15}H_{25}NO_6Na$ 338.1574; found 338.1579.

(±)-(1*r*,2*s*,3*r*)-3-[(*tert*-Butyloxycarbonyl)amino]-2-[(2-methoxyethoxy)methoxy]cyclopentanecarboxylic Acid (16): A solution of **15c** (25 mg, 0.79 mmol) and K_2CO_3 (43 mg, 0.32 mmol) in a mixture of methanol and water (3:1; 1 mL) was stirred at room temperature for 18 h. The resulting aqueous solution was carefully acidified with HCl (5% aq.) to pH = 4, and then the acidified aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solid residue was purified by flash chromatography (EtOAc) to give **16** (20 mg, 78%). R_f = 0.25 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.12 (br. s, 1 H, NH), 4.78 (s, 2 H, MEM), 4.12 (br. s, 1 H, 3-H), 3.87 (br. s, 1 H, 2-H), 3.71 (m, 2 H, MEM), 3.58 (m, 2 H, MEM), 3.39 (s, 3 H, MEM), 2.86 (m, 1 H, 1-H), 2.23–1.52 (m, 3 H, 5-H and 6-H), 1.61 (m, 1 H, 6-H), 1.44 (s, 9 H, Boc) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 179.2 (CO), 155.9 (CO), 95.1 (CH_2), 79.6 (C), 85.0 (CH), 71.7 (CH_2), 67.1 (CH_2), 59.1 (CH_3), 57.4 (CH), 48.9 (CH), 30.0 (CH_2), 28.5 (CH_3), 25.7 (CH_2) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3521, 3354, 2975, 2928, 2890, 1696, 1482, 1523, 1367, 1168, 1041 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 356 (81) $[M + Na]^+$, 334 (2) $[M + H]^+$, 300 (79) $[M + K – tBu]^+$, 256 (6) $[M + Na – Boc]^+$, 234 (7) $[M + H – Boc]^+$, 202 (56), 172 (100), 154 (54), 128 (66), 110 (40). HRMS (ESI): calcd. for $C_{15}H_{27}NO_7Na$ 356.1680; found 356.1683.

1,2-*O*-Isopropylidene-α-D-xylofuranose: Powdered D-xylose (32.5 g, 0.22 mol) was dissolved in a solution of H_2SO_4 (0.66 M) in acetone (780 mL), and the mixture was stirred at room temp. until the solid was fully dissolved (at least 30 min). A solution of sodium carbonate (39.0 g, 0.37 mol) in water (340 mL) was added, and the mixture was stirred for a further 2.5 h. Sodium carbonate was added until the mixture was neutralized (pH = 6–7). The mixture was filtered, and the salts were rinsed with acetone. The solvent was removed completely from the filtrate under reduced pressure, and the resulting residue was purified by flash chromatography over silica (10% MeOH/CH_2Cl_2) to give the desired product (39.3 g, 95%) as a pale yellow syrup.[29] R_f = 0.5 (10% MeOH/CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.93 (d, J = 3.7 Hz, 1 H, 1-H), 4.47 (d, J = 3.7 Hz, 1 H, 2-H), 4.45 (s, 1 H, -O*H*), 4.25 (m, 1 H, 3-H), 4.12 (m, 1 H, 4-H), 3.96 (m, 2 H, 5-H), 3.74 (s, 3 H, -O*H*), 1.44 (s, 3 H, Me), 1.28 (s, 3 H, Me) ppm.

1,2-*O*-Isopropylidene-3,5-di-*O*-methanesulfonyl-α-D-xylofuranose: 1,2-*O*-Isopropylidene-α-D-xylofuranose (33.2 g, 0.17 mol) was dis-

solved in dry CH_2Cl_2 (1.25 L), and triethylamine (61.0 mL, 0.44 mol) was added. The reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (34.0 mL, 0.44 mol) was added slowly, and the reaction mixture was warmed to room temp. and stirred at that temperature for 1 h. The solution was washed with $NaHCO_3$ (satd. aq.; 3 × 250 mL) and brine (500 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to give the product (58 g, 96%) as an orange solid that was used without further purification.[29] R_f = 0.85 (4% MeOH/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.98 (d, J = 3.6 Hz, 1 H, 1-H), 5.09 (d, J = 2.8 Hz, 1 H, 3-H), 4.82 (d, J = 3.6 Hz, 1 H, 2-H), 4.58 (dt, J = 6.1, and 2.8 Hz, 1 H, 4-H), 4.41 (d, J = 6.1 Hz, 2 H, 5-H), 3.12 (s, 3 H, SO_2Me), 3.08 (s, 3 H, SO_2Me), 1.51 (s, 3 H, Me), 1.32 (s, 3 H, Me) ppm.

(1*R*,2*R*,5*R*)-2-(Dimethoxymethyl)-3,6-dioxabicyclo[3.1.0]hexane (17): 1,2-*O*-Isopropylidene-3,5-di-*O*-methanesulfonyl-α-D-xylofuranose (70.0 g, 0.20 mol) was dissolved in dry methanol (1.25 L), and TFA (12.5 L) was added. The reaction mixture was heated under reflux for 40 h. Then it was cooled to room temp., K_2CO_3 (84.0 g, 0.60 mol) was added, and the mixture was stirred overnight. Water was added to dissolve the K_2CO_3 fully, and the product was extracted with CH_2Cl_2 (500 mL). The organic phase was washed with water (3 × 50 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (50% EtOAc in hexane) to give **17** (29.7 g, 93%) as an orange liquid.[29] R_f = 0.4 (50% EtOAc in hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.23 [d, J = 4.5 Hz, 1 H, C*H*(OMe)$_2$], 4.01 (d, J = 4.5 Hz, 1 H, 2-H), 3.92 (d, J = 10.1 Hz, 1 H, 4-H), 3.78 (d, J = 10.1 Hz, 1 H, 4-H), 3.76 (d, J = 3.0 Hz, 1 H, 5-H), 3.72 (d, J = 3.0 Hz, 1 H, 1-H), 3.40 (s, 3 H, MeO), 3.38 (s, 3 H, MeO) ppm.

(2*R*,3*R*,4*S*)-4-Azido-2-dimethoxymethyl-3-hydroxytetrahydrofuran (18a): Compound **17** (29.7 g, 0.18 mol) was dissolved in a mixture of ethanol and water (4:1; 1 L). Sodium azide (24.0 mL, 0.37 mol) and ammonium chloride (24.6 g, 0.46 mol) were added, and the reaction mixture was heated under reflux for 24 h. The mixture was allowed to cool down to room temp., and the solvent was removed under reduced pressure. The residue was washed with CH_2Cl_2 (5 × 30 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude product was purified by flash chromatography (40% EtOAc in hexane) to give **18a** (31.3 g, 83%) as a yellow-orange liquid.[29] R_f = 0.33 (40% EtOAc in hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.33 [d, J = 6.3 Hz, 1 H, C*H*(OMe)$_2$], 4.17 (m, 1 H, 3-H), 3.99 (dd, J = 9.4 and 5.4 Hz, 1 H, 5-H), 3.94 (m, 1 H, 4-H), 3.84 (dd, J = 9.4 and 3.5 Hz, 1 H, 5-H), 3.73 (dd, J = 6.3 and 4.8 Hz, 1 H, 2-H), 3.43 (s, 3 H, MeO), 3.40 (s, 3 H, MeO), 3.24 (br., 1 H, O*H*) ppm.

(2*R*,3*R*,4*S*)-4-Azido-3-benzyloxy-2-(dimethoxymethyl)tetrahydrofuran (18b): A solution of **18a** (7.5 g, 36.91 mmol) in dry THF (400 mL) under argon was treated with NaH (60% dispersion in mineral oil; 1.26 g, 52.50 mmol), and the reaction mixture was stirred for 30 min at room temp. Tetrabutylammonium iodide (6.8 g, 18.41 mmol) and benzyl bromide (6.6 g, 38.59 mmol) were added, and the mixture was stirred for 3 h. The reaction was quenched with water, and the THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were washed with $NaHCO_3$ (satd. aq.; 3 × 20 mL), dried with anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (25% EtOAc in hexane) to give **18b** (9.45 g, 87%) as a yellow liquid. R_f = 0.55 (25% EtOAc in hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ar), 4.54 (AB, J = 11.8 Hz, 1 H, Bn), 4.48 (AB, J = 11.8 Hz, 1 H, Bn), 4.35 [d, J = 6.2 Hz, 1 H, C*H*(OMe)$_2$], 3.35 (s, 3 H, MeO), 3.95–3.84 (m, 5 H, 2-H, 3-H, 4-H, and 5-H), 3.34 (s, 3 H, MeO) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 137.2 (C), 128.4 (CH), 127.9 (CH), 127.8 (CH), 103.6 (CH), 84.4 (CHO), 84.0 (CH), 72.0 (CH_2), 70.8 (CH_2), 65.6 (CH), 55.4 (CH_3), 54.0 (CH_3) ppm. MS (CI$^+$): *m*/*z* (%) = 234 (27) [M + H – (OMe) – N_2]$^+$, 204 (27) [M + H – (OMe)$_2$ – N_2]$^+$, 128 (39), 107 (89). HRMS (CI$^+$): calcd. for $C_{12}H_{16}N_3O_2$ 234.12425; found 234.12471. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 2935 (CH_2), 2831 (CH), 2104 (N=N), 1454, 1363, 1257, 1192, 1138, 1099, 943 cm^{-1}. $[\alpha]_D^{20}$ = +14.3 (c = 0.84 in MeOH).

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)tetrahydrofuran-2-carbaldehyde: Compound **18b** (950 mg, 4.06 mol) was stirred in a mixture of TFA and water (4:1; 100 mL) for 2 h at room temp. The mixture was diluted with water (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ (satd. aq.; 3 × 25 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the product (750 mg, 95%) as an orange oil that was used without further purification. R_f = 0.33 (30% EtOAc/hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.54 (br. s, 1 H, C*H*O), 7.29 (m, 5 H, Ar), 4.58 (AB, J = 11.5 Hz, 1 H, Bn), 4.49 (AB, J = 11.5 Hz, 1 H, Bn), 4.26 (br. s, 1 H, 2-H), 4.13–3.76 (s, 4 H, 3-H, 4-H, and 5-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 201.4 (CO), 136.7 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 87.6 (CH), 85.3 (CH), 72.3 (CH_2), 71.7 (CH), 64.5 (CH) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3421, 3060, 3031, 2929, 2873, 2106, 1718, 1496, 1454, 1259, 1079 cm^{-1}. MS (CI$^+$): *m*/*z* (%) = 248 (7) [M + H]$^+$, 220 (46) [M + H – CHO]$^+$, 133 (22), 107 (100). HRMS (CI$^+$): calcd. for $C_{12}H_{14}N_3O_3$ 248.10352; found 248.10408. $[\alpha]_D^{20}$ = +9.8 (c = 0.67 in MeOH).

Methyl (2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)tetrahydrofuran-2-carboxylate (19a): (2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)tetrahydrofuran-2-carbaldehyde (1.7 g, 6.85 mmol) was dissolved in acetonitrile (20 mL) and methanol (8 mL). NBS (6.3 g, 35.40 mmol) and potassium carbonate (4.9 g, 35.45 mmol) were added, and the mixture was stirred in the dark for 24 h at room temp. Water was added, and the remaining NBS was quenched with portions of $Na_2S_2O_5$. The yellow solution was extracted with a mixture of EtOAc and hexane (1:1; 3 × 30 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (25% EtOAc in hexane) to give pure **19a** (1.77 g, 90%) as a yellow liquid. R_f = 0.50 (25% EtOAc in hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (m, 5 H, Ar), 4.60 (AB, J = 11.8 Hz, 1 H, Bn), 4.52 (AB, J = 11.8 Hz, 1 H, Bn), 4.43 (d, J = 2.4 Hz, 1 H, 2-H), 4.12 (t, J = 1.9 Hz, 1 H, 2-H), 4.06 (dd, J = 10.5 and 5.8 Hz, 1 H, 5-H), 3.99–3.92 (m, 2 H, 4-H and 5-H), 3.69 (s, 3 H, MeO) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.5 (CO), 136.8 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 86.4 (CH), 81.9 (CH), 72.3 (CH_2), 71.4 (CH), 64.9 (CH), 52.6 (MeO) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3028, 2954, 2877, 2108, 1757, 1496, 1456, 1437, 1255, 1213, 1105, 1028 cm^{-1}. MS (FAB$^+$): *m*/*z* (%) = 300 (25) [M + Na]$^+$, 278 (31) [M + H]$^+$, 154 (97), 137. HRMS (FAB$^+$): calcd. for $C_{13}H_{16}N_3O_4$ 278.11408; found 278.11329. $[\alpha]_D^{20}$ = –16.6 (c = 1.6 in MeOH).

(2*R*,3*R*,4*S*)-4-Azido-3-(benzyloxy)tetrahydrofuran-2-carboxylic Acid (19b): Compound **19a** (6.5 g, 23.37 mmol) was dissolved in TFA (72 mL) and water (18 mL), and the mixture was stirred for 2 h at room temp. The resulting brown solution was diluted with water (200 mL), and THF was added until a one-phase system was formed (approx. 600 mL). Acetone (5 mL) and CrO_3 (6.66 g,

66.60 mmol) were added, and the solution was stirred overnight at room temp., which resulted in an intensely blue-coloured solution. The THF was removed on a rotary evaporator, and the residue was extracted with CH_2Cl_2 (5× 150 mL). The solution was concentrated, and the organic solution was washed with NaOH (1 M aq.; 3× 50 mL). The aqueous phases were combined and acidified to pH = 2 with HCl (10% aq.) and washed with CH_2Cl_2 (3× 50 mL). The organic extracts were combined, dried with anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give **19b** (3.89 g, 67%) as a brown syrup. R_f = 0.15 (5% MeOH/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.70 (br. s, 1 H, COO*H*), 7.26 (m, 5 H, Ar), 4.65 (AB, J = 11.7 Hz, 1 H, Bn), 4.54 (AB, J = 11.7 Hz, 1 H, Bn), 4.47 (br. s, 1 H, 2-H), 4.20 (br. s, 1 H, 3-H), 4.08 (m, 1 H, 5-H), 4.02 (m, 2 H, 4-H and 5-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.8 (CO), 136.6 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 86.2 (CH), 82.3 (CH), 72.4 (CH_2), 71.9 (CH_2), 64.7 (CH) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3400, 3029, 2943, 2108, 1749, 1456, 1255, 1205, 1101, 1028, 931 cm^{-1}. MS (ESI-TOF$^+$): *m*/*z* (%) = 286 [M + Na]$^+$ 264 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{13}N_3O_4Na$ 286.0798; found 286.0796. $[\alpha]_D^{20}$ = –0.81 (c = 0.80 in MeOH).

(2*R*,3*R*,4*S*)-Methyl 4-Amino-3-(benzyloxy)tetrahydrofuran-2-carboxylate [H-γ-Ahf(Bn)-OMe, 20a]: A solution of methyl ester **19a** (5.08 g, 18.33 mmol) in dry THF (50 mL) was treated with triphenylphosphane (6.70 g, 25.67 mmol), and the resulting mixture was stirred for 3 h. After the addition of water (5.6 mL), the mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (4% MeOH/CH_2Cl_2) to give amine **20a** (1.88 g, 41%). R_f = 0.29 (4% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (m, 5 H, Ar), 4.67 (AB, J = 11.9 Hz, 1 H, Bn), 4.57 (AB, J = 11.9 Hz, 1 H, Bn), 4.47 (d, J = 2.0 Hz, 1 H, 2-H), 4.12 (dd, J = 9.0 and 4.7 Hz, 1 H, 5-H), 3.96 (br. s, 1 H, 3-H), 3.84 (dd, J = 9.0 and 2.5 Hz, 1 H, 5-H), 3.76 (s, 3 H), 3.49 (br. s, 1 H, 4-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.0 (CO), 137.5 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 89.8 (CH), 81.9 (CH), 75.6 (CH_2), 71.8 (CH_2), 57.3 (CH), 52.4 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3367, 2945, 2833, 1670, 1541, 1456, 1271, 1219, 1095, 1028 cm^{-1}. MS (CI$^+$): *m*/*z* (%) = 252 (100) [M + H]$^+$, 237 (79) [M + H – Me]$^+$. HRMS (CI$^+$): calcd. for $C_{13}H_{18}NO_4$ 252.1236; found 252.1235. $[\alpha]_D^{20}$ = –62.3 (c = 0.87 in MeOH).

(2*R*,3*R*,4*S*)-Methyl 3-(Benzyloxy)-4-(*tert*-butoxycarbonylamino)-tetrahydrofuran-2-carboxylate: A solution of **20a** (250 mg, 0.99 mmol) in CH_2Cl_2 (20 mL) was successively treated with DIEA (520 μL, 2.98 mmol) and Boc_2O (325 mg, 1.49 mmol), and the mixture was stirred at room temp. for 6 h. The solution was washed with HCl (5% aq.; 3× 20 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (20% EtOAc/hexane) to give the desired product (296 mg, 85%) as a white solid. R_f = 0.70 (50% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 5 H, Ar), 5.02 (d, J = 6.4 Hz, 1 H, NH), 4.66 (AB, J = 11.8 Hz, 1 H, Bn), 4.57 (AB, J = 11.8 Hz, 1 H, Bn), 4.59 (m, 1 H, 4-H), 4.36 (d, J = 1.6 Hz, 1 H, 2-H), 4.16 (br. s, 1 H, 3-H), 4.06 (dd, J = 9.5 and 4.8 Hz, 1 H, 5-H), 3.86 (d, J = 8.7 Hz, 1 H, 5-H), 3.65 (s, 3 H, MeO), 1.35 (s, 9 H, Boc) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.6 (CO), 155.0 (CO), 137.3 (C), 128.4 (CH), 127.8 (CH), 87.2 (CH), 82.0 (CH), 79.8 (C), 73.1 (CH_2), 71.7 (CH_2), 55.8 (CH), 52.4 (CH_3), 28.3 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3390, 2956, 2925, 2854, 1716, 1674, 1520, 1456, 1367, 1265, 1095 cm^{-1}. MS (ESI-TOF$^+$): *m*/*z* (%) = 374 (100) [M + Na$^+$], 352 (20) [M + H$^+$]. HRMS (ESI): calcd. for $C_{18}H_{25}NO_6Na$ 374.1586; found 374.1574. $[\alpha]_D^{20}$ = –78.3 (c = 0.80 in MeOH).

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-(*tert*-butyloxycarbonylamino)tetrahydrofuran-2-carboxylic Acid [Boc-γ-Ahf(Bn)-OH, 20b]: A solution of (2*R*,3*R*,4*S*)-methyl 3-(benzyloxy)-4-(*tert*-butoxycarbonylamino)-tetrahydrofuran-2-carboxylate (100.0 mg, 0.91 mmol) in a mixture of MeOH and water (3:1; 5 mL) was treated with LiOH·H_2O (33.5 mg, 1.40 mmol), and the resulting mixture was stirred at room temp. for 4 h. After removal of the solvent, the residue was diluted with water (25 mL), and washed with CH_2Cl_2 (3× 10 mL), and the resulting aqueous solution was acidified to pH = 3 with HCl (10% aq.). The acidic solution was extracted with CH_2Cl_2 (3× 10 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **20b** (90 mg, 94%) as a colourless oil. R_f = 0.6 (4% CH_2Cl_2/MeOH). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 353 K):[30] δ = 8.00 (br. s, 1 H, COOH), 7.31 (m, 5 H, Ar), 4.70 (s, 2 H, Bn), 4.52 (s, 1 H, 2-H), 4.23 (m, 3 H, 3-H, 5-H), 4.02 (d, J = 9.0 Hz, 1 H, 4-H), 1.47 (s, 9 H, Boc) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 173.8 (CO), 157.2 (CO), 137.2 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 87.9 (CH), 82.5 (C), 81.0 (CH), 72.4 (CH_2), 71.6 (CH_2), 56.8 (CH), 28.4 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3331, 2977, 2931, 2875, 1714, 1518, 1455, 1368, 1250, 1166, 1096 cm^{-1}. MS (FAB$^+$): *m*/*z* (%) = 337 [M + H]$^+$. HRMS (ESI): calcd. for $C_{17}H_{23}NO_6Na$ 360.1424; found 360.1418. $[\alpha]_D^{20}$ = –46.5 (c = 0.80 in MeOH).

Methyl (2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-(2-nitrophenylsulfonamido)-tetrahydrofuran-2-carboxylate (22): A solution of **19a** (1.0 g, 3.59 mmol) in CH_2Cl_2 (50 mL) containing Pd/C (96.0 mg, 0.90 mmol) was stirred at room temp. for 2 h under a hydrogen atmosphere. The mixture was filtered through a Celite pad, the residue was washed with CH_2Cl_2, and the washings were concentrated under reduced pressure. The resulting material was dissolved in CH_2Cl_2 (20 mL) and treated with DIEA (4.1 mL, 23.48 mmol) and 2-nitrobenzene-1-sulfonyl chloride (1.3 g, 5.87 mmol). The mixture was stirred at room temp. for 5 h under argon, after which it was washed with HCl (5% aq.; 2× 20 mL) and with $NaHCO_3$ (satd. aq.; 2× 20 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to give **22** (1.1 g, 73%) as a yellow oil. R_f = 0.52 (CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.95 (dd, J = 7.5 and 1.6 Hz, 1 H, Ar), 7.76 (dd, J = 7.5 and 1.6 Hz, 1 H, Ar-H), 7.64 (dt, J = 7.5 and 1.6 Hz, 1 H, Ar-H), 7.26 (m, 5 H, Ar), 6.02 (br. d, J = 5.0 Hz, 1 H, N*H*), 4.54 (AB, J = 11.9 Hz, 1 H, Bn), 4.47 (AB, J = 11.9 Hz, 1 H, Bn), 4.39 (s, 1 H, 4-H), 4.03 (m, 3 H, 5-H, 2-H), 3.82 (d, J = 8.8 Hz, 1 H, 5-H), 3.66 (s, 3 H, MeO) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.3 (CO), 147.8 (C), 136.8 (C), 134.1 (CH), 134.0 (CH), 133.1 (CH), 130.6 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 125.5 (CH), 86.7 (CH), 81.8 (CH), 72.8 (CH_2), 71.9 (CH), 59.1 (CH_3), 52.8 (CH) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3310, 3094, 2954, 2886, 1754, 1541, 1440, 1363, 1205, 1170, 1097 cm^{-1}. MS (ESI-TOF$^+$): *m*/*z* (%) = 475 (9) [M + K]$^+$, 459 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_8SNa$ 459.0833; found 459.0813. $[\alpha]_D^{20}$ = –85.1 (c = 0.8 in MeOH).

Methyl (2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[(2-nitrophenylsulfon)methylamido]tetrahydrofuran-2-carboxylate (23): A solution of **22** (650 mg, 1.42 mmol) in dry DMF (15 mL) was treated with K_2CO_3 (2.5 g, 18.09 mmol) and MeI (740 μL, 11.88 mmol), and the mixture was stirred at room temp. for 4 h under argon. $NaHCO_3$ (satd. aq.; 25 mL) was slowly added, and the residue was extracted with CH_2Cl_2 (3× 25 mL). The combined organic extracts were washed with NaCl (satd. aq.; 100 mL), dried with anhydrous Na_2SO_4, fil-

tered, and concentrated under reduced pressure. The resulting material was purified by flash chromatography (CH_2Cl_2) to give **23** (520 mg, 77%) as a yellow oil. R_f = 0.62 (2% MeOH/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.98 (dd, J = 6.9 and 2.6 Hz, 1 H, Ar), 7.59 (m, 3 H, Ar), 7.29 (m, 5 H, Ar), 4.57 (m, 1 H, 4-H), 4.53 (s, 2 H, Bn), 4.31 (d, J = 4.7 Hz, 2 H, 2-H), 4.22 (dd, J = 4.7 and 3.0 Hz, 3-H), 4.08 (dd, J = 10.4 and 6.9 Hz, 1 H, 5-H), 3.91 (dd, J = 10.4 and 4.4 Hz, 1 H, 5-H), 3.65 (s, 3 H, MeO), 2.75 (s, 3 H, MeN) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.4 (CO), 147.8 (C), 136.8 (CH), 134.0 (CH), 131.8 (CH), 131.7 (CH), 131.1 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 124.2 (CH), 84.6 (CH), 81.8 (CH), 72.0 (CH_2), 68.9 (CH), 63.5 (CH), 52.4 (CH_3), 30.5 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3092, 3029, 2953, 2897, 1749, 1544, 1460, 1363, 1198, 1190 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 473 (100) [M + Na]$^+$, 489 (2) [M + K]$^+$. HRMS (ESI): calcd. for $C_{20}H_{22}N_2NaO_8S$ 473.0989; found 473.1002. $[\alpha]_D^{20}$ = –222.3 (c = 0.80 in MeOH).

Methyl (2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-(methylamino)tetrahydrofuran-2-carboxylate: A solution of **23** (500 mg, 1.06 mmol) in dry DMF (14 mL) was treated with K_2CO_3 (760 g, 5.50 mmol) and thiophenol (450 μL, 4.41 mmol), and the mixture was stirred at room temp. for 3 h under argon. $NaHCO_3$ (satd. aq.; 10 mL) was added, and the residue was extracted with CH_2Cl_2 (4× 10 mL). The combined organic extracts were washed with NaCl (satd. aq.; 2× 25 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining DMF was removed by distillation under vacuum. The crude product was purified by flash chromatography (2–5% MeOH/CH_2Cl_2) to give the desired product (210 g, 72%) as a yellow oil. R_f = 0.47 (5% MeOH/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.24 (m, 5 H, Ar), 4.54 (AB, J = 11.9 Hz, 1 H, Bn), 4.47 (AB, J = 11.9 Hz, 1 H, Bn), 4.42 (d, J = 1.9 Hz, 1 H, 2-H), 4.02 (m, 2 H, 5-H), 3.82 (dd, J = 9.2 and 2.7 Hz, 1 H, 5-H), 3.66 (s, 3 H, MeO), 3.12 (m, 1 H, 4-H), 2.26 (s, 3 H, MeN) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.6 (CO), 137.3 (C), 128.2 (CH), 127.7 (CH), 127.6 (CH), 86.1 (CH), 81.6 (CH), 72.9 (CH_2), 71.4 (CH), 65.6 (CH), 52.1 (OMe), 34.2 (MeN) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3330, 3064, 3030, 2950, 2881, 2797, 1750, 1455, 1276, 1207, 1098 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 288 (3) [M + Na]$^+$, 266 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{20}NO_4$ 266.1387; found 266.1393. $[\alpha]_D^{20}$ = –32.6 (c = 0.85 in MeOH).

Methyl (2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[*N*-(*tert*-butoxycarbonyl)methylamino]tetrahydrofuran-2-carboxylate (24a): A solution of (2*R*,3*R*,4*S*)-methyl 3-(benzyloxy)-4-(methylamino)tetrahydrofuran-2-carboxylate (20 mg, 0.75 mol) in CH_2Cl_2 (15 mL) was successively treated with DIEA (520 μL, 2.98 mmol) and Boc_2O (410 mg, 1.88 mmol), and the mixture was stirred at room temp. for 7 h. The solution was washed with HCl (5% aq.; 3× 15 mL), and the organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (2% MeOH/CH_2Cl_2) to give the desired product (250 mg, 90%) as a yellow oil R_f = 0.61 (5% MeOH/CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (m, 5 H, Ar), 4.67 (AB, J = 12.1 Hz, 1 H, Bn), 4.59 (AB, J = 11.9 Hz, 1 H, Bn), 4.60 (m, 1 H, 4-H), 4.32 (d, J = 4.4 Hz, 1 H, 2-H), 4.11 (br. s, 1 H, 3-H), 4.01 (dd, J = 9.9 and 7.1 Hz, 1 H, 5-H), 3.92 (dd, J = 9.9 and 5.2 Hz, 1 H, 5-H), 3.68 (s, 3 H, MeO), 2.69 (s, 3 H, MeN), 1.41 (s, 9 H, Boc) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.8 (CO), 155.0 (CO), 137.2 (C), 128.2 (CH), 127.7 (CH), 85.0 (CH), 82.0 (CH), 80.0 (C), 71.5 (CH_2), 69.0 (CH_2), 61.9 (CH), 52.1 (CH_3), 30.4 (CH_3), 28.3 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 2977, 2932, 2876, 1749, 1455, 1366, 1151, 1112 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 404.1 (1) [M + K]$^+$, 388 (38) [M + Na]$^+$, 365 (3) [M + H]$^+$, 332 (100). HRMS (ESI): calcd. for $C_{19}H_{27}NO_6Na$ 388.1731; found 388.1733. $[\alpha]_D^{20}$ = –63.8 (c = 1.1 in MeOH).

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[*N*-(*tert*-butoxycarbonyl)methylamino]tetrahydrofuran-2-carboxylic Acid [Boc-^{Me}*N*-γ-Ahf(Bn)-OH, 24b]: A solution of (2*R*,3*R*,4*S*)-methyl 3-(benzyloxy)-4-(methylamino)tetrahydrofuran-2-carboxylate (200 mg, 0.55 mmol) in a mixture of MeOH and water (3:1; 12 mL) was treated with LiOH (65.6 mg, 2.74 mmol). The solution was stirred at room temp. for 2 h, and then the solvent was removed under reduced pressure. The resulting residue was diluted with water (25 mL) and washed with CH_2Cl_2 (1× 10 mL), and the resulting aqueous solution was acidified to pH = 3 with HCl (5% aq.). The acidic solution was extracted with CH_2Cl_2 (3× 10 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **24b** (190 mg, 98%) as a pale yellow oil. R_f = 0.4 (5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (br., 1 H, COOH), 7.21 (m, 5 H, Ar), 4.64 (AB, J = 12.1 Hz, 1 H, Bn), 4.59 (AB, J = 11.9 Hz, 1 H, Bn), 4.61 (m, 1 H, 4-H), 4.37 (d, J = 4.3 Hz, 1 H, 2-H), 4.18 (t, J = 3.7 Hz, 1 H, 3-H), 4.03 (dd, J = 9.9 and 7.1 Hz, 1 H, 5-H), 3.94 (dd, J = 9.9 and 5.3 Hz, 1 H, 5-H), 2.67 (s, 3 H, MeN), 1.38 (s, 9 H, Boc) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.3 (CO), 155.5 (CO), 137.2 (C), 128.2 (CH), 127.9 (CH), 127.8 (CH), 85.2 (CH), 82.0 (CH), 80.9 (C), 71.9 (CH_2), 69.2 (CH_2), 62.5 (CH), 30.9 (CH_3), 28.4 (CH_3) ppm. FTIR (293 K, $CHCl_3$): $\tilde{\nu}$ = 3505, 3011, 2978, 2932, 2875, 1746, 1686, 1455, 1368, 1163, 1109 cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 390.1 (1) [M + K]$^+$, 374.1 (100) [M + Na]$^+$, 352.0 (3) [M + H]$^+$, 318.1 (36) [M + Na – tBu]$^+$, 296.1 (8) [M + H – tBu]$^+$, 274.1 (19) [M + Na – Boc]$^+$, 252.1 (70) [M + H – Boc]$^+$. HRMS (ESI): calcd. for $C_{18}H_{25}NO_6Na$ 374.1574; found 374.1565. $[\alpha]_D^{20}$ = –42.0 (c = 0.80 in MeOH).

CCDC-909272 (for **2b**), -909273 (for **2c**), -909274 (for **10**), -909275 (for **12a**), -909276 (for **12b**), and -909277 (for **13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of new compounds.

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