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Cyclobutane Amino Acid Analogues of Furanomycin Obtained by a Formal [2 + 2] Cycloaddition Strategy Promoted by Methylaluminoxane

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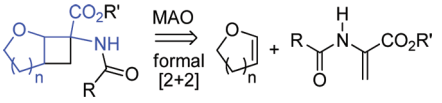

The synthesis and conformational analysis of a new type of conformationally restricted α-amino acid analogue of the amino acid antibiotic furanomycin is presented. The restriction involves the cis-fused cyclobutane and tetrahydrofuran units, generating the unusual 2-oxabicyclo[3.2.0]heptane core, which is found in a great number of biologically active natural products. The synthetic strategy is based on a formal [2 + 2] cycloaddition between 2-(acylamino)acrylates as acceptor alkenes and 2,3-dihydrofuran as a donor alkene, promoted by bulky aluminum-derived Lewis acids, particularly by methylaluminoxane (MAO). Additionally, following the same strategy, the synthesis of furanomycin analogues incorporating the 2-oxabicyclo[4.2.0]octane is reported.

Introduction

Since the isolation of the amino acid L-(+)-furanomycin in 1967 by Katagiri et al.,[1] and further discovery of its biological activity as an isoleucine antagonist,[2] several syntheses of this antibiotic and its stereoisomers have been developed[3] (Figure 1). Its absolute configuration was assigned as α*S*,2*R*,5*S* on the basis of the X-ray structure analysis of the corresponding *N*-acetyl derivative.[3j] The antibiotic activity of this *Streptomyces* metabolite results from its incorporation into bacterial proteins instead of isoleucine in the protein translation process. Therefore, this type of translatable amino acid analogues are of great interest for the preparation of peptides and proteins containing unusual amino acids.[4] The mechanism of action is highly interesting from a pharmaceutical point of view, hence several synthetic approaches toward different furanomycin analogues (norfuranomycin, dihydrofuranomycin, dihydronorfuranomycin, etc.) have been developed, and the antibacterial activity of some of them has been investigated (Figure 1).[3,5]

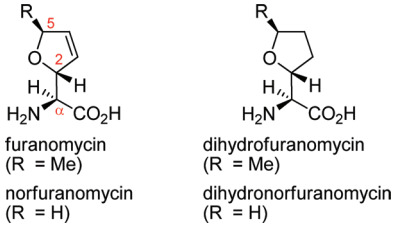

FIGURE 1. L-(+)-Furanomycin and some analogues.

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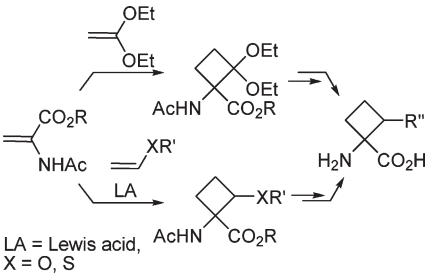
It is important to notice that the removal of the methyl group (norfuranomycin) did not have a significant effect on the activity, suggesting that this group is not essential for the biological activity.[5b] Given the importance of this kind of non-natural amino acids, several furanylglycines, dihydrofuranylglycines, and tetrahydrofuranylglycines have been synthesized as furanomycin analogues.[6] In this field, various carbaanalogues such as cyclopentylglycine, cyclopentenylglycine, cyclohexenylglycine, or L-carbafuranomycin have also been prepared, but their biological activities have not been reported.[5b,7] Nevertheless, concerning cyclobutenylglycine, it has been substituted effectively for valine and isoleucine in the translation process of green fluorescent protein in vitro.[8]

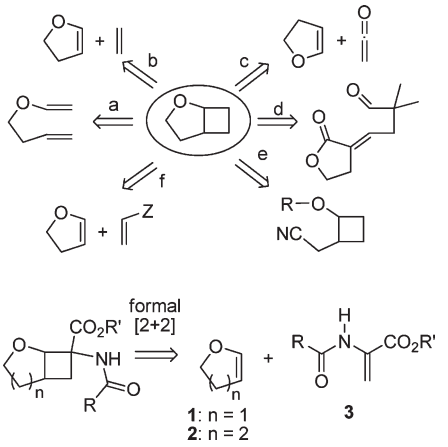
On the other hand, in the field of α,α-disubstituted α-amino acids,[9] although cycloalkane α-amino acid derivatives are easily accessible by several preparative methods, the amino acids of the cyclobutane series have received relatively little attention.[10] In particular, after some derivatives were found to be potent neurotransmitters,[11] synthetic efforts were extended to obtain a whole range of cyclobutane amino acids. Nevertheless, methods for the synthesis of 2-substituted cyclobutane amino acids are not very common in the literature.[12] In this context, we have recently reported the synthesis of some cyclobutane amino acid derivatives,[13] using, as the key step, a formal [2 + 2] cycloaddition of 2-acetamidoacrylates as acceptor alkenes and a variety of donor alkenes (Scheme 1). A mechanism for these reactions has been recently proposed[14] and involves a Michael−Dieckmann process for 1,1-dialkoxyethenes or a stereoselective Michael−aldol process for monosubstituted donor alkenes (vinyl ethers or thioethers), which needs activation by sterically hindered Lewis acids such as aluminum aryloxides or methylaluminoxane (MAO).[13d,15]

Therefore, cyclobutane α-amino acids are important targets in organic synthesis, and furanomycin is a significant amino acid antibiotic that has prompted the synthesis of

SCHEME 1. Formal [2 + 2] Cycloadditions of 2-Acetamidoacrylates



SCHEME 2. Retrosyntheses of 2-Oxabicyclo[3.2.0]heptane Core



numerous analogues. Bearing these facts in mind, we present here two new types of constrained amino acids, which are furanomycin, or more specifically, dihydronorfuranomycin analogues. The restriction includes specific covalent constraints of the side chain in order to fix the conformations in χ^1 space,[9e] which are valuable to provide insight into the topographical requirements for ligand receptor interactions. These new α-amino acid derivatives involve a cyclobutane unit cis-linked either to the tetrahydrofuran or tetrahydropyran motifs, leading to the 2-oxabicyclo[3.2.0]heptane and 2-oxabicyclo[4.2.0]octane cores, respectively (Scheme 2). In this sense, it is important to highlight that in the background of heterocyclic compounds incorporating the cis-fused cyclobutane unit, the 2-oxabicyclo[*n*.2.0] skeleton is an unusual substructure found in some interesting natural products. Particularly attractive is the 2-oxabicyclo[3.2.0]heptane skeleton, which appears in different cyclobutane analogues of β-lactam antibiotics.[16] Moreover, the structurally unique caryophyllene-type sesquiterpene, pestalotiopsin A,[17,18] is a natural product with immunosuppressive activity that contains this substructure. It is believed that the 2-oxabicyclo-[3.2.0]heptane core is the main structural feature responsible for its activity. This somehow atypical ring skeleton for a

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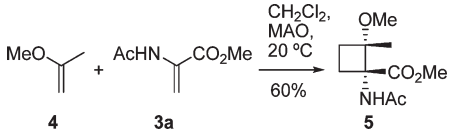
natural product is also present in haplodimerine[19] and elecanacin.[20,21] Additionally, other examples of organic compounds incorporating the 2-oxabicyclo[4.2.0]octane[22] and 2-oxabicyclo[3.2.0]heptane[23] structures obtained by intermolecular [2 + 2] cycloaddition have been reported.

To the best of our knowledge, only a few synthetic methodologies have been described for the synthesis of the 2-oxabicyclo[3.2.0]heptane core; either intramolecular[21,24] or intermolecular[23,25] [2 + 2] photocycloaddition (a and b in Scheme 2), thermal [$_s2_\pi$ + $_a2_\pi$] cycloaddition (c in Scheme 2),[16] and cyclization to form the tetrahydrofuran ring (d and e in Scheme 2).[18] This core has also been obtained recently by a catalytic formal [2 + 2] cycloaddition (f in Scheme 2).[23d] Given the reactivity of 2-acylaminoacrylates in formal [2 + 2] cycloadditions,[8,13d] simple retrosynthetic considerations suggest that amino acid derivatives should be accessible through a new methodology involving a stereoselective Michael−aldol process between 2,3-dihydrofuran (**1**) or 3,4-dihydro-2*H*-pyran (**2**) and derivatives **3** (Scheme 2).

Results and Discussion

Synthesis. First, in order to explore the behavior of 2-acylaminoacrylates with donor disubstituted alkenes bearing only one activating group, the reaction between 2-methoxypropene (**4**) as a donor alkene and methyl 2-acetamidoacrylate (**3a**) as an acceptor alkene was tested. Under the best conditions previously developed in our group (Michael aldol process),[13] the reaction did not progress (not even after heating) in the absence of Lewis acids. Second, activation of the reaction by addition of bulky aluminum-derived Lewis acids such as methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) or methylaluminum bis(2,4,6-trimethylphenoxide) (MAM) was attempted. However, formation of cyclobutane products was not observed at any of the temperatures assayed, and only starting materials or polymerization products were obtained instead. Finally, the reaction was carried out in methylene chloride at 20 °C in the presence of methylaluminoxane (MAO) (2 mL of MAO, 0.35 mmol of **3a** and 3.5 mmol of **4**) and the cyclobutane **5** was exclusively obtained in a 60% yield. The configuration of stereocenters in this compound was assessed by means of ge-2D COSY, phase sensitive ge-2D HSQC, ge-2D HMBC and phase-sensitive ge-2D NOESY. Figure 2 shows the most important NOE cross-peaks (Scheme 3 and Figure 2).

SCHEME 3. Formal [2 + 2] Reaction between Olefins 3a and 4



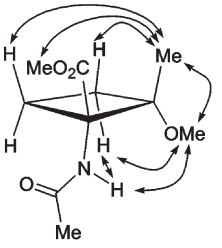


FIGURE 2. NOE cross-peaks of compound **5**.

In view of these results, MAO was the bulky aluminum-derived Lewis acid selected to achieve the principal goal of this work; the synthesis of cyclobutane amino acid derivatives incorporating the 2-oxabicyclo[3.2.0]heptane core by means of the reaction of methyl 2-acetamidoacrylate **3a** with 2,3-dihydrofuran **1**. Thus, using the same conditions described above, a mixture of compounds **6a** and **7a** in a 42% yield and in a 75:25 ratio in favor of **7a** was obtained (Table 1).

It is believed that MAO and MABR induce opposed selectivity in this kind of reactions.[15] Bearing this fact in mind, and despite the bad results obtained in the reaction between compounds **3a** and **4** in the presence of MABR, the formal [2 + 2] cycloaddition of **1** and **3a** with MABR as a Lewis acid was assayed, aiming at the change in the selectivity of the products **6a** and **7a** (Table 1).

In order to increase the yield of the reaction, the effect of the amide group in the acceptor alkene was also investigated. Thus, the reaction of methyl 2-trifluoroacetamidoacrylate (**3b**) with the donor alkene **1** was tested. The results obtained proved that this electron-withdrawing amide not only favors the reactivity, since it is possible to carry out the reaction at lower temperature (−20 °C), but also leads to the enhancement of the selectivity (19:81). Thus, the adduct **7b**, in which the trifluoroacetamide group and the hydrogen in the position 1 of the cycloadduct are located in the trans position, was the major product when MAO was used as a Lewis acid (entry 3, Table 1).

As can be deduced from the results obtained in the formal [2 + 2] cycloaddition between the acceptor alkenes **3a**,**b** and 2,3-dihydrofuran **1**, two main factors seem to be responsible for the stereochemical outcome of the reaction; first, as might be expected,[15] the nature of the Lewis acid used, and second, the electronic properties of the amide group in the acceptor alkenes **3**. In this sense, the cycloadduct with (1*S*,5*R*,7*S*) or (1*R*,5*S*,7*R*) configurations is the major product when 2-acetamidoacrylate **3a** or 2-trifluoroacetamidoacrylate **3b**

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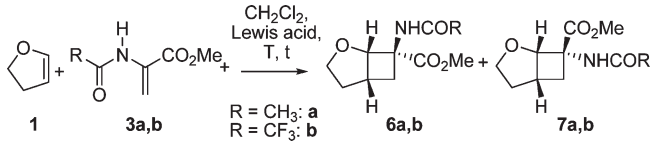
TABLE 1. Formal [2 + 2] Cycloaddition of Acceptor Alkenes 3a,b with Donor Alkene 1



entry	donor olefin **1** (equiv)	acceptor olefin (equiv)	Lewis acid (equiv)	temp (°C)	time (h)	ratio (**6a**,**b**/**7a**,**b**)[a]	yield[a] (%)
1	10.0	**3a** (1.0)	MABR (2.0)	20	5	**6a**/**7a** (50:50)	30
2	10.0	**3a** (1.0)	MAO (4.0)[b]	20	17	**6a**/**7a** (25:75)	42
3	5.0	**3b** (1.0)	MAO (4.0)[b]	−20	17	**6b**/**7b** (19:81)	75

[a]Ratio measured by ^{1}H NMR of the reaction crude and yield calculated from the products isolated after column chromatography. [b]4 mL of MAO 10% weight in toluene for 0.7 mmol of acceptor alkene.

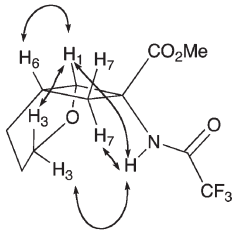


FIGURE 3. NOE cross-peaks of compound **9b**.

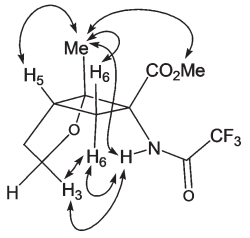


FIGURE 4. NOE cross-peaks of compound **11b**.

was used as the acceptor alkene in the presence of MAO. In addition, an enhancement of the selectivity can be achived by using 2-trifluoroacetamidoacrylate **3b** instead of its analogue **3a**.

The configuration of stereocenters of the different adducts was assigned by means of X-ray analysis. Single crystals of the cycloadducts **6a** and **7b** were grown by slow evaporation of concentrate solutions in hexane−ethyl acetate mixtures (Figure 5).

In order to extend the scope of the reactivity of the acceptor alkenes **3a**,**b** with other cyclic vinyl ethers, the cycloaddition with 3,4-dihydro-2*H*-pyran (**2**) in the presence of MABR and MAO as bulky aluminun Lewis acids was examined. This methodology would allow an easy generation of α-amino acid derivatives with the 2-oxabicyclo-[4.2.0]octane core. Initially, the reaction of the acrylate **3a** with the donor alkene **2** promoted by MABR was tested. However, only a 6% yield of a mixture of adducts **8a** and **9a** was obtained (Scheme 4).

Substitution of MABR by MAO did not improve the yield of the reaction; nonetheless, as previously described, we attempted to increase the yield by carrying out the reaction between the donor alkene **2** (10.0 equiv) and the acceptor alkene **3b** (1.0 equiv) in the presence of MAO as the Lewis acid (3 mL of MAO 10% weight in toluene for 0.5 mmol of acceptor alkene) at −20 °C for 17 h. As expected, the yield

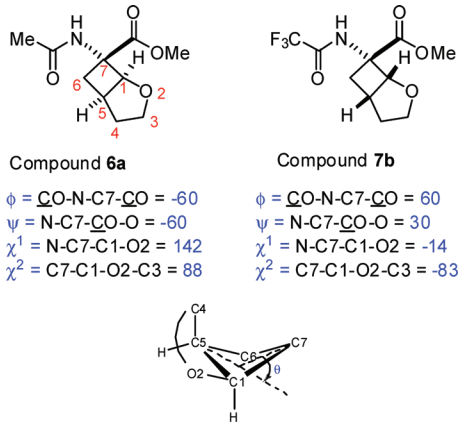
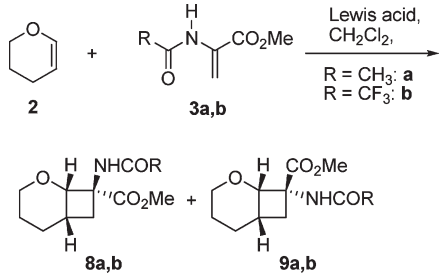


FIGURE 5. Definition of the dihedral angles of compounds **6a** (left) and **7b** (right).

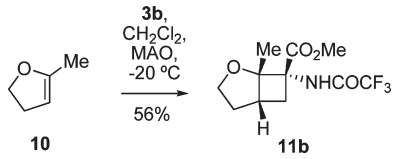
SCHEME 4. Formal [2 + 2] Cycloaddition of Alkenes 3a,b with Alkene 2



reached 42%, and in terms of selectivity, the major isomer obtained was the cycloadduct **9b**. The stereoisomer **8b** was not detected by ^{1}H NMR (Scheme 4), and the configuration of stereocenters of the cycloadduct **9b** was established by means of 2D NOESY, ge-2D COSY, phase-sensitive ge-2D HSQC, and phase-sensitive ge-2D NOESY experiments. Figure 3 shows the most important NOE cross-peaks. Therefore, it can be concluded that when MAO is used as a bulky aluminum Lewis acid in the reaction between the acrylate **3b** and cyclic vinyl ethers, the major products are those with the [*n*.2.0] core in which the acylamine group and the hydrogens in the bridge positions are located in the trans position.

Taking into account the reactivity displayed by the 2-acylaminoacrylates **3a**,**b** with the cyclic vinyl ethers **1** and **2**, we decided to explore their behavior in the reaction with a trisubstituted alkene bearing only one donor substituent: 5-methyl-2,3-dihydrofuran (**10**). The yield obtained under

SCHEME 5. Formal [2 + 2] Cycloaddition of Alkene 3b with Alkene 10



the best conditions found so far (MAO as a Lewis acid and acrylate **3b** as acceptor alkene) was quite high (56%), and regarding the selectivity, the cycloadduct **11b** was exclusively obtained. It is worth mentioning that, as expected, the trifluoroacetamide motif and the methyl group of the bridge are located in the trans position (Scheme 5). Again, the configuration of stereocenters of the stereoisomer **11b** was established by means of NMR experiments similar to that above-mentioned. Figure 4 shows the most important NOE cross-peaks.

Conformational Analysis. Conformational analysis of biologically active compounds is very important since it is known that the biological activity of a molecule is related to a limited conformational space, and it can have direct applications in the comprehension of the structure−activity relationship (SAR) and in the design of new drug candidates.[26] Conformational space can be accessed by several experimental techniques like X-ray crystallography (giving information of the compounds in solid state) or NMR (giving information of the compounds in solution), among others,[27] and by theoretical methods. In this context, molecular dynamics (MD) simulation[28] is a very useful technique in order to explore the structure and the dynamic behavior of molecules of biochemical interest.

Taking into account this fact, along with the importance of furanomycin derivatives in medicinal chemistry, we decided to explore the conformational space available to dihydronorfuranomycin analogues **6a** and **7b** presented here. Initially, we studied the most important dihedral angles (ϕ, ψ, χ^1, and χ^2 represented in Figure 5) using the information arising from the solid state of both compounds. The conformations of the two compounds are very different in the solid state, showing significant variations for all cited dihedral angles. The cyclobutane rings of compounds **6a** and **7b** adopt only one conformation, with values of 11.2° and 8.4° for the pucker angle θ, respectively (Figure 5). These angles are remarkably minor than those obtained for other similar cyclobutane derivatives previously studied in the solid state.[29] Therefore, it can be concluded that the cyclobutane ring adopts almost a planar conformation due to the restriction imposed by the cis-fused tetrahydrofuranyl cycle.

The next step was to investigate the conformational behavior of compounds **6a** and **7b** in solution using MD (molecular dynamics) simulations. Initially, unrestrained MD simulations were run in explicit $CHCl_3$. However, the

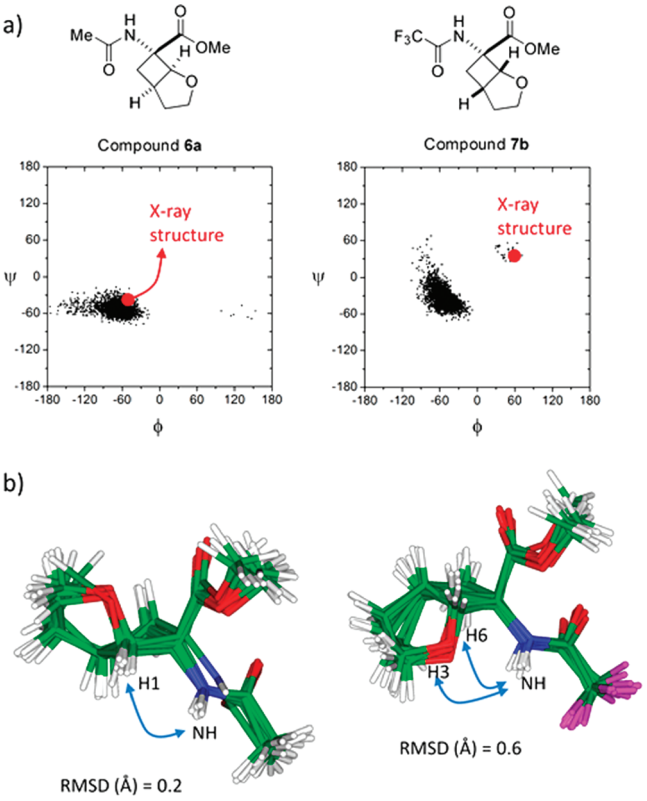


FIGURE 6. (a) ϕ/ψ distributions obtained from the MD-tar simulations for compounds **6a** and **7b**. (b) Calculated ensembles for compounds **6a** and **7b** showing the RMSDs for heavy atom superimposition and the most relevant NOE contacts.

major conformations obtained from these simulations were not totally in agreement with the experimental distances inferred from the NOESY experiments. Therefore, MD simulations with time-averaged restraints (MD-tar)[30] were run using a protocol[31] similar to that recently applied by our group to different model glycopeptides.

The proton−proton distances, relevant for the conformational analysis, were determined from NOESY experiments. These data were then used as restraints in MD-tar simulations with the aim of obtaining a distribution of conformers in solution able to quantitatively reproduce the NMR data. The MD-tar simulations were run with AMBER 6 (see the Experimental Section) and the General Amber Force Field (GAFF)[32] at 300 K with a total trajectory time of 80 ns and using a dielectric constant of 4 to simulate the $CHCl_3$ environment.

Figure 6a shows the ϕ/ψ distributions obtained from these simulations. As can be seen, both molecules are rather rigid in solution, showing only one major population (with ϕ and ψ around −60°). Although for compound **6a**, the major conformer presented in solution was similar to that observed in the crystallographic structure, this was not the case for

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derivative **7b**, which exhibited a completely different conformation in $CHCl_3$. In addition, Figure 6b shows the calculated ensembles for both compounds obtained from the MD simulations, showing the rmsd for heavy atom. These conformations are in good agreement with the experimental NOE cross-peaks observed in $CHCl_3$ (experimental distances H6−NH and H3−NH equal are to 3.3 and 2.8 Å, respectively, for compound **7b** and distance H1−NH equal to 2.2 for compound **6a**). Finally, concerning the χ^1 and χ^2 dihedral angles, the values were similar to those observed in the crystal structure as a consequence of the rigidity imposed by the cyclic systems.

Conclusion

We have developed a synthetic methodology for the preparation of cyclobutane α-amino acid derivative analogues of the antibiotic amino acid furanomycin. These new conformationally restricted amino acids incorporate the 2-oxabicyclo[*n*.2.0] substructures, important structural motifs found in bioactive natural products, whose synthesis is not trivial. The key step of the synthesis involves as the two main features the use of MAO as a bulky aluminum-derived Lewis acid to prompt the formal [2 + 2] cycloaddition between acylaminoacrylates and cyclic vinyl ethers and the use of the trifluoroacetamide group as a substituent in the acceptor alkene, which not only improves the yield of the reaction but also increases the selectivity.

Moreover, although X-ray crystallography has provided exact conformational parameters of cyclobutane dihydronorfuranomycin analogues **6a** and **7b**, because of limitations in the technique, the most interesting dynamic properties in solution remained unexplored. Therefore, we carried out a conformational analysis using the MD-tar protocol showing that both compounds are quite rigid. Nevertheless, it is important to notice that, in this particular case, while the preferred conformation of compound **6a** in solution seems to be the same as that reported in the solid state; in the parent compound **7b**, a particular conformation is also clearly preferred in solution, although different from the one showed by the crystallized form.

Experimental Section

General Procedures. Solvents were purified according to standard procedures. Column chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal reference (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants and ge-COSY and ge-HSQC experiments on a 400 MHz spectrometer. This spectrometer was also used for the 2D NOESY experiments described in the text. These experiments were processed with Mestre Nova software (Mestrelab Research, Spain). Melting points were determined on a melting point apparatus and are uncorrected. Microanalyses were carried out on an analyzer and are in good agreement with the calculated values.

(1*R*,2*S*)- and (1*S*,2*R*)-1-Acetamido-2-methoxy-2-methylcyclobutan-1-carboxylic acid methyl ester (5). MAO (10 wt. % in toluene) (2 mL) was slowly added at room temperature under an argon atmosphere to a solution containing **3a** (50 mg, 0.35 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 15 min and 2-methoxy-1-propene (**4**) (252 mg, 3.5 mmol) was then added. After 17 h stirring at the same temperature, H_2O (10 mL) was carefully added. The aqueous phase was washed with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue that was purified by silica gel column chromatography eluting with hexane/EtOAc (3:7) to afford **5** as a white solid (44 mg, 60%). Mp: 106−108 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.79−1.90 (m, 2H, H_3, H_4), 2.01 (s, 3H, $COCH_3$), 2.08 (q, 1H, J = 10.5, H_3), 2.48−2.57 (m, 1H, H_4), 3.25 (s, 3H, OCH_3), 3.70 (s, 3H, CO_2CH_3), 6.89 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 18.0 (CH_3), 22.5 (C_4), 22.9 ($COCH_3$), 30.1 (C_3), 50.8 (OCH_3), 52.1 (CO_2CH_3), 64.5 (C_1), 77.9 (C_2), 169.7, 171.0. ESI+ (m/z) = 216.4. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.82; H, 7.98; N, 6.60.

(1*S*,5*R*,7*S*)- and (1*R*,5*S*,7*R*)-7-Acetamido-2-oxabicyclo[3.2.0]-heptan-7-carboxylic Acid Methyl Ester (6a) and (1*S*,5*R*,7*R*)- and (1*R*,5*S*,7*S*)-7-Acetamido-2-oxabicyclo[3.2.0]heptan-7-carboxylic Acid Methyl Ester (7a). Method A: $AlMe_3$ (2 M in hexane) (1.05 mL, 2.1 mmol) was slowly added at room temperature under an argon atmosphere to a solution containing 2,6-di-*tert*-butyl-4-bromophenol (1.2 g, 4.2 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1 h, and **3a** (150 mg, 1.05 mmol) and 2,3-dihydrofuran (**1**) (0.8 mL, 10.5 mmol) were consecutively added. After the mixture was stirred for 5 h at the same temperature, an excess of $Na_2CO_3 \cdot 10H_2O$ was added. The solid was filtered off, and the liquid phase was concentrated in vacuum to give a residue that was purified by silica gel column chromatography eluting with MeOH/EtOAc (5:95) to afford a mixture of **6a** and **7a** in a 1:1 ratio (67 mg, 30%). Method B: MAO (10 wt % in toluene) (2 mL) was slowly added at room temperature under an argon atmosphere to a solution containing **3a** (50 mg, 0.35 mmol) in 5 mL of dry CH_2Cl_2. 2,3-Dihydrofuran (**1**) (0.26 mL, 3.5 mmol) was then added, the reaction was stirred at the same temperature for 17 h, and H_2O (10 mL) was carefully added. The aqueous phase was washed with EtOAc (3 × 20 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a mixture of the two products in a 25:75 ratio, determined by ^{1}H NMR. This mixture was purified and separated by silica gel column chromatography eluting with hexane/EtOAc (2:8), affording **6a** (8 mg, 11%) and **7a** (23 mg, 31%), both as white solids. Compound **6a**: mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 1.82−1.88 (m, 2H, $2H_4$), 2.01 (s, 3H, CH_3CO), 2.28−2.34 (m, 1H, H_6), 2.64 (dd, 1H, J = 6.8, J = 13.7, H_6), 3.15−3.22 (m, 1H, H_5), 3.74 (s, 3H, CH_3O), 4.07−4.19 (m, 2H, $2H_3$), 4.35−4.39 (m, 1H, H_1), 6.13 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.0 (CH_3CO), 30.8 (C_4), 31.0 (C_6), 35.5 (C_5), 52.4 (CH_3O), 61.9 (C_7), 70.8 (C_3), 61.3 (C_1), 170.1 (COO), 170.3 (CON); ESI+ (m/z) = 214.3. Anal. Calcd for ($C_{10}H_{15}NO_4$): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.09; H, 7.15; N, 6.48. Compound **7a**: mp 123−125 °C. ^{1}H NMR ($CDCl_3$) δ 1.59−1.67 (m, 1H, H_6), 1.72−1.86 (m, 2H, $2H_4$), 2.00 (s, 3H, CH_3CO), 3.09−3.24 (m, 2H, H_5, H_6), 3.74 (s, 3H, CH_3O), 3.92−3.99 (m, 1H, H_3), 4.22−4.30 (m, 1H, H_3), 4.44−4.50 (m, 1H, H_1), 6.35 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.8 (CH_3CO), 31.1 (C_4), 34.2 (C_6), 35.8 (C_5), 52.7 (CH_3O), 58.4 (C_7), 69.9 (C_3), 80.8 (C_1), 169.3 (COO), 172.3 (CON); ESI+ (m/z) = 214.3. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.21; H, 7.00; N, 6.68.

Crystal data of compound 6a: molecular formula $C_{10}H_{15}NO_4$ M_w = 213.23, colorless prism, T = 100 K, monoclinic, space group $P2_1/c$, Z = 4, a = 11.8280(5) Å, b = 8.9940(3) Å, c = 10.1781(3) Å, $\alpha = \gamma = 90.00°$, β = 96.828(10)°, V = 1041.30(6) Å^3, d_{calc} = 1.360 g cm^{-3}, $F(000)$ = 456, λ = 0.71073 Å (Mo, Kα),

μ = 0.105 mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.79−27.88°, 8523 collected reflections, 2469 unique, full-matrix least-squares (SHELXL97),[33] R_1 = 0.0526, wR_2 = 0.1318, (R_1 = 0.0896, wR_2 = 0.1508 all data), goodness of fit = 1.056, residual electron density between 0.242 and −0.248 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository no. CCDC 242254.

(1*S*,5*R*,7*S*)- and (1*R*,5*S*,7*R*)-7-(2′,2′,2′-Trifluoroacetamido)-2-oxabicyclo[3.2.0]heptane-7-carboxylic Acid Methyl Ester (6b) and (1*S*,5*R*,7*R*)- and (1*R*,5*S*,7*S*)-7-(2′,2′,2′-Trifluoroacetamido)-2-oxabicyclo[3.2.0]heptane-7-carboxylic Acid Methyl Ester (7b). MAO (10 wt. % in toluene) (3 mL) was slowly added at −20 °C under an argon atmosphere to a solution containing **3b** (100 mg, 0.50 mmol) in 10 mL of dry CH_2Cl_2. 2,3-Dihydrofuran (**1**) (0.38 mL, 2.6 mmol) was then added, the reaction mixture was stirred at the same temperature for 17 h, and H_2O (20 mL) was carefully added. The aqueous phase was washed with EtOAc (3 × 20 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue that was purified by silica gel column chromatography eluting with hexane/EtOAc (8:2). Thus, compounds **6b** and **7b** (100 mg, 75% yield) were obtained in a 19:81 ratio, determined by ^{1}H NMR. This mixture of compounds could not be separated by column chromatography; fortunately, compound **7b** was purified by recrystallization from a concentrate solution in hexane/EtOAc. Compound **7b**: mp 118−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.67−1.91 (m, 3H, H_6, $2H_4$), 3.18−3.22 (m, 2H, H_5, H_6), 3.78 (s, 3H, OCH_3), 3.93 (ddd, 1H, J = 5.7, J = 9.1, J = 10.8, H_3), 4.29−4.33 (m, 1H, H_3), 4.53−4.55 (m, 1H, H_1), 7.17 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 31.0 (C_6), 33.6 (C_4), 36.1 (C_5), 53.0 (CH_3), 58.0 (C_7), 70.1 (C_3), 80.3 (C_1), 115.5 (q, J_{C-F} = 286.0, CF_3), 156.2 (q, J_{C-F} = 37.0, *C*OCF$_3$), 170.5 (CO); ^{19}F NMR ($CDCl_3$) δ −76.1; ESI+ (m/z) = 268.5. Anal. Calcd for $C_{10}H_{12}F_3NO_4$: C, 44.95; H, 4.53; N, 5.24. Found: C, 45.07; H, 4.42; N, 5.12.

Crystal data of compound 7b: molecular formula $C_{10}H_{12}F_3NO_4$, M_w = 267.20, colorless prism, T = 100 K, orthorhombic, space group *Pbca*, Z = 8, a = 15.1509(6) Å, b = 8.9088(4) Å, c = 17.2247(8) Å, $\alpha = \beta = \gamma$ = 90°, V = 2324.9 (2) Å^3, d_{calc} = 1.527 g cm^{-3}, F(000) = 336, λ = 0.71073 Å (Mo Kα), μ = 0.147 mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.03−26.06°, 14308 collected reflections, 2268 unique, full-matrix least-squares (SHELXL97),[33] R_1 = 0.0619, wR_2 = 0.1561, (R_1 = 0.0871, wR_2 = 0.1764 all data), goodness of fit = 1.117, residual electron density between 0.299 and −0.259 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository no. CCDC 721605.

(1*S*,6*S*,8*R*)- and (1*R*,6*R*,8*S*)-8-Acetamido-2-oxabicyclo-[4.2.0]octane-8-carboxylic Acid Methyl Ester (9a). $AlMe_3$ (2 M in hexane) (0.7 mL, 1.4 mmol) was slowly added at room temperature under an argon atmosphere to a solution containing 2,6-di-*tert*-butyl-4-bromophenol (800 mg, 2.8 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1 h, and **3a** (100 mg, 0.7 mmol) and 3,4-dihydro-2*H*-pyran (**2**) (0.7 mL, 7 mmol) were consecutively added. The reaction was stirred for 15 h at the same temperature, and an excess of $Na_2CO_3 \cdot 10H_2O$ was added. The solid was filtered off, and the liquid phase was concentrated in vacuum to give a residue containing the isomers **8a** and **9a** in a 15:85 ratio determined by ^{1}H NMR. This residue was purified by silica gel column chromatography eluting with hexane/EtOAC (3:7) to afford only **9a** (10 mg, 6%) as a white solid: mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 1.42−1.50 (m, 1H), 1.58−1.67 (m, 2H), 1.75−1.86 (m, 1H), 2.00 (s, 3H, CH_3CO), 2.13 (t, 1H, J = 11.0, H_7), 2.49−2.58 (m, 1H, H_6), 2.88−2.92 (m, 1H, H_7), 3.32 (td, 1H, J = 2.0, J = 11.0, H_3), 3.74 (s, 3H, CH_3O), 3.90−3.93 (m, 1H, H_3), 4.25 (t, 1H, J = 4.4, H_1), 6.56 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.0, 22.4 (C_4, C_5), 22.7 (*C*H$_3$CO), 27.4 (C_6), 34.2 (C_7), 52.6 (CH_3O), 58.1 (C_8), 64.6 (C_3), 74.7 (C_1), 169.3 (COO), 172.1 (CON); ESI+ (m/z) = 228.4. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.07; H, 7.48; N, 6.20.

(1*S*,6*S*,8*R*)- and (1*R*,6*R*,8*S*)-8-(2′,2′,2′-Trifluoroacetamido)-2-oxabicyclo[4.2.0]octane-8-carboxylic Acid Methyl Ester (9b). MAO (10 wt % in toluene) (3 mL) was slowly added and at −20 °C under an argon atmosphere to a solution containing **3b** (100 mg, 0.50 mmol) in 10 mL of dry CH_2Cl_2. 3,4-Dihydro-2*H*-pyran (**2**) (0.46 mL, 5.1 mmol) was then added, the reaction mixture was stirred at the same temperature for 17 h, and H_2O (20 mL) was carefully added. The aqueous phase was washed with EtOAc (3 × 20 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue that was purified by silica gel column chromatography eluting with hexane/EtOAc (8:2) to afford exclusively compound **9b** as a white solid (60 mg, 42% yield): mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 1.47−1.66 (m, 4H, $2H_4$, $2H_5$), 2.19 (t, 1H, J = 11.1, H_7), 2.59−2.67 (m, 1H, H_6), 2.93−2.98 (m, 1H, H_7), 3.34 (dt, 1H, J = 2.0, J = 11.5, H_3), 3.75 (s, 3H, OCH_3), 3.92−3.95 (m, 1H, H_3), 4.25−4.27 (m, 1H, H_1), 7.42 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.6 (C_4), 22.1 (C_5), 27.4 (C_6), 33.7 (C_7), 52.9 (OCH_3), 57.7 (C_8), 64.7 (C_3), 73.9 (C_1), 115.5 (q, J_{C-F} = 286.0, CF_3), 156.0 (q, J_{C-F} = 38.0, *C*OCF$_3$), 170.3 (CO); ^{19}F NMR ($CDCl_3$) δ −76.0; ESI+ (m/z) = 282.4. Anal. Calcd for $C_{11}H_{14}F_3NO_4$: C, 46.98; H, 5.02; N, 4.98. Found: C, 47.03; H, 5.06; N, 4.85.

(1*S*,5*S*,7*R*)- and (1*R*,5*R*,7*S*)-1-Methyl-7-(2′,2′,2′-trifluoroacetamido)-2-oxabicyclo[3.2.0]heptane-7-carboxylic Acid Methyl Ester (11b). MAO (10 wt % in toluene) (3 mL) was slowly added at −20 °C under an argon atmosphere to a solution containing **3b** (100 mg, 0.50 mmol) in 10 mL of dry CH_2Cl_2. 5-Methyl-2,3-dihydrofuran (**10**) (0.46 mL, 5.1 mmol) was then added, the reaction mixture was stirred at the same temperature for 17 h, and H_2O (20 mL) was carefully added. The aqueous phase was washed with EtOAc (3 × 20 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue that was purified by silica gel column chromatography eluting with hexane/EtOAc (8:2) to afford exclusively compound **11b** as a white solid (80 mg, 56% yield): mp75−77 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3H, CH_3), 1.52 (dd, 1H, J = 6.6, J = 13.6, H_6), 1.76 (dd, 1H, J = 5.5, J = 12.7, H_4), 1.90−2.00 (m, 1H, H_4), 2.78 (dd, 1H, J = 7.0, J = 15.9, H_5), 3.29 (dd, 1H, J = 9.4, J = 13.6, H_6), 3.76 (s, 3H, OCH_3), 3.93 (dt, 1H, J = 5.6, J = 10.0, H_3), 4.31 (t, 1H, J = 8.5, H_3), 7.38 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.1 (CH_3), 30.9 (C_4), 31.3 (C_6), 40.5 (C_5), 52.8 (OCH_3), 61.4 (C_7), 70.0 (C_3), 86.8 (C_1), 115.5 (q, J_{C-F} = 288.0, CF_3), 156.1 (q, J_{C-F} = 38.0, *C*OCF$_3$), 170.1 (CO); ^{19}F NMR ($CDCl_3$) δ −76.1; ESI+ (m/z) = 282.5. Anal. Calcd for $C_{11}H_{14}F_3NO_4$: C, 46.98; H, 5.02; N, 4.98. Found: C, 46.95; H, 4.98; N, 4.93.

NMR Study. 2D NMR experiments: NMR spectroscopic experiments were recorded on a Bruker Avance 400 spectrometer at 298 K. Magnitude-mode ge-2D COSY spectra were recorded with gradients and by using the cosygpqf pulse program with 90° pulse width. Phase-sensitive ge-2D HSQC spectra were recorded by using z filter and selection before t1 and removing the decoupling during acquisition by use of the

(33) Sheldrick, G. M. SHELXL*97*. *Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.

invigpndph pulse program with CNST2 J(H,C) = 145 Hz. Magnitude-mode ge-2D HMBC spectra were recorded with gradients and with LOW-pass J filter. 2D NOESY experiments were made by using phase-sensitive ge-2D NOESY. These experiments were processed with Mestre Nova software (Mestrelab Research, Spain).

Molecular Dynamics Simulations. Unrestrained-MD simulations were performed with AMBER[34] 6, which was implemented with the General Amber Force Field (GAFF).[32] The following protocol was used: First, compounds **6a** and **7b** were immersed in a bath of 262 and 327 $CHCl_3$ molecules, respectively. Equilibration of the system was carried out as follows in both cases; as a first step, a short minimization with positional restraints on solute atoms was run to remove any potentially bad contact. The force constant for the positional constraints was 500 kcal·mol^{-1}·Å^{-2}. A 12.5 ps molecular dynamics calculation was then run at 300 K, maintaining positional restraints on the solute in order to equilibrate the $CHCl_3$ box. For these two steps, a 12 Å cutoff was used for the treatment of the electrostatic interactions. In the next step, the system was equilibrated using the mesh Ewald method. To this end, a short MD simulation (12.5 ps) was run at 300 K − also using the Ewald approach.[35] The system was then subjected to several minimization cycles (each one using 1000 steepest descent iterations) gradually reducing positional restraints on the solute from 500 kcal·mol^{-1}·Å^{-2} to 0. Finally, 20 ns MD trajectories at constant pressure (1 atm) and temperature (300 K) were collected and analyzed using the CARNAL module of AMBER 6.

MD-tar Simulations. NOE-derived distances were included as time-averaged distance constraints. A $< r^{-6} >^{-1/6}$ average was used for the distances. Final trajectories were run using an exponential decay constant of 8000 ps and a simulation length of 80 ns with a dielectric constant $\varepsilon = 4$.

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Supporting Information Available: Spectral characterization data corresponding to ^{1}H and ^{13}C NMR, COSY, HSQC, and 2D-NOESY experiments, PDB coordinates obtained from the MD-tar simulations for compounds **6a** and **7b**, as well as crystallographic information files (CIF) for compounds **6a** and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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