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Carbocyclic serine analogues: regio- and diastereoselective syntheses of new 1-amino-2,5-dihydroxycyclohexanecarboxylic acids

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Abstract—Spirooxazolones **3**, obtained by Diels–Alder reaction between oxazolone **1** and dienes **2**, are the key starting materials for the preparation of β-hydroxycyclohexenamino acid derivatives **4**–**6**. The regio- and diastereoselective functionalization of cyclohexyl ring with a second hydroxy group to give the new 1-amino-2,5-dihydroxycyclohexanecarboxylic acids **11**, **19** and the 2,4-dihydroxy derivative **20** was achieved when starting from compounds **4**–**6**. In fact, the iodo-oxazination reaction on compounds **4**, followed by reduction of the iodine atom, led to the dihydroxyamino acids **11** in which the *cis* relationship exists between the two hydroxy groups. The iodo-lactonization reaction, followed by reduction of the iodine atom, allowed for the formation of the *trans* dihydroxy derivatives **19** starting from the acids **5**.
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1. Introduction

Our previous researches were focused on the synthesis of carbocyclic constrained amino acids characterized by the presence of a heteroatom on the β-position.[1–3] Recently, we have reported on a high diastereoselective approach to 1-amino-6-hydroxy-3-cyclohexenecarboxylic acids **7**, which bear a hydroxy group at the β-carbon and in which the serine skeleton is included, when starting from 4-chloromethylene-5(4*H*)-oxazolone and dienes.[2]

The importance of constrained amino acids is due to their potential biological properties related to their structural features and the interest in the preparation of new compounds is increasing as shown in recent literature.[1–4] Clearly the presence of substituents on the ring plays a crucial role in the enzymatic interactions. So the possibility to realize regio- and stereocontrolled syntheses is of great interest to clarify these interactions.[4h,5]

In continuing our study, we now report on the preparation of new 1-amino-2,5-dihydroxycyclohexanecarboxylic acid derivatives.

To our knowledge, only few examples of 1-aminopolyhydroxycyclohexanecarboxylic acid derivatives are reported in the literature: the 3,4-[6] and 2,6-dihydroxy derivatives,[7] 3,4,5-tryhydroxy derivatives[8] and the 2,3,4,5-tetrahydroxy one.[9] The synthesis of the polyhydroxycyclohexanecarboxylic acid opens the interesting field of carbohydrate mimetics. The replacement of the oxygen atom on the pyranosyl ring with the methylene group is of particular interest since the resulting carbocyclic ring has a greater metabolic stability.

β-Hydroxycyclohexenylamino acid derivatives are our key starting materials for the preparation of the dihydroxy derivatives.

As mentioned before, the 4-chloromethylene-5(4*H*)-oxazolone has been used for the synthesis of these compounds. Efforts to find a more efficient synthon are in progress and the methyleneoxazolone **1**,[3] functionalized at the double bond with a carbonate group, has been found a more convenient starting material. As it will be described further on, the use of the compound **1** allowed the final amino acid derivatives **7** to be obtained in a better overall yield (50%, two steps) than with the chloromethylene-oxazolone (33%, four steps).

Starting from 1-amino-6-hydroxy-3-cyclohexenecarboxylic acid derivatives the new amino-2,5-dihydroxycyclohexanecarboxylic acids were prepared in which the *cis* or *trans* relationship exists. The goal of our syntheses is the possibility to control the stereochemistry of four centers using very simple stereocontrolled reactions.

2. Results and discussion

Ethyl 2-phenyl-5-oxo-oxazol-4-methylenecarbonate (*Z*-**1**)

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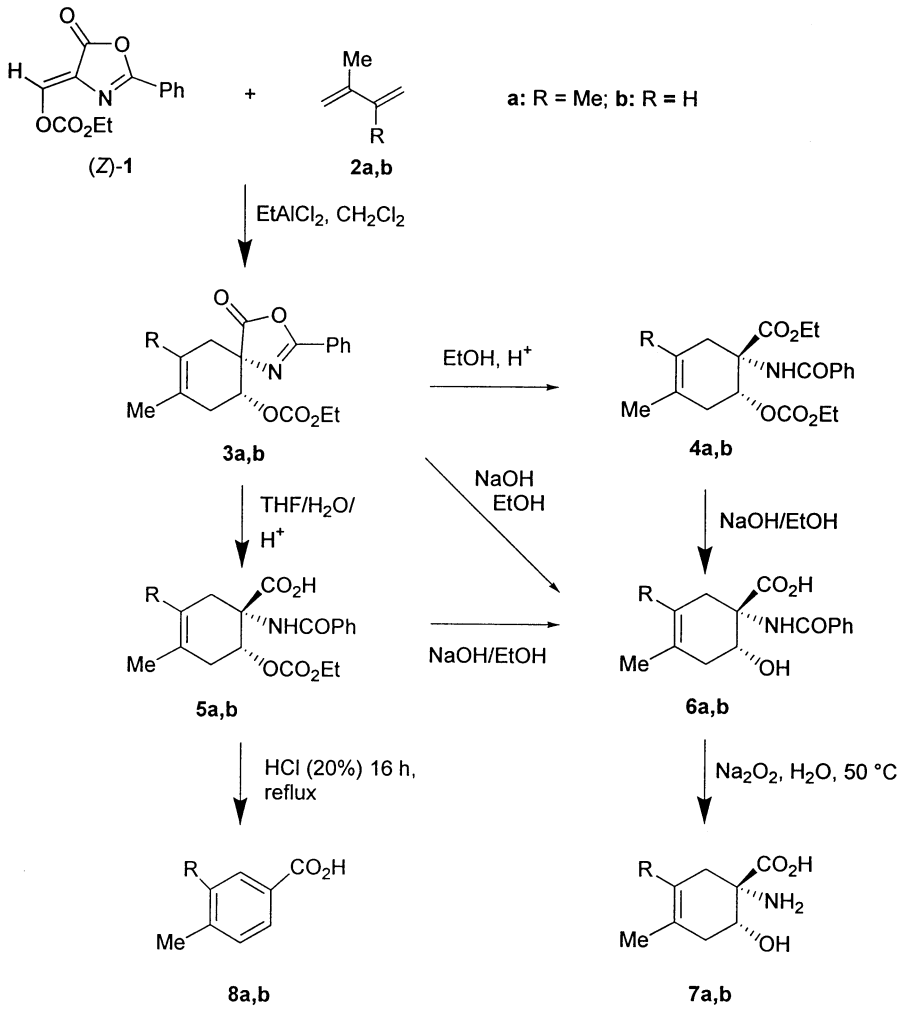


Scheme 1.

was reacted with 2,3-dimethylbutadiene (**2a**) in dichloromethane at −20°C and in presence of ethylaluminum dichloride. After 5 h, the ^{1}H NMR analysis of the crude mixture revealed the formation of the cycloadduct **3a**. Reaction workup resulted in partial transformation of **3a** into the corresponding ester **4a** and acid **5a**, which could be separated by chromatography (Scheme 1).

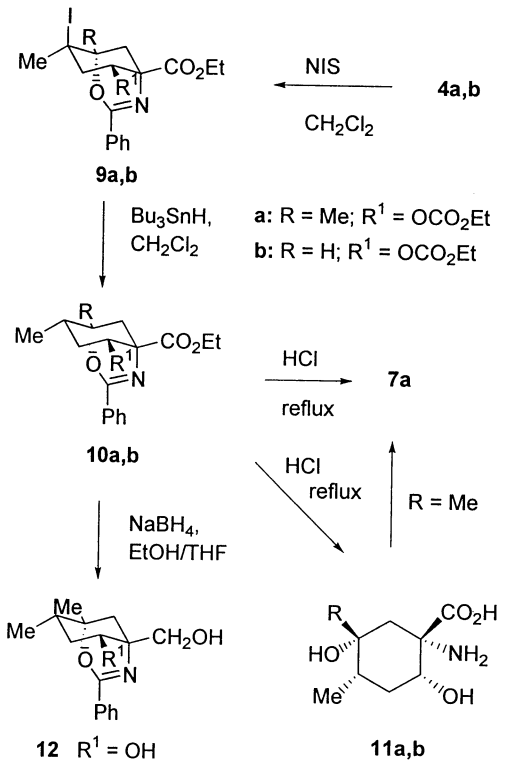
In order to avoid such a mixture of compounds, the crude reaction mixture can be directly treated with ethanol or water giving the corresponding ester **4a** or acid **5a**, respectively, which were obtained in about 70% yield.

The reaction of 2-methylbutadiene (**2b**) and oxazolone **1**, operating as described before, gave the cycloadduct **3b** which was transformed into ester **4b** or acid **5b** in 65 or 60% yield, respectively.

As shown, the cycloaddition reaction proceeded with high diastereoselectivity and the *cis* relationship between the nitrogen and oxygen atoms, such as in the starting dienophile, was maintained. Furthermore, when starting from the 2-methylbutadiene **2b**, the diastereoisomeric compound **3b** was obtained confirming the high regioselective control in the cycloaddition process. In fact, only traces of the other regioisomer were detected.

Selective hydrolysis of the functional groups was achieved in different ways or starting directly from the crude cycloaddition reaction mixture or from the isolated products. Cycloadducts **3a**,**b** were transformed into the corresponding acids **5a**,**b** in good yield by reaction in wet tetrahydrofuran and in presence of a catalytic amount of hydrogen chloride. The corresponding hydroxyacids **6a**,**b**, in which the hydroxy group has been deprotected, were obtained from compounds **5a**,**b** with sodium hydroxide in ethanol. It is possible to attain directly compounds **6a**,**b** when starting from oxazolone **3a**,**b** or ester **4a** (Scheme 1).

The structure of compounds **3**, **4**, **5** and **6** was confirmed by spectroscopic data. In the IR spectra of the compounds **3**, the characteristic absorption of the lactone group (1800 cm^{-1}) is present. According to the structure of cyclohexenyl ring, the ^{1}H NMR spectra of compounds **3**–**6** show an AB or ABX system (CH_2 groups α to the CNH) and an ABX system associated to CH_2 protons α to the CHOR group. As an example, the ^{1}H NMR spectrum of compound **5a** is detailed to demonstrate the configuration of substituents.



Scheme 2.

Signals at 5.57 and 2.75, 2.25 δ (ABX system, J=18.2, 6.2, 6.3 Hz) associated with H-6 and H-5 protons, respectively, and at 3.00, 2.88 δ (AB system, J=17.4 Hz), associated with H-2, are present. A strong positive NOE effect was observed between H-2 proton (δ=3.00) and H-6 and between this last and H-5 (δ=2.75). A positive effect was also observed between H-5 (δ=2.25) and NH proton (δ=6.92). Considering these spectroscopic data and on the basis of molecular model analysis, it can be assumed that the conformation of the compound **5a** is a twisted chair in which the OR group is in the equatorial position and the benzoylamino group is in the axial one, thus confirming the *cis* relationship between the two substituents.

The regiochemistry of the cycloaddition reaction in the case of monomethyl derivatives was established considering the multiplicity of the methylene protons and by a NOE experiment on compound **3b** in which a positive Overhauser effect was observed between the methyl group and H-7 (δ=2.60–2.50) and between the olefinic proton at δ=5.40 and H-10 (δ=2.14).

Acidic hydrolysis of the benzoylamino group of compounds **5a**,**b** did not allow one to obtain the expected amino acids **7a**,**b**. In fact, operating in hydrochloric acid (20%) at reflux for 16 h, benzoic acid and the substituted benzoic acids **8a**,**b** were isolated (Scheme 1). Their formation is explained by water elimination, probably favored by a previous acid-catalyzed isomerization of the double bond, giving a cyclohexadiene intermediate from which, after ammonia elimination, benzoic acid derivatives **8** are formed.

The preparation of the amino acids **7** was achieved operating in basic conditions.[10] Acids **6a**,**b** were reacted with sodium peroxide in water at 50°C and the amino acids **7a**,**b** were isolated in satisfactory yield (Scheme 1).

The regio- and diastereoselective functionalization of C-5 with a hydroxy group to give the corresponding 1-amino-2,5-dihydroxycyclohexanecarboxylic acids was achieved when starting from compounds **4**–**6**. The stereochemical control on C-5 was favored by the presence both of the benzoylamino group and carboxylic group which were utilized in the iodo-oxazination[11] and iodo-lactonization[12] reactions, respectively.

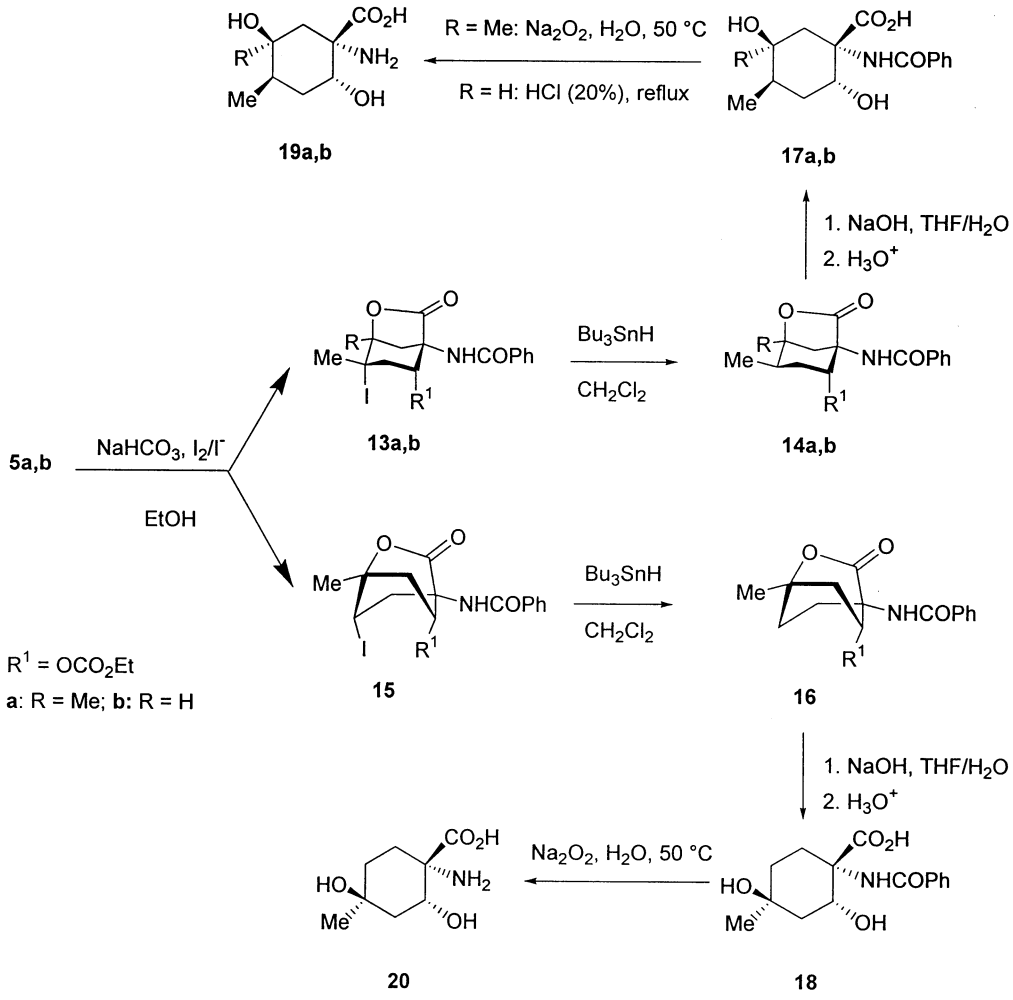
Starting from compounds **4a**,**b**, the iodo-oxazine derivatives **9a**,**b** were obtained in good yield by reaction in dichloromethane with *N*-iodosuccinimide at room temperature, according to the mechanism reported in the literature.[11] The reduction of compounds **9a**,**b** with tributyltin hydride allowed one to obtain compounds **10a**,**b**, as single diastereoisomers, in 75–70% overall yield (Scheme 2).

The structure of compounds **9**–**10** was assigned by ^{1}H NMR, COSY and NOE experiments. COSY and hetero-correlated (C/H) experiments allowed to assign the chemical shift to all protons and to establish the regiochemistry of the iodo-oxazination reaction. Particularly, the formation of the oxazine ring was confirmed by ^{1}H NMR spectra of compounds **10** in which the signal associated with the NH proton is absent and the multiplicity of Me-8 (d, δ=1.17–1.06 region) reveals the saturation of the double bond. The conformational rigidity of the backbone allows us to establish the configuration of compounds **10**. Considering that the nitrogen and oxygen atoms in the oxazine ring should be in the axial position, that the ethoxycarbonyloxy group and the nitrogen atom are *cis*, as demonstrated before, and that the J values between H-6 (5.78–5.35 δ region) and H-7 are 11–10 and 6–4 Hz, it was possible to assign unequivocally the axial configuration of H-6. This result is decisive to assign the configuration of Me-8 group. The NOE experiment on compound **10a** showed evidence of close proximity between H-6 (5.35 δ), H-7 (2.05–1.95 δ) and H-9 (2.12 δ), confirming the equatorial position of the Me-8 group.

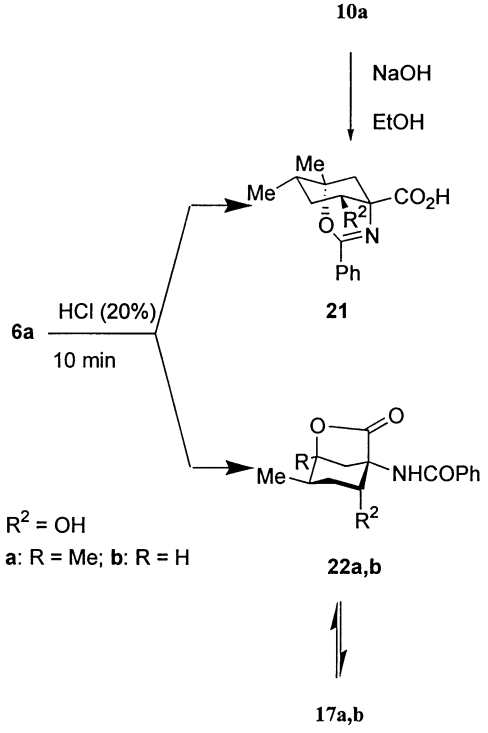
According to these results, we concluded that the iodo-oxazination reaction was regioselective and *anti*-diastereoselective. This is in agreement with similar cases reported in the literature.[11] Furthermore, the reduction of iodine atom proceeded with retention of the configuration and produced a single diastereoisomer. As a further confirmation of this configurational assignment (see below), both the carbonate and ester groups in **10a** were hydrolyzed in ethanol and in the presence of sodium hydroxide, giving compound **21** (Scheme 4).

The hydrolysis of compounds **10a** and **b** in acidic conditions (HCl 20%, 16 h) resulted in the formation of the amino acids **7a** and **11b**, respectively (Scheme 2).

The formation of **7a**, besides the expected dihydroxy compound **11a**, has to be ascribed to the transformation of **10a** into a hydroxy intermediate which was transformed into **7a** on water elimination favored by the formation of the tetra substituted olefin.



Scheme 3.



Scheme 4.

To overcome this problem, the oxazine derivative **10a** was tentatively reduced with sodium borohydride in ethanol, by a modification of the procedure described in the literature.[13] Unfortunately, the reduction reaction resulted in the formation of the compound **12** in 86% yield in which the ester function was reduced to alcohol.

The structure of compound **12** was established by ^{1}H NMR and COSY experiments. The chemical shifts (δ=4.50, 3.86, 3.28) and the multiplicity of the signals (ABX system, J=10.3, 6.0, 5.4 Hz) confirmed the presence of the CH_2OH group.

To control the *trans* relationship between the two hydroxy groups, the iodo-lactonization reaction was used. Starting from **5a** and by reaction in ethanol, sodium hydrogencarbonate and in presence of a solution of I_2/I^-, the iodolactone **13a** was obtained which was reduced to the lactone **14a** (41% overall yield) with tributyltin hydride (Scheme 3).

In the case of **5b** a mixture of the regioisomeric iodolactones **13b** and **15** was found operating with the same reagents both at room temperature (1:2 ratio) and at reflux (1:3.5 ratio). Reduction of these compounds allowed us to obtain lactones **14b** and **16** (Scheme 3).

It is known that the intramolecular iodo-lactonization reaction normally shows a preference for the formation of five-membered over six-membered rings and *anti* stereospecific addition is generally observed.[12] In the present case, the formation of the six-membered lactone **15** can be justified considering that the carboxylic group reacts with the more stable tertiary carbon of the iodonium intermediate.

The structure of compounds **13**–**16** was confirmed by spectroscopic data. The IR spectra showed absorptions at 1780–1760 and 1740 cm^{-1}, typical for the five- and six-membered lactones, respectively. The chemical shifts of signals of methyl groups linked to the oxygen-bearing and iodine-bearing carbons are, respectively, in the δ=1.87–1.64 region and δ=2.20–2.09 region. Compounds **14a**,**b** present a characteristic doublet associated with Me-4 (δ=1.10–1.00) which is absent in compound **16**, thus confirming the formation of the five- and six-membered lactone rings, respectively. The configuration of the methyl group on C-4 of compound **14b** was confirmed by NMR data and the chemical shifts have been assigned unequivocally by the COSY and hetero-correlation (C/H) experiments. The molecular model analysis suggested that two conformations are possible for the bicyclic ring but the *J* values of H-2 are very small suggesting that a configuration is preferred in which this proton is in the equatorial position. Significantly, a strong NOE effect was observed between H-4 (2.18 δ) and H-8 (2.49 δ) allowing the axial position to be assigned to H-4.

This result is a further confirmation that the reduction of the iodine group occurs with retention of the configuration.

The lactones **14a**,**b** and **16** were quantitatively transformed into the dihydroxyamino acids **17a**,**b** and **18**, respectively, by reaction in tetrahydrofuran and in presence of sodium hydroxide (Scheme 3). The acid **17a** was readily transformed in solution into the lactones **22a** (Scheme 4) as demonstrated by TLC and ^{1}H NMR analyses and its mass spectroscopy analysis (M^+=289). Compound **17b** was more stable in solution but was transformed into **22b** by heating (Scheme 4).

Interestingly, it is possible to obtain the hydroxy analogous of **10a** and **14a**, namely **21** and **22**, when directly starting from the hydroxy acid **6a**. By heating of this compound in a HCl solution (20%) for 10 min, a mixture of **21** and **22** (3:2 ratio) was isolated in 62% overall yield (Scheme 4).

This result allows us to avoid the two-step reaction described before (i.e. the iodo-oxazination or iodo-lactonization reaction followed by reduction) and to our knowledge represents the first example of direct oxazination and lactonization reactions.

Starting from **6b** operating in the same reaction conditions, the formation of the above compounds was not observed.

Finally, the compounds **17a**,**b** and **18** were debenzoylated giving the expected 1-amino-2,5-dihydroxycyclohexanecarboxylic acids **19a**,**b** and **20**. Acidic conditions (HCl 20%) were achieved in the case of **17b** and sodium peroxide in water was preferred in the case of **17a** and **18**.

In conclusion, by simple reactions, it was possible to prepare the 1-amino-2,5-dihydroxycyclohexanecarboxylic acids in which the *trans* or *cis* relationship between the two hydroxy groups can be chosen. Furthermore, the high diastereoselectivity of the reactions used allowed for the satisfactory control of the stereochemistry of four centers.

3. Experimental

3.1. General

Melting points were determined using an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ as the solvent with Bruker Avance 300 and Varian Gemini 200 instruments. Coupling constants values (*J*) are given in hertz. Mass spectra were obtained by electron impact ionization at 70 eV from a Finningan INCOS 50 instrument using the direct exposure probe (DP). Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolone **1**[3] is a known compound.

3.2. General procedures for the Diels–Alder reaction

To a stirred solution of oxazolone (*Z*)-**1a** (1.56 g, 6 mmol) and diene **2** (24 mmol) in anhydrous CH_2Cl_2 (10 mL) under the nitrogen atmosphere at −20°C, was added $EtAlCl_2$ (3.3 mL, 6 equiv., 1.8 M in toluene). The stirring was continued at −20°C for 5 h. The reaction was monitored by ^{1}H NMR. The reaction mixture was worked up as described below. (i) The solvent was evaporated and the crude reaction mixture was chromatographed [*n*-pentane/AcOEt (20:1)] giving two fractions containing, respectively, the pure cycloadduct **3** (**3a**: 35%, **3b**: 47%), the ester **4** (**4a**: 30%, **4b**: 13%). Elution with AcOEt/MeOH allowed us to obtain a third fraction containing the acid **5** (**5a**: 8%, **5b**: 7%). (ii) Anhydrous EtOH (20 mL) was added to the crude reaction mixture and the solution was stirred for 12 h after which a solid was separated, filtered and washed with EtOH (10 mL). The organic solution was evaporated and the reaction mixture was chromatographed (*n*-pentane/CH_2Cl_2 1:0 to 0:1). Ester **4** (**4a**: 70%, **4b**: 65%) was isolated as pure compound. (iii) The solvent was evaporated and the crude reaction mixture was taken up with THF (20 mL) and a catalytic amount of HCl (37%) was added. After 2 h, a solid was separated, filtered off and washed with THF (10 mL). The organic solvent was eliminated in vacuum. The solid was dissolved in AcOEt (10 mL) and extracted with a solution of $NaHCO_3$ (5×3 mL). The aqueous solution was acidified with HCl (10%, Congo red) and extracted with CH_2Cl_2 (3×10 mL). After drying over Na_2SO_4 and recrystallization, the pure acid **5** (**5a**: 68%, **5b**: 60%) was obtained. (iv) The solvent was evaporated and the crude reaction mixture was taken up with THF (20 ml) and a solution of NaOH (20 mL, 10%) was added. The stirring was continued for 48 h after which THF was evaporated and the aqueous layer was extracted with AcOEt (10 mL). Then the aqueous solution was acidified with HCl (10%, Congo red) and extracted with CH_2Cl_2 (4×10 mL). After drying over Na_2SO_4 and recrystallization, pure acid **6a** (68%) was isolated.

3.3. General procedure for hydrolysis of spirooxazolone

Cycloadduct **3** (1 mmol) was dissolved in THF (5 mL) in the presence of a catalytic amount of HCl (37%). The solution was stirred at room temperature for 1 h. Solvent was evaporated and the solid was taken up with in CH_2Cl_2 (10 mL) and dried over Na_2SO_4. After solvent evaporation and after recrystallization, the pure acid **5** was obtained (**5a**: 94%, **5b**: 93%).

3.4. General procedure for hydrolysis of carbonate

Ester **4a** (389 mg, 1 mmol) or acid **5** (1 mmol) was suspended in EtOH (6 mL) and a solution of NaOH (10%, 6 mL) was added. The solution was stirred at room temperature for 24 h. After solvent evaporation, the residue was taken up with an aqueous solution of HCl (10 mL, 10%) and extracted with AcOEt (3×15 mL). The organic layers were dried over Na_2SO_4. After recrystallization, the pure compound **6** (**6a**: 90% from **4a**; 94% from **5a**; **6b**: 96% from **5b**) was isolated.

3.4.1. Ethyl (5*S, 6*R**)-8,9-dimethyl-4-oxo-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,8-dien-6-carbonate (3a).** Mp 119°C (*i*Pr_2O); IR ν_{max} 1800, 1740, 1640 cm^{-1}; ^1H NMR δ 8.20–7.20 (m, 5H), 5.19 (dd, *J*=9.2, 7.1 Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 2.82, 2.14 (AB system, *J*=17.3 Hz, 2H), 2.65–2.45 (m, 2H), 1.74, 1.67 (two s, 6H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 14.6, 18.6, 19.5, 33.9, 41.4, 64.7, 72.2, 76.0, 121.6, 124.1, 126.4, 128.8, 129.1, 133.2, 154.5, 161.9, 179.2. Anal. calcd: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.30; H, 6.21; N, 4.00.

3.4.2. Ethyl (5*S, 6*R**)-8-methyl-4-oxo-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,8-dien-6-carbonate (3b).** Mp 110°C (*i*Pr_2O); IR ν_{max} 1800, 1720, 1630 cm^{-1}; ^1H NMR δ 8.09–7.43 (m, 5H), 5.40 (bs, 1H), 5.19 (dd, *J*=8.9, 7.1 Hz, 1H), 4.14 (q, *J*=7.1 Hz, 2H), 2.80 (d, *J*=17.5 Hz, 1H), 2.60–2.50 (m, 2H), 2.14 (dd, *J*=17.5, 3.8 Hz, 1H), 1.80 (s, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 14.4, 23.4, 32.8, 35.5, 64.7, 71.2, 75.9, 116.4, 126.2, 128.7, 129.1, 132.5, 133.2, 154.4, 161.9, 179.3. Anal. calcd: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.48; H, 5.88; N 4.22.

3.4.3. Ethyl (1*S, 6*R**)-1-benzoylamino-6-ethoxycarbonyloxy-3,4-dimethylcyclohex-3-enecarboxylate (4a).** Oil; IR ν_{max} 3350, 1730, 1620 cm^{-1}; ^1H NMR δ 7.77–7.39 (m, 5H), 6.76 (s, 1H, exch.), 5.32, 2.54, 2.29 (ABX system, *J*=18.0, 8.9, 7.2 Hz, 3H), 4.25–4.15 (m, 4H), 3.03, 2.85 (AB system, *J*=17.6 Hz, 2H), 1.70 (two s, 6H), 1.30, 1.22 (two t, *J*=7.2, 7.1 Hz, 6H); Anal. calcd: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.50; H, 7.15; N, 3.47.

3.4.4. Ethyl (1*S, 6*R**)-1-benzoylamino-6-ethoxycarbonyloxy-4-methylcyclohex-3-enecarboxylate (4b).** Oil; IR ν_{max} 3350, 1730, 1720, 1620 cm^{-1}; ^1H NMR δ 7.77–7.38 (m, 5H), 6.66 (s, 1H, exch.), 5.41–5.37 (m, 2H), 4.26–4.14 (m, 4H), 2.96 (bs, 2H), 2.60 (dd, *J*=18.3, 4.5 Hz, 1H), 2.26 (dd, *J*=17.4, 5.4 Hz, 1H), 1.69 (s, 3H), 1.28, 1.25 (two t, *J*=7.2, 7.1 Hz, 6H); Anal. calcd: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.71; H, 6.77; N, 3.53.

3.4.5. (1*S, 6*R**)-1-Benzoylamino-6-ethoxycarbonyloxy-3,4-dimethylcyclohex-3-ene carboxylic acid (5a).** Mp 155°C (CH_2Cl_2/*i*Pr_2O); IR ν_{max} 3700–3000, 1730, 1700, 1620 cm^{-1}; ^1H NMR δ 10.0 (bs, 1H, exch.), 7.77–7.42 (m, 5H), 6.92 (s, 1H, exch.), 5.57, 2.75, 2.25 (ABX system, *J*=18.2, 6.2, 6.3 Hz, 3H), 4.22 (q, *J*=7.1 Hz, 2H), 3.00, 2.88 (AB system, *J*=17.4 Hz, 2H), 1.67 (s, 6H), 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 14.6, 18.8, 18.9, 34.9, 36.4, 62.6, 65.1, 75.0, 121.5, 122.9, 127.7, 129.1, 132.7, 133.7, 155.2, 169.6, 173.4. Anal. calcd: C, 63.51; H, 6.41; N, 3.88. Found: C, 63.83; H, 6.41; N 4.14.

3.4.6. (1*S, 6*R**)-1-Benzoylamino-6-ethoxycarbonyloxy-4-methylcyclohex-3-ene carboxylic acid (5b).** Mp 218°C (CH_2Cl_2). IR ν_{max} 3305, 3300–2800, 1740, 1710, 1620 cm^{-1}; ^1H NMR δ 10.0 (bs, 1H, exch.), 7.79–7.00 (m, 5H), 6.90 (s, 1H, exch.), 5.50, 2.80, 2.27 (ABX system, *J*=18.7, 6.5, 6.0 Hz, 3H), 5.36 (bs, 1H), 4.25 (q, *J*=7.1 Hz, 2H), 3.03–2.85 (m, 2H), 1.75 (s, 3H), 1.32 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 14.5, 23.1, 30.8, 34.0, 61.1, 64.8, 75.1, 118.2, 127.5, 128.8, 129.8, 132.0, 134.6, 155.3, 168.1, 172.5. Anal. calcd: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.55; H, 6.17; N, 4.12.

3.4.7. (1*S, 6*R**)-1-Benzoylamino-6-hydroxy-3,4-dimethylcyclohex-3-enecarboxylic acid (6a).** Mp 202°C (CH_2Cl_2); IR ν_{max} 3400, 3300, 1700, 1600 cm^{-1}; ^1H NMR δ ($CDCl_3$/DMSO-d_6) 7.86–7.44 (m, 5H), 6.70 (s, 1H, exch.), 5.50–4.20 (bs, 2H, exch.), 4.29, 2.36, 2.15 (ABX system, *J*=11.0, 9.1, 5.8 Hz, 3H), 2.82, 2.57 (AB system, *J*=17.6 Hz, 2H), 1.60 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 18.6, 18.8, 37.7, 63.7, 69.2, 122.1, 122.3, 127.7, 128.5, 131.6, 134.7, 167.8, 173.3. Anal. calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.40; H, 6.43; N, 4.58.

3.4.8. (1*S, 6*R**)-1-Benzoylamino-6-hydroxy-4-methylcyclohex-3-enecarboxylic acid (6b).** Mp 168°C (CH_2Cl_2/Et_2O); IR ν_{max} 3400, 3300, 1720, 1620 cm^{-1}; ^1H NMR δ (DMSO-d_6) 12.98–11.00 (bs, 1H exch.), 7.78–7.42 (m, 6H), 6.00–5.00 (bs, 1H exch.), 5.22 (bs, 1H), 4.07, 2.26, 2.08 (ABX system, *J*=17.5, 7.6, 5.1 Hz, 3H), 2.84, 2.64 (AB system, *J*=17.0 Hz, 2H), 1.62 (s, 3H); ^{13}C NMR δ (DMSO-d_6) 23.5, 32.0, 37.0, 63.54, 69.8, 118.3, 128.1, 129.0, 131.3, 132.1, 135.4, 168.3, 173.9. Anal. calcd: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.09; H, 6.40; N, 4.88.

3.5. General procedures for hydrolysis of benzoylamino group

(i) Operating in a sealed tube, the compound **5** (1 mmol) was suspended in a solution of HCl (4 mL, 20%). The solution was heated at 100°C for 16 h. The reaction mixture was extracted with Et_2O (2×10 mL). After drying over Na_2SO_4, a mixture of benzoic acid and the derivative **8** (1:1 ratio, ^1H NMR) was obtained which were separated by chromatography (CH_2Cl_2/Et_2O). **8a**: 94%; mp 166°C (H_2O); **8b**: 95%; mp 180°C (H_2O). (ii) Compound **6** (1 mmol) was suspended in H_2O (20 mL) and Na_2O_2 (374.4 mg, 4.8 mmol) was added. The mixture was heated at 50°C for 24 h. The aqueous solution was acidified with HCl (10%, Congo red) and extracted with CH_2Cl_2 (2×10 mL). The aqueous layer was evaporated to dryness and the crude mixture was taken up with EtOH (2 mL) and inorganic salts were filtered. EtOH was evaporated. The

solid was dissolved in a minimum amount of H_2O and desalted on a column of Amberlite IR-120 (PLUS) ion-exchange resin. The column was eluted with H_2O until the eluate was shown to be free of halide ion. The amino acid was then eluted with a solution of pyridine (20% in H_2O). The solvent was evaporated and pure compound **7** (**7a**: 74%, **7b**: 78%) was isolated.

3.5.1. (1*S, 6*R**)-1-Amino-6-hydroxy-3,4-dimethylcyclohex-3-enecarboxylic acid (7a).** Mp dec. (EtOH). IR ν_{max} 3215, 1660 cm^{-1}; ^1H NMR (D_2O/CF_3CO_2D)^2 δ 4.30, 2.41, 1.87 (ABX system, J=17.6, 9.9, 7.0 Hz, 3H), 2.75, 2.19 (AB system, J=18.3 Hz, 2H), 1.54 (s, 6H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 17.0, 17.4, 34.4, 36.7, 63.2, 66.6, 120.1, 123.5, 172.4. Anal. calcd: C, 58.35; H, 8.17; N, 7.56. Found: C, 58.02; H, 8.27; N, 7.24.

3.5.2. (1*S, 6*R**)-1-Amino-6-hydroxy-4-methylcyclohex-3-enecarboxylic acid (7b).** Mp dec. (EtOH). IR ν_{max} 3200, 1650 cm^{-1}; ^1H NMR (D_2O/CF_3CO_2D) δ 5.35 (bs, 1H), 4.44 (dd, J=9.4, 6.7 Hz, 1H), 2.82 (d, J=18.7 Hz, 1H), 2.59–1.90 (m, 4H), 1.68 (s, 3H); ^{13}C NMR δ 21.8, 31.4, 33.6, 62.7, 67.1, 113.3, 114.7, 172.9. Anal. calcd: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.83; H, 7.91; N, 7.88.

3.6. General procedure for the iodo-oxazination reaction

To a stirred solution of ester **4** (1 mmol) in anhydrous CH_2Cl_2 (5 mL), the NIS (247 mg, 1.1 mmol) was added at room temperature. After 1 h, the organic solution was washed with a solution of $Na_2S_2O_4$ (2×5 mL, 5%), H_2O (5 mL) and dried over Na_2SO_4 giving pure compound **9** (**9a**: 94%, **9b**: 90%).

3.6.1. Ethyl (1*R, 5*S**, 6*R**, 8*R**)-6-ethoxycarbonyloxy-8-iodo-1,8-dimethylcyclohex-2-oxa-3-phenyl-4-azabicyclo-[3.3.1]non-3-ene-5-carboxylate (9a).** Oil; IR ν_{max} 1710, 1630 cm^{-1}; ^1H NMR δ 8.08–7.35 (m, 5H), 5.78, 2.52, 1.58 (ABX system, J=14.6, 11.4, 4.7 Hz, 3H), 4.42–4.15 (m, 4H), 3.09, 1.85 (AB system, J=14.1 Hz, 2H), 2.16 (s, 3H), 1.74 (s, 3H),1.40–1.22 (m, 6H). Anal. calcd: C, 48.94; H, 5.09; N, 2.72. Found: C, 49.04; H, 5.19; N, 2.81.

3.6.2. Ethyl (1*R, 5*S**, 6*R**, 8*R**)-6-ethoxycarbonyloxy-8-iodo-8-methylcyclohex-2-oxa-3-phenyl-4-azabicyclo[3.3.1]-non-3-ene-5-carboxylate (9b).** Oil; IR ν_{max} 1715, 1630 cm^{-1}; ^1H NMR δ 8.08–7.37 (m, 5H), 5.72, 2.55, 1.51 (ABX system, J=15.4, 11.3, 4.4 Hz, 3H), 4.62–4.58 (m, 1H), 4.43–4.15 (m, 4H), 3.18 (dd, J=13.9, 1.4 Hz, 1H), 2.19 (dd, J=13.9, 4.01 Hz, 1H), 2.27 (s, 3H),1.38–1.24 (m, 6H). Anal. calcd: C, 47.92; H, 4.83; N, 2.79. Found: C, 47.58; H, 5.00; N, 2.89.

3.7. General procedure for preparation of compounds 10

To a stirred solution of iodo-oxazine **9** (1 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen atmosphere, the Bu_3SnH (344 μL, 1.1 mmol) was added. The solution was refluxed for 2 h and after solvent evaporation, the crude reaction mixture was chromatographed (CH_2Cl_2/Et_2O, 1:0 to 0:1) giving compound **10** which was crystallized (**10a**: 80%, **10b**: 78%).

3.7.1. Ethyl (1*R, 5*S**, 6*R**, 8*S**)-6-ethoxycarbonyloxy-1,8-dimethylcyclohex-2-oxa-3-phenyl-4-azabicyclo[3.3.1]-non-3-ene-5-carboxylate (10a).** Mp 135°C (Et_2O); IR ν_{max} 1720, 1630 cm^{-1}; ^1H NMR δ 8.10–7.32 (m, 5H), 5.35 (dd, J=11.4, 4.9 Hz, 1H), 4.40–4.10 (m, 4H), 2.12, 1.88 (AB system, J=13.4 Hz, 2H), 2.05–1.95 (m, 1H), 1.90–1.70 (m, 1H), 1.39 (s, 3H), 1.35–1.20 (m, 7H), 1.06 (d, J= 6.6 Hz, 3H); ^{13}C NMR 14.5, 14.6, 15.3, 25.3, 32.9, 38.7, 41.3, 61.9, 62.5, 64.4, 76.1, 79.6, 128.3, 128.3, 131.1, 133.7, 155.3, 158.0, 172.5. Anal. calcd: C, 64.78; H, 6.94; N, 3.59. Found: C, 64.68; H, 7.10; N, 3.61. m/z 389 (M^+).

3.7.2. Ethyl (1*R, 5*S**, 6*R*, 8*S**)-6-ethoxycarbonyloxy-8-methylcyclohex-2-oxa-3-phenyl-4-azabicyclo[3.3.1]non-3-ene-5-carboxylate (10b).** Mp 123°C (Et_2O); IR ν_{max} 1725, 1625 cm^{-1}; ^1H NMR δ 8.01–7.34 (m, 5H), 5.39 (dd, J=11.3, 4.4 Hz, 1H), 4.40–4.38 (m, 1H), 4.39–4.12 (m, 4H), 2.20–1.56 (m, 4H), 1.48–1.20 (m, 7H), 1.17 (d, J=6.2 Hz, 3H); ^{13}C NMR δ 14.1, 14.2, 17.7, 31.3, 31.4, 37.3, 59.9, 61.5, 63.9, 73.6, 79.4, 127.8, 127.9, 130.8, 133.2, 154.8, 157.1, 172.2. Anal. calcd: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.18; H, 6.95; N, 3.55.

3.7.3. (1*R, 5*S**, 6*R**, 8*S**)-5-Hydroxymethyl-1,8-dimethyl-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-6-ole (12).** Oxazine derivative **10a** (389 mg, 1 mmol) was dissolved in EtOH (3 mL, 96%) and THF (3 mL). The solution was cooled at −25°C after which $NaBH_4$ (185 mg, 5 mmol) was added. The solution was stirred for 16 h. After solvent elimination, the reaction mixture was taken up with AcOEt (20 mL) and washed with H_2O (2×5 mL). Pure compound **12** (247 mg, 86%) was isolated from the dried organic layer (Na_2SO_4) after crystallization: mp 195°C (CH_2Cl_2). IR ν_{max} 3600–3000, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.89–7.36 (m, 5H), 4.50, 3.86, 3.28 (ABX system, J=10.3, 6.0, 5.4 Hz, 3H), 4.13, (d, J=6.8 Hz, 1H, exch.), 3.79–3.70 (m, 1H), 1.80, 1.41 (AB system, J=13.4 Hz, 2H), 1.68–1.63 (m, 2H), 1.29 (s, 3H), 0.92 (d, J=6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 15.9, 25.7, 37.5, 38.3, 41.0, 59.4, 66.8, 71.9, 77.4, 127.8, 128.7, 131.0, 134.6, 155.8. Calcd: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.38; H, 7.79; N, 5.20.

3.7.4. (1*S, 2*R**, 4*S**, 5*R**)-1-Amino-2,5-dihydroxy-4-methylcyclohexanecarboxylic acid (11b).** Operating in a sealed tube, the compound **10b** (361 mg, 1 mmol) was suspended in a solution of HCl (4 mL, 20%). The solution was heated at 100°C for 16 h. The reaction mixture was extracted with Et_2O (2×10 mL) and H_2O was evaporated in vacuum to dryness. Pure amino acid hydrochloride **11b** (207 mg, 92%) was isolated. Mp 300°C dec. (EtOH/propylene oxide); IR ν_{max} 3400–3100, 1590 cm^{-1}; ^1H NMR (D_2O) δ 4.15 (dd, J=12.1, 5.1 Hz, 1H), 3.95, 2.10, 1.98 (ABX system, J=15.5, 3.0, 2.7 Hz, 3H), 1.92–1.75 (m, 2H), 1.45–1.32 (m, 1H), 0.93 (d, J=7.4 Hz, 3H); ^{13}C NMR (D_2O) δ 17.0, 31.3, 34.0, 36.2, 65.0, 68.6, 69.7, 175.4. Anal. calcd: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.10; H, 8.14; N, 7.21.

3.8. General procedure for the iodo-lactonization reaction

To a mixture of compound **5** (1 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in EtOH (7 mL), a solution of I_2/I^-

(H_2O: 7 mL, I_2: 572 mg, 2.2 mmol, KI: 1.1 g, 6.6 mmol) was added. The mixture was stirred at room temperature for 24 h (compound **5b**) or refluxed for 1.30 h (compounds **5a**,**b**). After cooling, a solid was separated. The solvent was evaporated and the residue was taken up with CH_2Cl_2 and washed with a solution of $Na_2S_2O_4$ (2×5 mL, 5%), H_2O (5 mL) and dried over Na_2SO_4. The crude reaction mixture was chromatographed (CH_2Cl_2/Et_2O, 1:0 to 0:1) giving compound **13**. In the case of **5b**, a second fraction containing lactone **15** was isolated. After crystallization, pure compounds **13a** (268 mg, 55%), **13b** (102 mg, 22%, 25°C; 85 mg, 18%, reflux) and **15** (205 mg, 43%, 25°C; 294 mg, 62%, reflux) were isolated.

3.8.1. Ethyl (1*S, 2*R**, 4*S**, 5*S**)-1-benzoylamino-4-iodo-4,5-dimethyl-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-yl-carbonate (13a).** Mp 189°C (CH_2Cl_2/Et_2O). IR ν_{max} 3310, 1765, 1710, 1630 cm^{-1}; ^1H NMR δ 7.83–7.42 (m, 5H), 7.59 (s, 1H, exch.), 5.20–5.10 (m, 1H), 4.39 (q, *J*=7.3 Hz, 2H), 3.40 (d, *J*=12.1 Hz, 1H), 3.30 (dd, *J*=12.1, 1.4 Hz, 1H), 2.87 (dd, *J*=17.6, 1.4 Hz, 1H), 2.47 (dd, *J*=17.6, 4.8 Hz, 1H), 2.20 (s, 3H), 1.87 (s, 3H), 1.40 (t, *J*=7.3 Hz, 3H). Anal. calcd: C, 46.83; H, 4.55; N, 2.87. Found: C, 46.60; H, 4.33; N, 2.61.

3.8.2. Ethyl (1*S, 2*R**, 4*S**, 5*S**)-1-benzoylamino-4-iodo-4-methyl-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-yl-carbonate (13b).** Mp 166°C (CH_2Cl_2/Et_2O). IR ν_{max} 3300, 1770, 1700, 1650 cm^{-1}; ^1H NMR δ 7.87–7.41 (m, 5H), 7.66 (s, 1H, exch.), 5.20–5.10 (m, 1H), 4.87 (d, *J*=6.2 Hz, 1H), 4.31 (q, *J*=7.3 Hz, 2H), 3.61–3.45 (m, 1H), 3.30 (d, *J*=12.5 Hz, 1H), 2.90 (d, *J*=17.6 Hz, 1H), 2.40 (dd, *J*=17.6, 4.8 Hz, 1H), 2.20 (s, 3H), 1.40 (t, *J*=7.3 Hz, 3H). Anal. calcd: C, 45.68; H, 4.26; N, 2.96. Found: C, 45.40; H, 4.38; N, 3.21.

3.8.3. Ethyl (1*R, 4*S**, 5*R**, 7*R**)-4-benzoylamino-7-iodo-1-methyl-3-oxo-2-oxa-bicyclo[2.2.2]oct-5-yl-carbonate (15).** Mp 169°C (CH_2Cl_2/Et_2O). IR ν_{max} 3350, 1740, 1660 cm^{-1}; ^1H NMR δ 7.82–7.40 (m, 5H), 7.14 (s, 1H, exch), 5.39–5.31 (m, 1H), 4.40–4.30 (m, 1H), 4.30 (q, *J*=7.3 Hz, 2H), 3.53–3.38 (m, 1H), 3.23 (dd, *J*=14.6, 2.2 Hz, 1H), 2.70 (dd, *J*=15.8, 3.3 Hz, 1H), 2.62–2.50 (dq, *J*=15.8, 9.5, 2.6 Hz, 1H), 1.64 (s, 3H), 1.35 (t, *J*=7.3 Hz, 3H). Anal. calcd: C, 45.68; H, 4.26; N, 2.96. Found: C, 45.51; H, 4.30; N, 3.15.

3.9. General procedure for the preparation of compounds 14 and 16

Bu_3SnH (0.27 mL, 1 mmol) was added to a solution of the iodolactone derivative **13** or **15** (1 mmol) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere. The reaction mixture was refluxed for 6 h and, after solvent evaporation, the crude reaction mixture was recrystallized from CH_2Cl_2/*i*-Pr_2O giving pure compound **14** (**14a**: 75%, **14b**: 74%) or **16** (80%).

3.9.1. Ethyl (1*S, 2*R**, 4*R**, 5*S**)-1-benzoylamino-4,5-dimethylcyclohex-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-yl-carbonate (14a).** Mp 123°C (Et_2O). IR ν_{max} 3250, 1780, 1725, 1620 cm^{-1}; ^1H NMR δ 7.85–7.42 (m, 6H), 5.18–5.03 (m, 1H), 4.32 (q, *J*=7.3 Hz, 2H), 3.19 (dd, *J*=11.7, 1.8 Hz, 1H), 2.47 (d, *J*=11.7 Hz, 1H), 2.17–1.60 (m, 3H), 1. 56 (s, 3H), 1.40 (t, *J*=7.3 Hz, 3H), 1.00 (d, *J*=6.2 Hz, 3H). Anal. calcd: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.10; H, 6.38; N, 3.94.

3.9.2. Ethyl (1*S, 2*R**, 4*R**, 5*S**)-1-benzoylamino-4-methylcyclohex-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-yl-carbonate (14b).** Mp 134°C (CH_2Cl_2/*i*Pr_2O). IR ν_{max} 3220, 1780, 1740, 1620 cm^{-1}; ^1H NMR δ 7.84–7.41 (m, 6H), 5.13–5.10 (m, 1H), 4.69 (d, *J*=6.2 Hz, 1H), 4.32 (q, *J*=7.3 Hz, 2H), 3.51–3.39 (m, 1H), 2.44 (d, *J*=11.7 Hz, 1H), 2.22–2.04 (m, 2H), 1.88–1.71 (m, 1H), 1.40 (t, *J*=7.3 Hz, 3H), 1.10 (d, *J*=6.6 Hz, 3H). ^{13}C NMR δ 14.6, 18.4, 31.5, 33.4, 33.9, 64.0, 65.8, 74.5, 80.8, 127.4, 128.9, 132.4, 133.4, 156.8, 166.7, 173.1. Anal. calcd: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.01; H, 6.27; N, 3.82.

3.9.3. Ethyl (1*S, 4*S**, 5*R**)-4-benzoylamino-1-methyl-3-oxo-2-oxa-bicyclo[2.2.2]oct-5-yl-carbonate (16).** Mp 155°C (CH_2Cl_2/*i*Pr_2O). IR ν_{max} 3325, 1740, 1729, 1660 cm^{-1}; ^1H NMR δ 7.84–7.40 (m, 5H), 7.02 (s, 1H, exch.), 5.46 (dt, *J*=9.7, 2.0 Hz, 1H), 4.22 (q, *J*=7.3 Hz, 2H), 3.10–3.00 (m, 1H), 2.58–2.50 (m, 1H), 2.40–2.30 (m, 1H), 2.11–2.05 (m, 2H), 1.97 (dd, *J*=15.3, 2.2 Hz, 1H), 1.49 (s, 3H), 1.32 (t, *J*=7.3 Hz, 3H); ^{13}C NMR δ 14.6, 21.4, 25.3, 31.2, 41.2, 60.3, 65.3, 73.2, 80.5, 127.5, 128.9, 132.1, 134.8, 155.4, 167.4, 171.6. Anal. calcd: C, 62.24; H, 6.09; N, 4.03. Found: C, 63.11; H, 6.13; N, 3.78.

3.10. General procedure for hydrolysis of lactone

Lactone **14** or **16** (1 mmol) was suspended in THF (10 mL). H_2O (0.4 mL) and NaOH (152 mg, 4 mmol) were added and the mixture was stirred at room temperature for 1 h. The water solution was extracted with CH_2Cl_2 (1×10 mL) and then acidified with HCl (10%, Congo red) and extracted with AcOEt (3×10 mL). After drying over Na_2SO_4 and recrystallization pure acid **17** (**17a**: 95%; **17b**: 97%) or **18** (93%) was isolated.

3.10.1. (1*S, 2*R**, 4*R**, 5*S**)-1-Benzoylamino-2,5-dihydroxy-4,5-dimethylcyclohexanecarboxylic acid (17a).** Mp 250°C (CH_2Cl_2). IR ν_{max} 3315, 1705, 1640 cm^{-1}; ^1H NMR (MeOD) δ 7.87–7.44 (m, 5H), 4.35–4.34 (m, 1H), 2.58 (d, *J*=14.4 Hz, 1H), 2.00–1.84 (m, 3H), 1.72–1.63 (m, 1H), 1.23 (s, 3H), 0.97 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 13.2, 27.8, 33.5, 34.7, 41.7, 62.9, 64.7, 70.2, 127.4, 128.5, 131.8, 134.4, 167.6, 176.5. Anal. calcd: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.32; H, 6.60; N, 4.76.

3.10.2. (1*S, 2*R**, 4*R**, 5*S**)-1-Benzoylamino-2,5-dihydroxy-4-methylcyclohexanecarboxylic acid (17b).** Mp 187°C (CH_2Cl_2). IR ν_{max} 3310, 1700, 1630 cm^{-1}; ^1H NMR (MeOD) δ 7.83–7.46 (m, 5H), 4.28 (dd, *J*=6.4, 6.3 Hz, 1H), 3.91–3.86 (m, 1H), 2.67 (d, *J*=13.6 Hz, 1H), 2.40–2.32 (dd, *J*=13.6, 9.0 Hz), 2.17–2.13 (m, 1H), 1.86–1.83 (m, 2H), 1.06 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (MeOD) δ 12.9, 32.1, 32.9, 34.5, 64.2, 67.95, 67.99, 127.2, 128.6, 131.8, 134.9, 169.7, 174.9. Anal. calcd: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.28; H, 6.70; N, 4.51.

3.10.3. (1*S, 2*R**, 4*S**)-1-Benzoylamino-2,4-dihydroxy-4-**

methylcyclohexanecarboxylic acid (18) Mp 105°C dec. (CH_2Cl_2/iPr_2O). IR ν_{max} 3475–3100, 1700, 1690, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.30 (s, 1H, exch.), 7.81–7.20 (m, 5H), 7.20 (s, 1H, exch.), 5.24 (d, J=7.9 Hz, 1H, exch.), 4.24 (s, 1H, exch.), 4.07 (dd, J=11.4, 4.8 Hz, 1H), 2.63 (d, J=13.2 Hz, 1H), 2.21–2.00 (m, 1H), 1.78–1.50 (m, 2H), 1.38–1.21 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 30.9, 33.1, 43.0, 64.4, 68.3, 69.4, 127.1, 128.3, 131.2, 135.1, 167.6, 174.0. Anal. calcd: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.43; H, 8.10; N, 7.22.

3.10.4. (1*S, 2*R**, 4*R**, 5*S**)-1-Amino-2,5-dihydroxy-4,5-dimethylcyclohexanecarboxylic acid (19a).** Compound **19a** was obtained as described for **7a** in 70% yield. Mp 152°C (acetone/Et_2O). IR ν_{max} 3500–3100, 1590 cm^{-1}; ^1H NMR (D_2O/DCl) δ 4.09–4.06 (m, 1H), 2.64 (d, J=12.1 Hz, 1H), 2.20 (dd, J=12.1, 1.9 Hz, 1H), 1.98–1.87 (m, 2H), 1.52–1.46 (m, 1H), 1.43 (s, 3H), 0.82 (d, J=6.6 Hz, 3H). Anal. calcd: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.00; H, 8.67; N, 6.61.

3.10.5. (1*S, 2*R**, 4*R**, 5*S**)-1-Amino-2,5-dihydroxy-4-methylcyclohexanecarboxylic acid (19b).** Compound **19b** was obtained as described for **11b** in 92% yield. Mp 260°C dec. (acetone); IR ν_{max} 3450–3000, 1600 cm^{-1}; ^1H NMR (D_2O) δ 4.72 (d, J=6.3 Hz, 1H), 4.00–3.98 (m, 1H), 2.51 (d, J=11.7 Hz, 1H), 2.37 (ddd, J=11.7, 6.2 Hz, 1.8, 1H), 2.04–1.81 (m, 2H), 1.47–1.31 (m, 1H), 0.81 (d, J=6.6 Hz, 3H); ^{13}C NMR (D_2O) δ 18.3, 30.1, 33.9, 34.5, 62.8, 65.9, 84.0,174.3. Anal. calcd: C, 42.58; H, 7.15; N, 6.21. Found: C, 42.23; H, 7.44; N, 6.00.

3.10.6. (1*S, 2*R**, 4*S**)-1-Amino-2,4-dihydroxy-4-methylcyclohexanecarboxylic acid (20).** Compound **20** was obtained as described for **7a** in 60% yield. Mp 236°C (EtOH); IR ν_{max} 3500–3000, 1595 cm^{-1}; ^1H NMR (D_2O, DCl) δ 4.36 (dd, J=12.1, 5.1 Hz, 1H), 2.30–2.10 (m, 1H), 2.00–1.31 (m, 5H), 1.18 (s, 3H); ^{13}C NMR 2.48, 30.9, 33.1, 43.0, 64.4, 68.3, 69.4, 127.1, 128.3, 131.2, 135.1, 167.6, 174.0. Anal. calcd: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.40; H, 8.22; N, 7.18.

3.11. Oxazination reaction of 6a

Compound **6a** (665 mg, 2.3 mmol) was added to a hot solution (100°C) of HCl (15 mL, 20%) and the mixture was refluxed for 15 min. After cooling, the water solution was extracted with CH_2Cl_2 (3×5 mL). After drying over Na_2SO_4 and recrystallization, the pure lactone **22** (179 mg, 27%) was isolated. The water was concentrated and the pH reaction was adjusted until **5** with a solution of NH_3 (25%). The water solution was extracted with CH_2Cl_2 (3×5 mL). After drying over Na_2SO_4 and recrystallization, the pure oxazine **21** (267 mg, 40%) was isolated.

3.11.1. (1*R, 5*S**, 6*R*, 8*S**)-6-Hydroxy-1,8-dimethylcyclohex-2-oxa-3-phenyl-4-azabicyclo[3.3.1]non-3-ene-5-carboxylic acid (21).** Mp 164°C (H_2O); IR ν_{max} 3600–3000, 1620 cm^{-1}; ^1H NMR (CD_3OD) δ 8.06–7.41 (m, 5H), 4.25 (dd, J=11.3, 4.7 Hz, 1H), 2.12, 1.88 (AB system, J=13.9 Hz, 2H), 1.95–1.80 (m, 2H), 1.45 (s, 3H), 1.19–1.06 (m, 1H), 1.09 (d, J=6.7 Hz, 3H). Anal. calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.19; H, 6.87; N, 4.69. m/z 289 (M^+).

3.11.2. (1*S, 2*R**, 4*R**, 5*S**)-*N*-(2-Hydroxy-4,5-dimethyl-7-oxo-6-oxabicyclo[3.2.1]oct-1-yl)-benzamide (22a).** Mp 250°C (CH_2Cl_2); IR ν_{max} 3300–3150, 1775, 1625 cm^{-1}; ^1H NMR δ 8.14–7.46 (m, 5H), 7.22 (s, 1H, exch.), 4.19–4.17 (m, 1H), 3.46 (d, J=11.4 Hz, 1H), 2.35–2.13 (m, 1H), 2.08 (dd, J=11.4, 1.6 Hz, 1H), 2.00 (dq, J=15.0, 5.6, 1.7 Hz, 1H), 1.53 (s, 3H), 1.41 (dq, J=15.0, 11.5, 3.7 Hz, 1H), 1.00 (d, J=6.2 Hz, 3H); ^1H NMR (CD_3OD) δ 8.06–7.44 (m, 6H), 4.10–4.05 (m, 1H), 2.88 (dd, J=11.0, 1.5 Hz, 1H), 2.56 (d, J=11.2 Hz, 1H), 2.35–1.88 (m, 2H), 1.52 (s, 3H), 0.97 (d, J=6.6 Hz, 3H); ^{13}C NMR δ 15.1, 22.7, 33.0, 37.0, 43.1, 67.0, 71.7, 88.3, 127.4, 128.5, 128.9, 169.8, 175.0. Anal. calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.21; H, 6.84; N, 4.73.

3.11.3. (1*S, 2*R**, 4*R**, 5*S**)-*N*-(2-Hydroxy-4,5-dimethyl-7-oxo-6-oxabicyclo[3.2.1]oct-1-yl)-benzamide (22b).** Mp 187°C (CH_2Cl_2); IR ν_{max} 3300–3200, 1770, 1620 cm^{-1}; ^1H NMR (CD_3OD) δ 7.86–7.48 (m, 6H), 4.65 (d, J=6.4 Hz, 1H), 4.06–4.04 (m, 1H), 3.14 (ddd, J=11.1, 6.6, 1.7 Hz, 1H), 2.51 (d, J=11.1 Hz, 1H), 2.25–1.88 (m, 2H), 157–1.51 (m, 1H), 1.03 (d, J=6.8 Hz, 3H). Anal. calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.21; H, 6.84; N, 4.73.

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References

1. Clerici, F.; Gelmi, M. L.; Pocar, D. *J. Org. Chem.* **1999**, *64*, 726–730.
2. Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**, *64*, 5764–5767 (and references therein).
3. Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2000**, *65*, 6138–6141.
4. (a) Toniolo, C. *Jansen Chim. Acta* **1993**, *11*, 10–16. (b) Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, *36*, 625–628. (c) Bisang, C.; Weber, C.; Inglis, J.; Schiffe, C. A.; van Gunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904–7915. (d) Dubuisson, C.; Fukumoto, Y.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3697–3704. (e) Avenoza, A.; Busto, J. H.; Paris, M.; Peregrina, J. M.; Cativiela, C. *J. Heterocycl. Chem.* **1997**, *34*, 1099–1111 (and references therein). (f) Hanessian, S.; McNaugton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *38*, 12789–12854. (g) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050–2056. (h) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
5. (a) Tellier, F.; Acher, F.; Brabet, I.; Pin, J.-P.; Azerad, R. *Biorg. Med. Chem.* **1998**, *6*, 195–208. (b) Charette, A. B.; Coté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721–12732. (c) Buñuel, E.; Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1521–1528. (d) Mickos, H.; Sundberg, K.; Lüning, B. *Acta Chim. Scand.* **1992**, *46*, 989–993.

6. Hammer, K.; Wang, J.; Falck-Pedersen, M. L.; Romming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1691–1695.
7. Zen, S.; Takedo, Y.; Yasuda, A.; Umezawa, S. *Bull. Soc. Chem. Jpn* **1967**, *40*, 431.
8. (a) Yamada, S.; Achiwa, K. *Chem. Pharm. Bull.* **1966**, *14*, 537. (b) Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1964**, *12*, 1525.
9. Fairbanks, A. J.; Hui, A.; Skead, B. M.; Lilley, P. M.; de, Q.; Lamont, R. B.; Storer, R.; Saunders, J.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *47*, 8891–8894.
10. Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187–1189.
11. (a) Kuivila, H. G. *Synthesis* **1970**, 499. (b) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932–933. (c) Avenoza, A.; Cativiela, C.; Peregrina, J. M. *Tetrahedron* **1994**, *33*, 10021–10028.
12. Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171–197.
13. Meyer, A. I.; Nabeya, A.; Adiknes, H. W.; Politzer, I. R.; Malone, G. R.; Kovalesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36–56.