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Article

Reductive Decarboxylation of Bicyclic Prolinic Systems. A New Approach to the Enantioselective Synthesis of the Geissman-Waiss Lactone. X-ray Structure Determination of a Key Lactone Intermediate

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Duas sínteses do conhecido precursor de bases necínicas, (1*R*,5*R*)-*N*-Cbz e *N*-Boc 2-oxa-6-azabiciclo[3.3.0]octan-3-onas (lactonas de Geissman-Waiss) foram realizadas com rendimentos globais de 23% e 26%, em seis e cinco etapas respectivamente, a partir de enecarbamatos endocíclicos de cinco membros enantiomericamente puros. A estratégia sintética adotada está fundamentada em uma reação de cicloadição [2+2] eficiente e altamente estereosseletiva de enecarbamatos de cinco membros com diclorocetenos, assim como em uma eficaz descarboxilação de α-amino ácidos bicíclicos pelo método de Boger, que utiliza a redução de selenetos de acila por hidretos de estanho. Aspectos relativos a regiosseletividade da reação de oxidação de azabiciclo ciclobutanonas pelo método de Baeyer-Villiger são também descritos, com destaque para um potencial controle regioquímico advindo de aspectos estéreos em contraposição a aspectos estereoeletrônicos.

Two concise and enantioselective syntheses of the necine base precursors (1*R*,5*R*)-*N*-Cbz and *N*-Boc-2-oxa-6-azabicyclo[3.3.0]octan-3-ones (Geissman-Waiss lactones) were carried out from two enantiomerically pure endocyclic five-membered enecarbamates with overall yields of 23% and 26%, respectively. The synthetic strategy made use of a highly effective and stereoselective [2+2]cycloaddition of enantiomerically pure endocyclic enecarbamates with dichloroketene, as well as an efficient decarboxylation step of a bicyclic α-amino acid employing Boger's acyl selenide protocol employing tributyltin hydride. Interesting aspects concerning the regiochemical outcome of Baeyer-Villiger oxidations of bicyclic cyclobutanones are also reported, in which the usual stereoelectronic bias of Baeyer-Villiger oxidation seems to be counterbalanced by steric effects on the putative Criegee intermediate.

Keywords: Geissman-Waiss lactone, [2+2]cycloadditions, decarboxylation, pyrrolizidine alkaloids

Introduction

Pyrrolizidine alkaloids (PAs) are a large family of natural products bearing a azabicyclic[3.3.0]heptane structural core, the necine base, esterified to a diversity of mono and dicarboxylic acids (Figure 1).[1] PAs possess quite interesting biological and pharmacological activities and have been the subject of much attention among chemists and biologists.[1] Of the several strategies devised to prepare PAs or the necine bases, the ones relying on the key 2-oxa-6-azabicyclo[3.3.0]octan-3-one (Geissman-Waiss lactone or GWL) have been extensively used since it allows easy access to saturated, unsaturated and polyhydroxylated necine bases such as platynecine, retronecine and

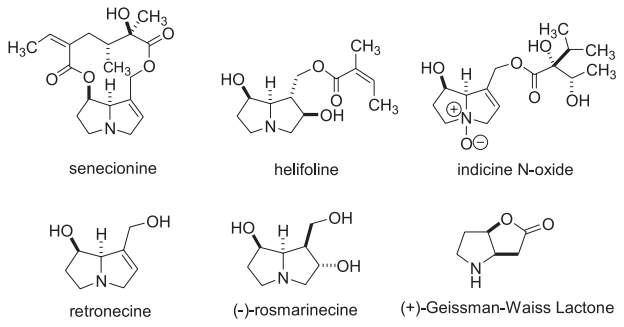

Figure 1. Examples of pyroolizidine alkaloids, necine bases and the structure of the GWL.

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croalbinecine.[2] In view of the pivotal role of the Geissman-Waiss lactone in necine base synthesis, considerable efforts have been put forward to devise efficient strategies directed towards its synthesis, mainly to the stereoisomer possessing the (1*R*, 5*R*) stereocenters, for this allows the enantioselective construction of the natural necine bases.[3]

In previous work we described the synthesis of the (±)-Geissman-Waiss lactone from a five-membered endocyclic enecarbamate in only four steps using a then novel approach involving the [2+2]cycloaddition of enecarbamates to dichloroketenes.[3] More recently, we succeeded in preparing new enantiomerically pure endocyclic enecarbamates aiming at the synthesis of several pyrrolidine containing natural products.[4]

In principle, to make such strategies amenable to the synthesis of enantiomerically pure *N*-heterocycles a removable stereodirecting element could be added to the endocyclic enecarbamate and removed efficiently later on. Although synthetic strategies bearing this fundamental concept are already described in the literature,[5] it remained to be tested for the synthesis of enantiomerically pure *N*-heterocycles from endocyclic enecarbamates. Application of such a strategy to endocyclic enecarbamates could lead to the construction of several enantiomerically pure *N*-heterocycles (Figure 2). One of our first objectives envisaged testing the feasibility of this strategy for the (1*R*,5*R*)-Geissman-Waiss lactone, in view of its pivotal role in necine base synthesis and its rather simple structure.

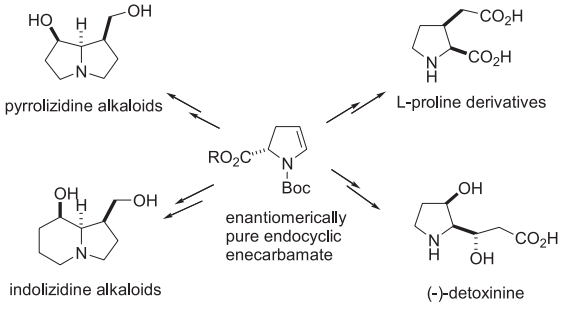
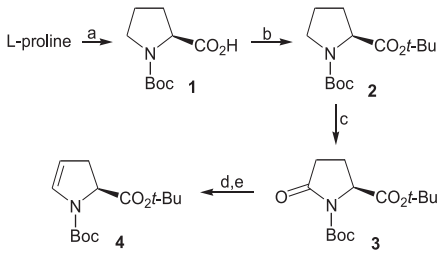


Figure 2. Natural an unnatural compouds obtained from endocyclic enecarbamates.

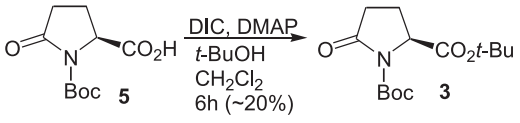
Results and Discussion

The enantioselective synthesis of the (1*R*,5*R*)-Geissman-Waiss lactone started with the preparation of the enantiomerically pure enecarbamate **4** from L-proline. The synthesis proceeded in a good overall yield (41%), as indicated in Scheme 1, employing previously developed methodology.[4] A five-step synthesis was necessary to prepare the enecarbamate **4** instead of an originally planned four-step synthesis starting from L-pyroglutamic acid. This was due to the low yield obtained when preparing the *tert*-butylester **3** from the pyroglutamic intermediate **5** (maximum yield of 20% under the conditions shown in equation 1). Although one step longer, the route described in Scheme 1 is very efficient and permitted the synthesis of enecarbamate **4** on a multigram scale. The *tert*-butyl group was installed on the carboxyl group to induce the best possible stereoselectivity in the critical [2+2]cycloaddition process in view of its bulk.



a: $(Boc)_2O$, 1N Na_2CO_3, dioxane, 0°C to rt, 30 min (98%);
b: DIC, DMAP, *t*-Butanol, CH_2Cl_2, 0°C to rt, 3h (75%);
c: $RuCl_3$ (10 mol%), $NaIO_4$, EtOAc, rt, 2h (83%); **d:** DIBAL-H, THF, -78°C, 1.5h; **e:** $(CF_3CO_2)_2O$, 2,6-lutidine, 0°C to rt, then reflux for 2.5h (68% over two steps)

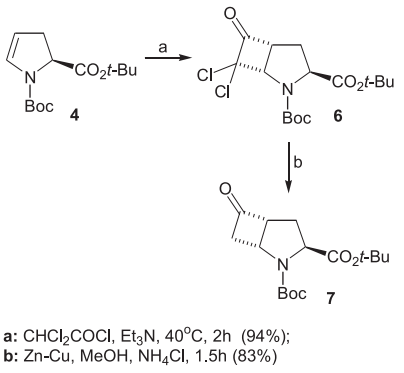
Scheme 1. Synthesis of enecarbamate **4** from L-proline.



(1)

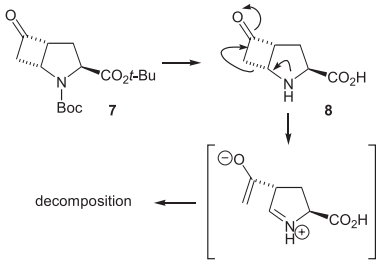
[2+2]Cycloaddition of enecarbamate **4** with dichloroketene (generated *in situ* from dichloro acetylchloride and triethylamine) occurred smoothly to provide the desired dichlorocyclobutanone **6** in 94% isolated yield with very high diastereoselectivity.[6] Cyclobutanone **6** was obtained as a single stereoisomer. Reductive dechlorination proceeded cleanly with Zn/Cu alloy in the presence of ammonium chloride[7] to provide the corresponding azabicyclic cyclobutanone **7** in 83% yield. Although not strictly necessary at this stage, the reductive dechlorination gave a more manageable intermediate (the dichlorocyclobutanone spreads on a TLC plate and is difficult to stain).

The next step in the synthesis called for a free carboxylic acid for the decarboxylation step. Attempts to selectively hydrolyze the *tert*-butyl ester **6** using acetic acid or formic acid failed, as well as attempts to obtain the free amino acid using trifluoroacetic acid in presence of triethylsilane (to capture the *t*-butyl cation).[8] It is



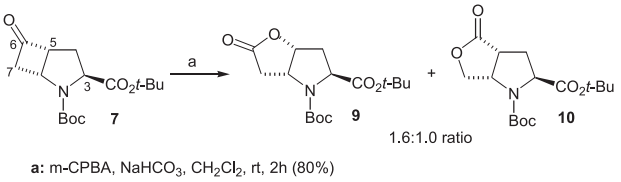
Scheme 2. Preparation of azabicyclo cyclobutanone **7**.

conceivable that this failure might be related to a partial retro [2+2]cycloaddition of the cyclobutanone ring of the amino acid intermediate **8** thus generating an unstable and very reactive enol-iminium intermediate that leads to several unidentified products (Scheme 3).



Scheme 3. Cyclobutanone opening leading to the enol-iminium.

In view of the difficulties in preparing the carboxylic acid, we proceeded to the lactone stage, hoping in this way to circumvent the unexpected cyclobutanone ring opening problem. As anticipated, Baeyer-Villiger oxidation of azabicyclic cyclobutanone **7** employing m-CPBA occurred with good yield (80%), but with a surprising lower regioselectivity (**9**:**10**, 1.6:1 ratio).[9] This low regioselectivity for the Baeyer-Villiger reaction was even more surprising in view of our own previous results with similar systems,[3] as well as some literature precedents, since it is well-documented that oxygen insertion occurs predominantly at the more nucleophilic C-C bond of bicyclic systems (corresponding to C5-C6 in our azabicyclic cyclobutanone **7**).[9] As shown later on, the presence of the ester group at C3 seems to strongly influence the regioselectivity of the ring expansion. We hypothesize that the stereoelectronic factors controlling the regioselectivity are somehow counterbalanced by steric factors decreasing migration of the more substituted C5 carbon.[10]



Scheme 4. Baeyer-Villiger oxidation of cyclobutanone **7**.

In spite of the low regioselectivity of the Baeyer-Villiger step, the regioisomeric lactones **9** and **10** could be easily separated by flash chromatography (50% isolated yield for the major lactone **9**), thus providing another opportunity to test the decarboxylation reaction at the lactone stage. Full characterization of the abnormal Baeyer-Villiger product **10** was facilitated by the fact that the minor regioisomeric lactone formed monocrystals, which permitted its structure determination by X-ray diffraction (Figure 3).

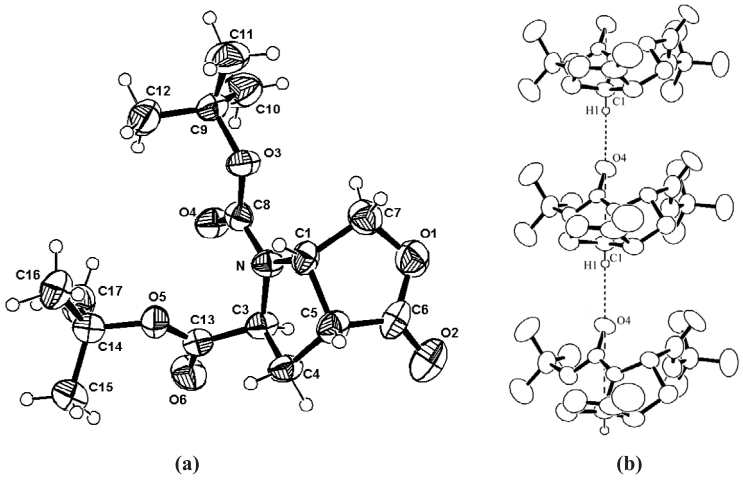
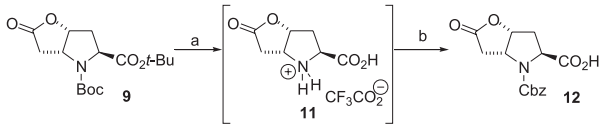


Figure 3. (a) ORTEP representation (40% of probability) of the compound 10. (b) Molecule pile in the crystal packing. The dashed line indicates the non conventional hydrogen bond.

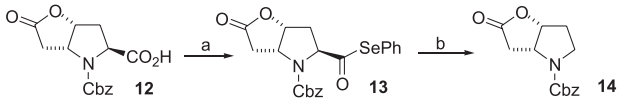
The protecting groups on the major bicyclic lactone **9** were then removed with trifluoroacetic acid/triethylsilane[8] to give a trifluoroacetate salt **11.** This compound was used without further purification in the next step where the amino group of **11** was protected as a carbobenzyloxy group using benzylchloroformate under the conditions described in Scheme 5, providing the interesting lactone amino acid **12** as a stable compound.



a: TFA, Et_3SiH, CH_2Cl_2, 0°C to rt, 45min; **b:**Cbz-Cl, Na_2CO_3, rt, 1h

Scheme 5. Removal of the protecting group on lactone **9**.

Amino acid **12** was obtained as an almost pure compound. Therefore, for practical reasons it was directly used in the decarboxylation step, employing Boger's protocol.[11] Following this procedure, acid **12** was reacted with isobutyl chloroformate to give a putative mixed anhydride, which was further reacted with sodium phenylselenide (from the reduction of Ph_2Se_2 with $NaBH_4$) to give a rather stable acyl selenide **13**. The acyl selenide was immediately reduced with *n*-tributyltin hydride/AIBN in benzene at reflux to provide the desired *N*-Cbz Geissman-Waiss lactone **14** in an good overall yield of 60% from the protected bicyclic lactone **9**, over four steps.

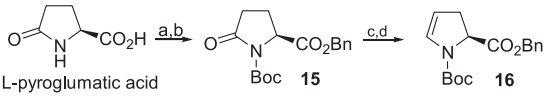


a: i) $ClCO_2CH_2CH(CH_3)_2$, *N*-methylmorpholine, -10 °C to rt; ii): PhSeNa;
b: Bu_3SnH, AIBN, benzene, reflux, 3h (60% overall yield from **9**)

Scheme 6. Decarboxylation of carboxylic acid **12** under Boger's protocol.

Overall, the results presented above demonstrated the feasibility of the decarboxylation strategy. The (-)-(1*R*,5*R*)-*N*-Cbz-Geissman-Waiss lactone **14** was obtained from the endocyclic enecarbamate **4** in six steps with an overall yield of 23%. More importantly, these initial results also indicated that a flexible route to necine bases, the Geissman-Waiss lactone and other *N*-heterocycles could be devised in case the decarboxylation step could be performed with an intermediate cyclobutanone. A synthetic plan having the decarboxylation step prior to Baeyer-Villiger ring expansion could overcome the critical low regioselectivity obtained in the transformation of cyclobutanone **7** into lactone **9**.[12] The hypothesis underlying this approach was the perception that the carboalkoxyl group at C3 in cyclobutanone **9** was influencing the regiochemical outcome of the Baeyer-Villiger oxidation. Therefore, a second generation route to the (1*R*,5*R*)-Geissman-Waiss lactone was devised and pursued.

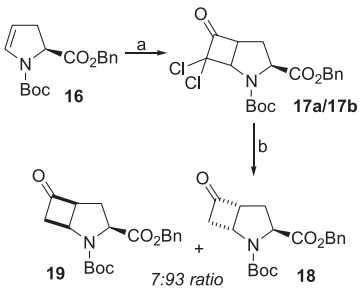
In this second-generation approach to the (1*R*,5*R*)-Geissman-Waiss lactone a new five-membered endocyclic enecarbamate was constructed. The synthesis plan called for orthogonal protection at the nitrogen and carboxylic acid functions of pyroglutamic acid. Enecarbamate **16** displays these synthetic requirements and was efficiently prepared as described in Scheme 7.



a: $SOCl_2$, BnOH, rt, 72h (67%); **b:** $(Boc)_2O$, DMAP, CH_3CN, 40 min (100%); **c:** DIBAL-H, THF, -78°C, 1.5 h; **d:** TFAA, 2,6-lutidine, toluene, 2h, then reflux for 30 min (76% over two steps)

Scheme 7. Preparation of endocyclic enecarbamate **16**.

The first step in this new route also produced an interesting result. In carrying out the [2+2]cycloaddition of enecarbamate **16** with dichloroketene, a significant decrease in the facial diastereoselectivity was noticed (Scheme 8). The presence of diastereomers at the cycloaddition step was not clear at first, since chromatographic separation and analyses of the dichlorocyclobutanones **17a/b** by TLC, capillary GC or HPLC was not possible. Fortunately, dechlorination of the dichlorocyclobutanones **17a/b** with Zn-Cu provided a separable mixture of azabicyclic cyclobutanones **18** and **19** in 81% yield in a ratio of 93:07. The lower stereoselectivity for the [2+2]cycloaddition was credited to the less bulky nature of the benzyl ester group at C5 of enecarbamate **16** when compared to the *tert*-butyl ester present in enecarbamate **4**.



a: $CHCl_2COCl$, Et_3N, 40 °C, 2h (95%);
b: Zn-Cu, MeOH, NH_4Cl, 1.5 h (81%)

Scheme 8. Synthesis of cyclobutanones **18** and **19**.

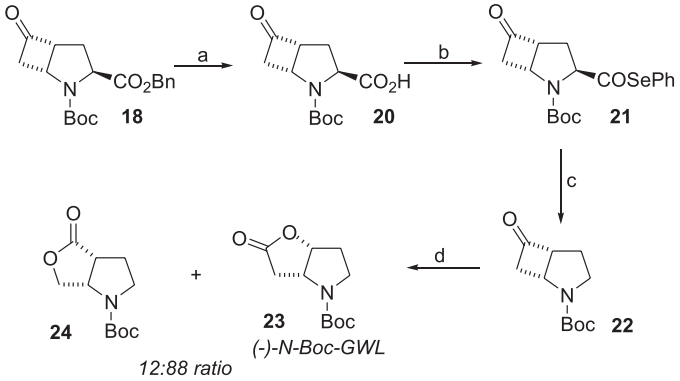
The major cyclobutanone **18** then underwent hydrogenolysis (Scheme 9) to cleanly provide the carboxylic acid derivative **20**. With this intermediate in hand we were, once again, at the position of performing the decarboxylation reaction in order to prepare the desired bicyclic cyclobutanone **22** in enantiomerically pure form.

The decarboxylation procedure was conducted as described in Scheme 6, without purification of the intermediates. Gratifyingly, this three-step procedure furnished the desired bicyclic cyclobutanone **22** in an overall yield of 49% from the benzyl ester **18**. Finally, Baeyer-Villiger oxidation of the bicyclic cyclobutanone **22** provided, as anticipated, the (-)-*N*-Boc Geissman-Waiss lactone as the major regioisomer (7:1 ratio), thus confirming the greater tendency for oxygen insertion at the bridgehead C5-C6 bond in the absence of substituents at C3 on the 2-azabicyclo[3.2.0]heptan-6-one system. The spectroscopic data of the (-)-(1*R*,5*R*)-*N*-Boc Geissman-Waiss lactone was identical in all respects to those reported in the literature.[3]

This second-generation synthesis of the protected Geissman-Waiss lactone was accomplished in only 5 steps with an overall yield of 26% from the endocyclic enecarbamate **16**. Compared to the first-generation synthesis, this new route is shorter (5 steps against 6 steps), but the overall yield was only slightly better than that of the first generation synthesis (23% overall yield). The main reason for this difference in yields is due to the lower overall yield obtained for the decarboxylation sequence when applied to the intermediate carboxylic acid **20** (49% overall yield against 60% overall yield from the carboxylic ester **9**). However, it should be mentioned that the decarboxylation sequence applied to acid **20** leaves room for further improvements.

Experimental

Unless noted otherwise, all reactions were carried out under atmospheres of dry nitrogen or argon, in oven-dried glassware. Methylene chloride, triethylamine, 2,6-lutidine, cyclohexane, and diisopropylamine were distilled from CaH_2 and, except for methylene chloride, were stored over 4 Å molecular sieves. Tetrahydrofuran was distilled from sodium/benzophenone ketyl prior to use. Benzene was distilled from metallic sodium or potassium and stored over 4Å molecular sieves. Trifluoroacetic anhydride was distilled from P_2O_5. Dichloroacetyl chloride and *N*-methylmorpholine were previously distilled and stored under argon prior to use. Commercial BuLi hexane solution was titrated with *N*-pivaloyl-*o*-toluidine. All other reagents were purchased from traditional commercial sources and used without further manipulations. Flash column chromatography was performed employing Merck silica gel 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel 60/F-254 aluminum-backed plates, and visualized by UV light and/or phosphomolybdic acid. Analytical high-performance liquid chromatography was carried out on a Varian 9010 or HP 1100 series chromatograph equipped with a refractive index detector. Chiral phase HPLC was performed employing a Chiracel OD column (250 mm x 4.6 mm) from Diacel Chemical Industries. Capillary GLC analyses were performed on a Hewlett-Packard 6890 chromatography equipped with fused-silica capillary column (30 m x 0.32 mm) wall coated with HP-5. Chiral phase GLC analyses were performed employing a Chrompack WCOT Fused Silica (25m x 0.32mm) column coated with CP-Chirasil-Dex CB. Melting points were measured on a Thomas Hoover capillary melting



a: $Pd(OH)_2$, H_2, MeOH, rt, 45 min; (95%); **b:** (i) isobutylchloroformate, *N*-methylmorpholine, THF, -20 °C (15 min) then at rt for 30 min and back to -20 °C, (ii) PhSeNa, THF/t-BuOH, -20 °C for 30 min then to rt for 30 min; **c:** Bu_3SnH (3 equiv), AIBN (0.2 equiv), benzene, reflux, 30 min (49% over the last two steps involving three operations); **d:** H_2O_2, AcOH, 4 °C, 3 h (80% for **23**)

Scheme 9. Completion of the synthesis of the (-)-*N*-Boc-GWL.

point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded as solutions in the indicated solvents on Varian Gemini 300, Brucker AC-300P or Brucker AW-80 spectrometers. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane or $CDCl_3$ (residual $CHCl_3$) as internal standards (^{1}H NMR). When CCl_4 was used as solvent a capillary containing D_2O was used as internal standard. Infrared spectra were recorded on Perkin-Elmer 399B, Perkin-Elmer 1600 (FTIR) or Nicolet Impact 410 spectrometers. Low-resolution GC-MS was obtained on a Shimadzu QP5000, equipped with a HP-1 column (20m x 0.20mm) and high resolution mass spectra on a VG Autospec Instrument. Optical rotations were measured on a Carl Zeiss Polamat A (mercury lamp at 546 nm) and corrected to the sodium D line at 589 nm. Elemental analyses were performed on a Perkin Elmer 2400 series II CHNS/O analyzer. All measurements were carried out at the Chemistry Institute of the Universidade Estadual de Campinas.

The crystal data were collected using a turbo CAD4 diffractometer at the Instituto de Química de São Carlos, Universidade de São Paulo.

Abbreviations used in this work

AIBN = 2,2'-azobisisobutyronitrile; Ac = acetyl; Boc = *tert*-butoxycarbonyl; DIC = diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; DIBAL-H = diisobutylaluminum hydride; *t*-BuOH = *tert*-butanol; *m*-CPBA = 3-chloroperoxybenzoic acid; TFA = trifluoroacetic acid; Cbz-Cl = benzylchloroformate; BnOH = benzylic alcohol; $(Boc)_2O$ = bis-*tert*-butoxycarbonyl carbonate; TFAA = trifluoroacetic acid anhydride;

*Synthesis of the 2-oxo-N-(tert-butoxycarbonyl)-L-proline tert-butyl ester (***3***)*[13]

1.64 g (6.1 mmol) of the L-proline *tert*-butyl ester **2** were dissolved in 21 mL of ethyl acetate. To the flask was added 61 mL of a 10% $NaIO_4$ solution (6.11 g of $NaIO_4$ in 61 mL of water). The biphasic mixture was cooled with an ice/water bath and 0.21 g of $RuCl_3$ was added. The bath was removed and the reaction stirred at room temperature for 3 h. After the starting material had reacted completely (TLC analysis) the biphasic mixture was transferred to a separation funnel and the aqueous phase discarded. The organic layer was washed with a saturated solution of sodium thiosulfate and the procedure repeated until the organic layer became colorless. The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The yellowish oil was purified by flash chromatography (30% ethyl acetate in hexane) yielding 1.44 g of a colorless oil (83% yield) corresponding to the lactam **3**. R*f*: 0.5 (Hex/EtOAc 30%); IR ν_{max}/cm^{-1}: 2979, 2933, 1795, 1739, 1716, 1369, 1313, 1155, 1022, 843, 755 (film); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47-1.49 (s, 18H), 1.92-2.08 (1H, m), 2.15-2.65 (3H, m), 4.46 (1H, dd, ^3J 2.6 and 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_2), 28.0 (6 CH_3), 31.0 (CH_2), 59.7 (CH), 82.1 (C), 83.2 (C), 149.2 (C=O), 170.4 (C=O), 173.5 (C=O); EIMS (70 eV) *m/z*: 57(100%), 84, 129, 184, 214, 230, 285(M^+); HRMS (EI) : Calcd for $C_{14}H_{23}NO_5$: 285.25763; Found: 285.26746.

*Synthesis of the N-(tert-butoxycarbonyl)-4,5-dehydro-L-proline tert-butyl ester (***4***)*

To a solution of 300 mg (1.05 mmol) of lactam **3** in 5 mL of dry THF at –78 °C were added 1.1 mL of a 1 mol L^{-1} solution of DIBAL-H in toluene (1.1 mmol). After complete consumption of the starting material (TLC analysis, after 1.5 h), 5 mL of a saturated solution of potassium sodium tartrate tetrahydrate (Rochelle salt) were added, and the biphasic mixture was stirred for 1 h at room temperature. The mixture was then transferred to a separation funnel and the aqueous phase discarded. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The oil obtained, corresponding to the diastereomeric mixture of hemiaminals, was characterized by IR, which indicated complete reduction of the lactam function. The product was used in the next step without further purification.

The crude diastereomeric mixture of hemiaminals was dissolved in dry toluene under nitrogen. The reaction was cooled in an ice/water bath followed by addition of 0.63 mL of 2,6-lutidine (5.4 mmol, 5.0 equiv) and 0.9 mL of a 1.2 mol L^{-1} solution of trifluoroacetic acid in toluene (1.1 mmol, 1.0 equiv). The ice/water bath was removed and the reaction mixture was stirred at rt for 3 h. Once TLC analysis indicated complete consumption of the starting hemiaminal a reflux condenser was adapted to the round bottom flask and the reaction mixture was heated to reflux (110 °C) for 30 min. The solution was then transferred to a separation funnel and was washed twice with water and a saturated solution of $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The oil obtained was purified by flash chromatography (8% ethyl acetate in hexane) leading to 192 mg of enecarbamate **4** as a colorless oil (68% yield over two steps). R*f*: 0.40 (Hex/EtOAc 10%); $[\alpha]_D^{20}$ = -55.0 (*c* 3.5, EtOAc); IR ν_{max}/cm^{-1}: 2976, 2933, 1749, 1709, 1624, 1394, 1367. 1176, 1139, 754, 698 (film); ^{1}H NMR (300

MHz, $CDCl_3$), with duplicated signals due to rotamers: δ 1.38-1.51 (3s, 18H), 2.55 (m, 1H), 2.98 (m, 1H), 4.38 (dt, ^3J 5.0 and 11.0 Hz, 1H), 4.79 (m, 1H), 6.41-6.58 (2bd, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), with duplicated signals due to rotamers: δ 27.9/28.2 (6 CH_3), 33.9/35.4 (CH_2), 58.1/58.3 (CH), 79.4/80.0 (C), 103.1/103.6 (C), 130.3/130.8 (CH), 150.1/150.2 (C=O), 169.3/169.6 (C=O); EIMS (70 eV) *m/z*: 57, 91(100%), 114, 142 158, 176, 204, 220, 249, 269 (M^+); HRMS (EI): Calcd for $C_{14}H_{23}NO_4$: 269.16271; Found: 269.15693.

*Synthesis of the N-(tert-butoxycarbonyl)-7,7-dichloro-3-tert-butoxy-carbonyl-2-azabicyclo[3.2.0]heptan-6-one (**6**)*

To a solution of enecarbamate **4** (330 mg, 1.22 mmol) and Et_3N (0.34 mL, 2.44 mmol) in 17 mL of cyclohexane at 40 °C was slowly added a cyclohexane solution of dichloroacetyl chloride (0.17 mL, 1.6 mmol, dissolved in 9 mL of cyclohexane) using a syringe pump over a period of 2 h. After addition of the dichloroacetyl chloride was complete the reaction mixture was stirred for an additional 20 min. The reaction mixture was then cooled to rt and filtered through Celite® to remove the triethylammonium chloride salt formed in the reaction. The filtrate was rotaevaporated to give a brown-colored oil. Flash chromatography (Hex/EtOAc, 4:1) provided 436 mg of a slightly yellow oil (96% yield) corresponding to the dichlorocyclobutanone **6** as a homogeneous material by TLC. R*f*: 0.30 (Hex/EtOAc 20%); $[\alpha]_D^{20}$ = -118.7 (*c* 2.5 EtOAc); IR ν_{max}/cm^{-1}: 2979, 2933, 1813, 1739, 1714, 1369, 1253, 1223, 1153, 843, 775 (film); ^{1}H NMR (300 MHz, $CDCl_3$): duplicated signals due to rotamers δ 1.47-1.52 (2s, 18H), 2.17-2.28 (m, 1H), 2.59-2.70 (m, 1H), 4.05-4.20 (m, 1H), 4.34-4.43 (m, 1H), [4.81(d, ^3J 8.0 Hz) + 4.95 (d, ^3J 8.0 Hz), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$): duplicated signals due to rotamers δ 27.8/28.0 (6 CH_3), 30.7/31.6 (CH_2), 57.1/58.5 (CH), 62.4/62.5 (CH), 82.0 (C), 82.3/82.5 (C), 88.4 (C), 153.4/153.9 (C=O), 170.2/170.4 (C=O), 194.9 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 113, 140, 178, 223, 279, 325, 379(M^+); HRMS (EI): Calcd for $C_{16}H_{23}Cl_2NO_5$: 379.09533; Found: 379.09833.

*Synthesis of the N-(tert-butoxycarbonyl)-3-tert-butoxy-carbonyl-2-azabicyclo[3.2.0] heptan-6-one (**7**)*

A solution of dichlorocyclobutanone **6** (185 mg, 0.48 mmol) in 12 mL of methanol (previously saturated with ammonium chloride) was bubbled with dry argon for 30 min to remove traces of oxygen. To this oxygen-free solution was then added 0.34 g of a previously prepared Zn/Cu alloy. The resulting suspension was stirred for 3 h at rt, until TLC indicated complete consumption of the starting dichlorocyclobutanone **6**. The methanol was removed *in vacuo*, and the residue extracted with EtOAc. The ethyl acetate suspension was filtered through Celite® and the filtrate was rotaevaporated to give a colorless oil. Flash chromatography (30% EtOAc in hexane) provided 125 mg (83% yield) of a crystalline white solid corresponding to cyclobutanone **7**. mp 65-68 °C; R*f*: 0.35 (Hex/EtOAc 30%); $[\alpha]_D^{20}$ = -170.0 (*c* 2.8 em EtOAc); IR ν_{max}/cm^{-1}: 2976, 2933, 1790, 1743, 1705, 1385, 1194, 1136, 1028, 960, 856, 773 (film); ^{1}H NMR (300 MHz, $CDCl_3$): duplicated signals due to rotamers δ 1.45-1.47 (s, 18H), [2.01 (dd, ^3J 5.0 and 11.0 Hz) + 2.08 (dd, ^3J 5.0 and 11.0 Hz) 1H], 2.51-2.64 (m, 1H), 2.92-3.06 (m, 1H), 3.26-3.38 (m, 1H), 3.81-3.82 (m, 1H), [4.35 (dd, ^3J 3.7 and 8.8 Hz) + 4.43 (dd, ^3J 3.7 and 8.8 Hz), 1H], [4.50 (td, ^3J 2.9 and 7.3 Hz) and 4.58 (td, ^3J 2.9 and 7.3 Hz), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 27.9/28.3 (6 CH_3), 29.9 (CH_2), 49.6/50.2 (CH), 53.2/53.5(CH_2), 61.2 (CH), 62.3/62.6 (CH), 80.5/80.8 (C), 81.6 (C), 154.0 (C=O), 171.3/171.5 (C=O), 208.1/208.3 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 83, 113, 154, 211, 228, 269, 311 (M^+); HRMS (EI): Calcd for $C_{16}H_{25}NO_5$: 311.17327; Found: 311.17271.

*Synthesis of the γ-lactones **9** and **10***

Procedure A: To a solution of cyclobutanone **7** (226 mg, 0.73 mmol) in 5 mL of dichloromethane were added 122 mg of $NaHCO_3$ (1.54 mmol) and the mixture was cooled in an ice-bath. Next, *m*-CPBA (360 mg, 1.54 mmol) was added, the ice-bath was removed and the reaction mixture was stirred at rt for 2.5 h. After this period, the reaction mixture was transferred to a separatory funnel and washed with saturated Na_2SO_3 and saturated $NaHCO_3$ solutions. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give a solid material. Flash chromatography (40% EtOAc in hexane) provided 120 mg of γ-lactone **9** and 72 mg of γ-lactone **10** (combined yield of 81%).

Procedure B: To a solution of cyclobutanone **7** (80 mg, 0.26 mmol) in 2 mL of acetic acid, at 0 °C, were added 0.25 mL of H_2O_2 (30 wt % in H_2O, 75 mg of H_2O_2). The ice-bath was then removed and the reaction mixture was stirred at rt for 3 h. After this period, the reaction mixture was transferred to a separatory funnel and washed with water and saturated $NaHCO_3$. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give a solid material. Flash chromatography (40% EtOAc in hexane) provided 47 mg

of γ-lactone **9** and 28 mg of γ-lactone **10** (combined yield of 90%).

Major compound **9**: mp 159-161°C; R*f*: 0.40 (Hex/EtOAc 40%); $[\alpha]_D^{20}$ = - 85.0 (*c* 1.4 EtOAc); IR ν_{max}/cm^{-1}: 2978, 2933, 1790, 1738, 1699, 1392, 1367, 1161, 1070, 847, 773 (film); ^{1}H NMR (300 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 1.44-1.48 (s, 18H); [2.23 (t, ^3J 5.9 Hz) + 2.28 (t, ^3J 5.9 Hz), 1H], 2.55-2.64 (m, 1H), 2.80-2.88 (m, 1H), [3.03 (d, ^3J 2.2 Hz) and 3.09 (d, ^3J 2.2 Hz), 1H], 4.30-4.37 (m, 1H), 4.54-4.62 (m, 1H), 4.99-5.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 27.8/28.2 (6 CH_3), 34.7/35.5 (CH_2), 35.7/36.7 (CH_2), 58.3/58.9 (CH), 59.6/59.8 (CH), 81.1/81.3 (CH), 82.0/82.2 (C), 153.7/154.0 (C=O), 171.3/171.5 (C=O), 175.2/175.6 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 84, 131, 154, 181, 203, 245, 281, 303. Minor product **10**: mp 153-155°C; R*f*: 0.35 (Hex/EtOAc 40%); $[\alpha]_D$ = -159.4 (c 0.8 EtOAc); IR ν_{max}/cm^{-1}: 2974, 2931, 1751, 1728, 1689, 1377, 1157, 102, 976, 837 (film); ^{1}H NMR (300 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 1.44-1.48 (s, 18H), 2.17-2.32 (m, 1H), 2.60-2.73 (m, 1H), 3.18-3.26 (m, 1H), 4.23-4.33 (m, 1H), 4.38-4.47 (m, 1H), 4.63-4.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 27.9/28.1 (6 CH_3), 35.6/35.7 (CH_2), 42.5/43.0 (CH), 59.6/59.8 (CH), 60.7/61.2 (CH), 71.6 (CH_2), 81.1/81.3 (C), 82.0 (C), 153.8 (C=O), 171.3 (C=O), 175.4 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 126, 170, 226, 281.

X-ray structure determination of (1R,3S,5R)-tert-butyl-2-aza-3-[(tert-butyl)oxycarbonyl]-7-oxa-6-oxobicyclo [3.3.0]octane-2-carboxylate (lactone **10***)*[14]

The crystal data were collected using a turbo CAD4 diffractometer. A summary of the crystal data and refinement conditions is presented in Table 1. The structure was solved and refined using the WinGX system.[15] The data were correct by PSISCAN[16] (T_{min} = 0.9770 and T_{max} = 0.9861). The strutucture was solved by SIR92[17] and refined by SHELX97.[18] All hydrogen atoms were positioned and not refined.

The structure consists of $C_{16}H_{25}NO_6$ units, with the three asymmetric carbon atoms (C1, C3 and C5) in the RSR configuration. The crystal packing consists of piles of molecules generated by translation in the crystallographic a axis, linked by non conventional hydrogen bond with dC1…O4 and angle C1–H1...O4 respectively equal to 3.091(9)Å and 128.9°. The C=O distances in the CO_2-*t*-Bu groups C6–O2 (1.204(9)Å) C8–O4 (1.219(9)Å) and C13–O6 (1.234(9)Å) are normal for this kind of compound. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 183539. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK ; fax: +44 1223 336033 ; or e-mail: deposit@ccdc.cam.ac.uk).

Table 1. Crystal Data and Details of the Structure Determination for Compound **10**

Formula	$C_{16}H_{25}NO_6$
Formula Weight	327.37
Crystal System	Orthorhombic
Space group	$P2_12_12_1$
a; b; c [Å]	6.341(1);14.618(2); 19.135(2)
V [Å]	1773.7(4)
Z	4
D(calc) [g/cm^3]	1.226
μ(MoKα) [mm^{-1}]	0.093
F(000)	704
Crystal Size [mm]	0.15 x 0.17 x 0.25
Temperature (K)	293
Radiation MoKα [Å]	0.71073
θ min-max [°]	2.5, 28.0
Dataset	-8: 2; -19: 4; -1: 25
Tot., Uniq. Data, R(int)	2650, 2493, 0.103
Observed data [I > 2.0 σ(I)]	920
Nref, Npar	2493, 214
R, wR2, S	0.0704, 0.2631, 0.91
w = 1/[σ^2(Fo^2)+(0.1386P)^2]	where P=(Fo^2+2Fc^2)/3
Min. and Max. Resd. Dens. [e/Å^3]	-0.30, 0.30

Synthesis of the N-(carbobenzyloxy)-2-oxa-6-azabicyclo[3.2.0]octan-3-one (N-Cbz-Geissman-Waiss lactone **14***)*

To a solution of lactone **9** (88 mg, 0.27 mmol) in 1 mL of dichloromethane, at 0 °C, were added triethylsilane (0.11 mL, 0.68 mmol) and trifluoroacetic acid (0.27 mL, 3.53 mmol). After 45 min, TLC indicated complete consumption of the starting lactone **9**. The solvent was then removed *in vacuo*, the residue was dissolved in 2 mL of H_2O followed by addition of Na_2CO_3 (72 mg), and 47 μL of benzyl chloroformate (0.33 mmol). The mixture was stirred for 1 h at rt. Next, the reaction mixture was transferred to a separatory funnel and extracted with EtOAc several times. The combined organic layers were washed with saturated NH_4Cl, saturated $NaHCO_3$, saturated NaCl and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo* and the crude carboxylic acid **12** was used in the next step without further purification. IR ν_{max}/cm^{-1}: 3500-2500 (broad); 1788, 1711, 1265, 739, 704

To a solution of the crude carboxylic acid **12** in 11 mL

of THF at –20 °C were added 35 μL of *N*-methylmorpholine (0.32 mmol), 42 μL of isobutyl chloroformate and the reaction mixture was stirred at – 20 °C for 15 min. The cooling bath was removed and the reaction stirred at rt for 30 min. After this period the reaction was cooled again to – 20 °C followed by addition of a THF/*t*-BuOH solution of PhSeNa[19] and stirred for 30 min. The cooling bath was removed and the reaction stirred at rt for 30 min. Removal of the solvent *in vacuo* provided the crude acyl selenide **13**. The crude acyl selenide **13** was taken up in 7 mL of dry benzene followed by addition of 0.2 mL of *n*-tributyltin hydride (0.81 mmol) and 9 mg of AIBN (0.05 mmol). The reaction was heated to reflux for 3 h, when TLC indicated complete consumption of the starting acyl selenide **13**. The reaction mixture was cooled to rt followed by the addition 7 mL of a 30% KF solution. The resulting biphasic system was stirred for 1 h and then transferred to a separatory funnel. The organic layer was dried over anhydrous Na_2CO_3, filtered and the solvent was evaporated *in vacuo* to furnish an oil. Flash chromatography (40% EtOAc in hexane) provided 43 mg of the lactone **14** as a crystalline solid (60 % yield over 4 steps). $[\alpha]_D^{20}$ = -118 (*c* 0.6, MeOH); IR ν_{max}/cm^{-1}: 2954, 2889, 1782, 1701, 1415, 1358, 1223, 1169, 1115, 1030, 984 (film); ^{1}H NMR (300 MHz, $CDCl_3$): duplicated signals due to rotamers δ 1.95-2.14 (m, 1H), [2.31 (d, ^3J 6.6 Hz) + 2.36 (d, ^3J 5,9 Hz), 1H], 2.71-2.93 (m, 2H), 3.37-3.51 (m, 1H), 3.74-3.91 (m, 1H), 4.44-4.58 (m,1H), 5.00-5.24 (m, 3H), 7.35(s, 5H).

*Synthesis of the (1S,3S,5R)-N-(tert-butoxycarbonyl)-7,7-dichloro-3-benzyloxycarbonyl-2-azabicyclo [3.2.0]heptan-6-one (***17a***) and (1R,3S,5S)-N-(tert-Butoxycarbonyl)-7,7-dichloro-3-benzyloxycarbonyl-2-azabicyclo[3.2.0]heptan-6-one (***17b***)*

[2+2]Cycloaddition on enecarbamate **16** was performed as described for the cycloaddition of enecarbamate **4** with dichloroketene. Dichlorocyclobutanones **17a/17b** were obtained as a 13:1 diastereomeric mixture after flash chromatography (EtOAc/hexane, 1:3) in 95% yield. Data for the major cycloadduct **17a**: R*f*: 0.30 (Hex/EtOAc 25%); $[\alpha]_D^{20}$ = -114 (*c* 2.6, EtOAc); IR ν_{max}/cm^{-1}: 2978, 2931, 1813, 1747, 1712, 1454, 1369, 1184, 1153, 771, 752 (film); ^{1}H NMR (300 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 1.38-1.51 (s, 9H), 2.17-2.27 (m, 1H), 2.57-2.66 (m, 1H), 4.10-4.18 (m, 1H), [4.44 (dd, ^3J 6.0 Hz) and 4.56 (dd, ^3J 6.0 Hz), 1H], [4.83 (d, ^3J 8.0 Hz) and 4.98 (d, ^3J 8.0 Hz), 1H], 5.13-5.29 (m, 2H), 7.34 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 27.9/28.0 (3 CH_3), 30.7/31.6 (CH_2), 57.3/58.5 (CH), 61.5/61.6 (CH), 66.2/66.7 (CH), 67.3/67.4 (CH_2), 82.1/82.2 (C), 88.4/88.5 (C), 128.2/128.7 (5 aromatic CH), 134.9/135.2 (aromatic C), 153.3/153.5 (C=O), 170.6/170.9 (C=O), 194.6/194.9 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 91, 203, 313, 413(M$^+$), 415(M$^+$+ 2).

*Synthesis of the (1S,3S,5R)-N-(tert-butoxycarbonyl)-3-benzyloxycarbonyl-2-azabicyclo[3.2.0]heptan-6-one (***18***) and (1R,3S,5S)-N-(tert-butoxycarbonyl)-3-benzyl-oxycarbonyl-2-azabicyclo[3.2.0]heptan-6-one (***19***)*

Dechlorination of dichlorocyclobutanones **17a/17b** was carried out as performed on dichloro azabicyclic cyclobutanone **6**. Flash chromatography (30% EtOAc in hexane) provided cyclobutanones **18** and **19** in a combined yield of 81%. Cyclobutanone **18**: R*f*: 0.30 (Hex/EtOAc 30%); $[\alpha]_D^{20}$ = -136 (*c* 2.5, EtOAc); IR ν_{max}/cm^{-1}: 2978, 2931, 1790, 1747, 1714, 1311, 1288, 1188, 1153, 748, 698 (film); ^{1}H NMR (300 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 1.34-1.45 (s, 9H), 2.01-2.11 (m, 1H), 2.52-2.65 (m, 1H), 2.91-3.05 (m, 1H), 3.27-3.38 (m, 1H), 3.78-3.85 (m, 1H), 4.46-4.62 (m, 2H), 5.07-5.27 (m, 2H), 7.34 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 28.0/28.3 (3 CH_3), 29.8 (CH_2), 49.5/50.2 (CH), 53.3/53.5 (CH_2), 61.3 (CH), 61.7 (CH), 62.2 (CH), 67.0 (CH_2), 80.8/81.0 (C), 128.1 to 128,6 (5 aromatic CH), 135.2/135.4 (aromatic C); 153.7/154.0 (C=O), 171.8/172.1 (C=O), 207.7/208.0 (C=O); EIMS (70 eV) *m/z*: 57 (100%), 91, 124, 154, 203, 245, 289, 345(M$^+$); HRMS: Calcd: 345.15762, found: 345.15782. Compound **19**: R*f*: 0.25 (Hex/EtOAc 30%); IR ν_{max}/cm^{-1}: 2978, 2935, 1790, 1747, 1697, 1385, 1184, 1138, 1011, 964, 748, 698 (film); ^{1}H NMR (300 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 1.23-1.34 (s, 9H), 2.04-2.11 (m, 1H), 2.31-2.40 (m, 1H), 3.22-3.48 (m, 2H), 3.80-3.84 (m, 1H), 4.51-4.70 (m, 2H); 5.02-5.29 (m, 2H), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): with duplicated signals due to rotamers δ 28.1/28.3 (3 CH_3), 29.7 (CH_2), 49.8/50.1 (CH), 53.3/53.4 (CH_2), 61.0 (CH), 61.3 (CH), 62.4 (CH), 67.3 (CH_2), 80.7/81.1 (C), 128.1 to 128.8 (5 aromatic CH), 135.1/135.2 (aromatic C), 153.5/153.7 (C=O), 172.3/172.6 (C=O), 208.9/209.1 (C=O).

*Synthesis of the (1S,3S,5R)-N-(tert-butoxycarbonyl)-3-carboxy-2-azabicyclo[3.2.0]heptan-6-one (***20***)*

To a solution of 186 mg of benzyl ester **18** (0.54 mmol) in 5 mL of methanol were added 8 mg of palladium hydroxide on carbon powder (Pearlman's catalyst, 20% Pd). The resulting suspension was purged with hydrogen for 30 min and attached to a balloon filled with hydrogen for 45 min. Next, the suspension was filtered through

Celite® and the solvent was removed *in vacuo*. The crude product was dissolved in EtOAc, transferred to a separatory funnel and extracted with saturated $NaHCO_3$. The aqueous layer was separated, extracted with CH_2Cl_2 (twice) and acidified with 5% HCl to pH 2-3. The aqueous layer was then extracted with EtOAc and CH_2Cl_2 several times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give a viscous oil corresponding to carboxylic acid **20**. This compound was used in the next step without further purification. R*f*: 0.4 ($CHCl_3$/MeOH 20%); $[\alpha]_D^{20}$ = -167.9 (*c* 2.3, EtOAc); IR ν_{max}/cm^{-1}: 3400-2700 (broad); 1790, 1743, 1703, 1392, 1174, 1144; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43-1.47 (bs, 9H), 2.10-2.29 (m, 1H), 2.55-2.72 (m, 1H), 2.92-3.16 (m, 1H), 3.27-3.43 (m, 1H), 3.82-3.96 (m, 1H), 4.43-4.66 (m, 2H), 7.62 (sl, 1H); EIMS (70 eV) *m/z*: 57 (100%), 80, 113, 131, 154, 181, 199, 231, 255(M^+); HRMS (EI): Calcd for $C_{12}H_{17}NO_5$: 255.11067; Found: 255.11040.

*Synthesis of the (1S,3S,5R)-N-(tert-butoxycarbonyl)-3-carbophenylselenide-2-azabicyclo[3.2.0]heptan-6-one (***21***)*

To a cooled solution of 130 mg of the carboxylic acid **20** (0.51 mmol) in 5 mL of dry THF, at –20 °C, were added 0.07 mL of *N*-methylmorpholine (0.61 mmol), and 0.08 mL of isobutylchloroformate (0.61 mmol). The reaction mixture was stirred at –20 °C for 15 min, the cooling bath was removed, and the reaction mixture was stirred at rt for 30 min. Next, the mixture was cooled again to –20 °C, followed by addition of a previously prepared THF/t-BuOH solution of NaSePh. After stirring at –20 °C for 30 min, the cooling bath was removed and the mixture was evaporated *in vacuo*. The residue was chromatographed on silica gel (15% EtOAc in hexane) to give an oil corresponding to the acyl selenide **21**, which was used in the decarboxylation step without further purification. IR ν_{max}/cm^{-1}: 2978, 2931, 1790, 1709, 1369, 1173, 1138, 856, 751 (film); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50-1.52 (s, 9H), 2.17-2.30 (m, 1H), 2.51-2.69 (m, 1H), [3.05 (t, ^3J 2.6 Hz) + 3.10 (t, ^3J 2.6 Hz), 1H], 3.31-3.49 (m, 1H), 3.86-3.97 (m, 1H), 4.54-4.80 (m, 2H), 7.35-7.42 (m, 3H), 7.44-7.52 (m, 2H).

*Synthesis of the (1S,3S,5R)-N-(tert-butoxycarbonyl)-2-azabicyclo[3.2.0]heptan-6-one (***22***)*

The procedure used was identical to the one described for the conversion of the acyl selenide **13** to the Geissman-Waiss lactone **14**. The acyl selenide **21** was used without purification and 130 mg of the carboxylic acid **20** provided 52 mg of the cyclobutanone **22** (49% overall yield over two steps). R*f*: 0.20 (Hex/EtOAc 30%); $[\alpha]_D^{20}$ = -170.0 (c 1.7, EtOAc); IR ν_{max}/cm^{-1}: 2976, 2933, 2889, 1782, 1693, 1398, 1169, 1117, 984, 903, 773 (film); ^{1}H NMR (300 MHz, $CDCl_3$): some duplicated signals due to rotamers δ 1.41 (s, 9H), 1.88-2.05 (m, 1H), 2.15-2.26 (m, 1H), [2.82 (bs) + 2.88 (bs), 1H], 3.24-3.51 (m, 2H), 3.65-3.96 (m, 2H), [4.43 (bs) + 4.68 (bs), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$): some duplicated signals due to rotamers δ 28.4 (3 CH_3), 29.7 (CH_2), 46.2 (CH_2), 48.3 (CH), 53.7 (CH_2), 63.6/64.5 (CH), 80.0 (C), 154.1 (C=O), 210.0 (C=O); EIMS (70 eV) *m/z*: 57, 69, 113, 138 (100%), 155, 169, 184, 196, 211(M^+); HRMS (EI): Calcd for $C_{11}H_{17}NO_3$: 211.12084; found: 211.11957.

Synthesis of the (1R,5R)-N-tert-butoxycarbonyl-2-oxa-6-azabicyclo[3.3.0]octan-3-one (Geissman-Waiss lactone **23***)*

To a solution of 40 mg of cyclobutanone **22** (0.19 mmol) in 1 mL of acetic acid, at ~4 °C (ice-bath) were added 0.02 mL of 30% H_2O_2. The ice-bath was removed and the mixture was stirred at rt for 3 h. Next, 10 mL of CH_2Cl_2 were added to the reaction mixture, the solution was transferred to a separatory funnel and extracted with H_2O and saturated $NaHCO_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. Flash chromatography (40% EtOAc in hexane) provided 34 mg of the (-)-Geissman-Waiss lactone **23** (80% yield). $[\alpha]_D^{20}$ = -122.2 (*c* 1.0, EtOAc); IR ν_{max}/cm^{-1}: 2978, 2935, 2889, 1790, 1693, 1396, 1169, 1115, 984, 903, 771; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.94-2.11 (m, 1H), [2.27 (d, ^3J 6.0 Hz) and 2.32 (d, ^3J 6.0 Hz), 1H], 2.72-2.86 (m, 1H), 3.28-3.42 (m, 1H), [3.69 (t, ^3J 9.9 Hz), 3.79 (t, ^3J 9.9 Hz), 1H], 4.36-4.48 (m, 1H), 5.06 (bd, ^3J 4.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4 (3 CH_3), 30.1/30.6 (CH_2), 35.8/36.6 (CH_2), 43.9/44.4 (CH_2), 57.8 (CH), 80.5 (CH), 83.1/84.1 (C), 153.2/153.7 (C=O), 175.4/175.8 (C=O).

Conclusions

The syntheses of the important necine base precursors, (1*R*,5*R*)-*N*-carbobenzyloxy-2-oxa-6-azabicyclo [3.3.0]octan-3-one **14** and (1*R*,5*R*)-*N-tert*-butoxycarbonyl-2-oxa-6-azabicyclo[3.3.0]octan-3-one **23** (Geissman-Waiss lactones) were accomplished from the enantiomerically pure endocyclic enecarbamates **4** and **16** with overall yields of 23% and 26%, respectively. The synthetic strategy relied on an efficient and stereoselective [2+2]cycloaddition

reaction of the enecarbamates with dichloroketene that established the correct configuration of the chiral centers at C1 and C5 of the target compound. The stereocontrolling carboxylic ester groups present at C5 in the chiral endocyclic enecarbamates were efficiently removed by applying Boger's decarboxylation protocol to the respective carboxylic acids. Interesting aspects concerning the regioselectivity of the Baeyer-Villiger oxidation of azabicyclic cyclobutanones **7** and **22** were also observed. The regiochemical outcome of these oxidations seem to be controlled by steric factors which somehow counterbalance the stereoelectronic bias imposed on the ring expansion of azabicyclic cyclobutanones.

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