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FULL PAPER

One-pot preparation of functionalized azabicyclo[6.3.0]alkanone amino acids by tandem cross enyne metathesis/ring closing metathesis

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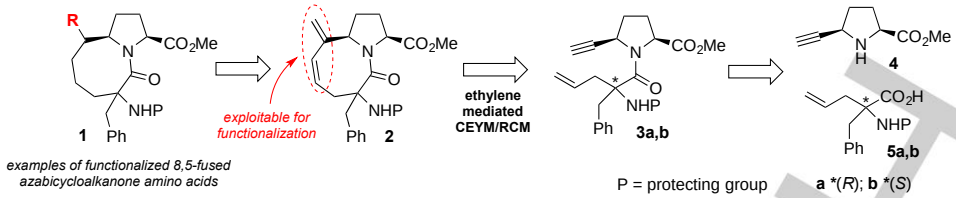
Abstract: Here we report an efficient one-pot procedure for the preparation of functionalized azabicyclo[6.3.0]alkanone amino acid derivatives. The synthetic protocol exploits an ethylene-mediated cross enyne metathesis followed by a ring closing metathesis. The reactivity of the newly synthesized 8,5-fused bicyclic scaffolds has then been investigated to obtain variously functionalized derivatives with potential applications in the field of peptides/peptidomimetics.

Introduction

In recent years, peptide and peptidomimetic derivatives have gained considerable interest due to their possible application as therapeutics in medicine,[1] material science, catalysis, and nanotechnology.[2] The optimal interaction between a peptide and its biological target strongly depends on peptide secondary structure, *i.e.* the spatial conformation adopted by the peptide backbone or by particular regions of the peptide chain. The reverse turn is one of the most recurring non-regular secondary structures, and it is involved in many recognition processes of biologically active peptides. Peptide or peptide mimetic structures capable of imparting conformational restrictions have become increasingly important in the last few decades. In particular, azabicyclo[X.Y.0]alkanone amino acids have shown to be one of the most attractive classes of constrained mimics.[3] These rigid dipeptide surrogates, which are able to replicate different turn motifs, have been widely employed to study conformation–activity relationships of biologically active peptides.[4] During our research on these topics we have already synthesized [4.3.0] and [5.3.0] azabicyclolactams for the attainment of RGD-based $\alpha_v\beta_3/\alpha_v\beta_5$ integrin antagonists.[5] The synthesis of 8,5-fused system is nevertheless interesting, since over the years they have been used as intermediates for the preparation of a wide range of bioactive compounds, such as macrocyclic analogues of the neuroprotective agent glycyl-l-prolyl-l-glutamic acid (GPE),[6] interleukin-1β converting enzyme (ICE) inhibitors,[7] Smac mimetic/XIAP inhibitors,[8] signal transducer and activator of transcription 3 (STAT3) inhibitors,[9] and cIAP-1/2 inhibitors.[10] The preparation of 8,5-fused azabicyclolactam derivatives was performed following essentially two different approaches: a) radical cyclization of an α-*N*-acetyl acrylamide promoted by AIBN and nBu_3SnH;[11] b) ring closing metathesis (RCM) of dipeptide derivatives arising from condensation between various 5-allyl prolines and *N*-Boc-allylglycine.[6, 7, 10, 12] The main limitations of these synthetic methods are the low yields of the condensation step required for the preparation of the dipeptide starting material,[12] the impossibility of generating determinate stereoisomers,[7] and the lack of 8,5-fused systems carrying a substituent at C3 which, in the case of 6,5- and 7,5-fused analogues, allowed the attainment of more active derivatives.[5a, 13] Moreover, among all the approaches so far reported, only that of Wang and coworkers involved the preparation of modified azabicycloalkanone scaffolds.[10] In this work they exploited a hydroboration/oxidation reaction with 9-BBN to convert the bicyclic alkene arising from RCM into the corresponding C5- and C6-hydroxy derivatives, followed by a Mitsunobu reaction to introduce an azido group in C6.

In the context of our research program regarding the use of metathesis reactions for the preparation of azabicyclolactam derivatives, we set out to develop a new synthetic protocol for the attainment of 8,5-fused derivatives characterized by: a) low cost and good availability of the starting materials; b) fast (ideally one-pot) attainment of “easily to functionalize” azabicycloalkanone scaffolds; c) installation of a substituent at C3. These last two features should be useful to increase the number of available structures for applications such as drug discovery/design, natural product synthesis, and synthesis of reverse turn mimics. Because of the significance of phenylalanine in biologically active peptides,[13c] we focused our attention on the installation at C3 of a benzyl side chain, which could be accomplished by condensing a 5-ethynyl proline derivative with α-allyl phenylalanine in place of the reported allylglycine. We therefore envisioned the synthetic strategy depicted in Scheme 1.

Scheme 1. Retrosynthetic analysis for the preparation of functionalized [6.3.0] azabicycloalkanone scaffolds.



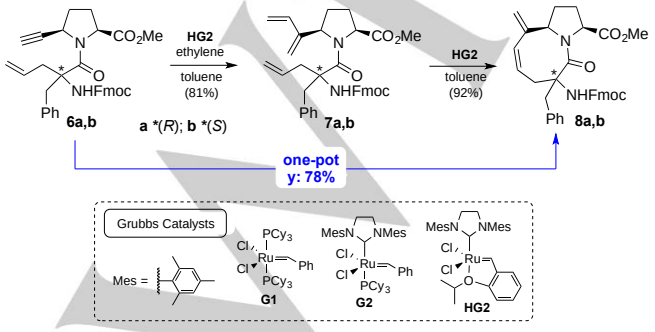
The idea is to exploit a tandem cross enyne metathesis/ring closing metathesis (CEYM/RCM) sequence to convert the dipeptide **3** into the 8,5-fused diene **2**.[14] This goal should be achieved through the intermediate formation of a trienic species generated by CEYM reaction between the ethynyl moiety of **3** and ethylene. The newly synthesized azabicycloalkane derivatives **2** would be characterized by the presence of a conjugate diene system, which could be manipulated to introduce additional functional groups, side chains, or pharmacophore moieties to design compounds with improved activity. Moreover, the installation of a suitable linker could pave the way to the conjugation of bioactive compounds. After functionalization of the diene system, a reduction reaction would allow the attainment of modified azabicyclo[6.3.0]alkanone amino acids of the type **1**.

Results and Discussion

The synthesis of 8,5-fused azabicycloalkane scaffolds has been initially attempted by submitting an equimolar diastereoisomeric mixture of the Fmoc-protected dipeptide **6**,[5c] which can be prepared through a condensation reaction between (2*S*,5*R*)-5-ethynylpyrrolidine-2-methyl ester **4** and racemic quaternary amino acid **5** (P = Fmoc), to a CEYM reaction with gaseous ethylene in the presence of the Hoveyda-Grubbs catalyst **HG2** (Scheme 2). Working in toluene at rt with 10% of **HG2** and standard 0.1 M concentration, the corresponding trienes **7a** and **7b** were obtained in 69% yield and identical diastereoisomeric ratio. Replacing toluene with dichloroethane, the yield was slightly lower (62%), while decreasing the amount of catalyst up to 7.5% did not affect both the yield and the reaction rate.

After chromatographic purification, the inseparable mixture of diastereiosomers **7** was then submitted to RCM reaction in refluxing toluene with the same **HG2** catalyst.

The cyclization went to completion in 24 hours, affording the desired dienes **8a** and **8b** in 92 % yield.

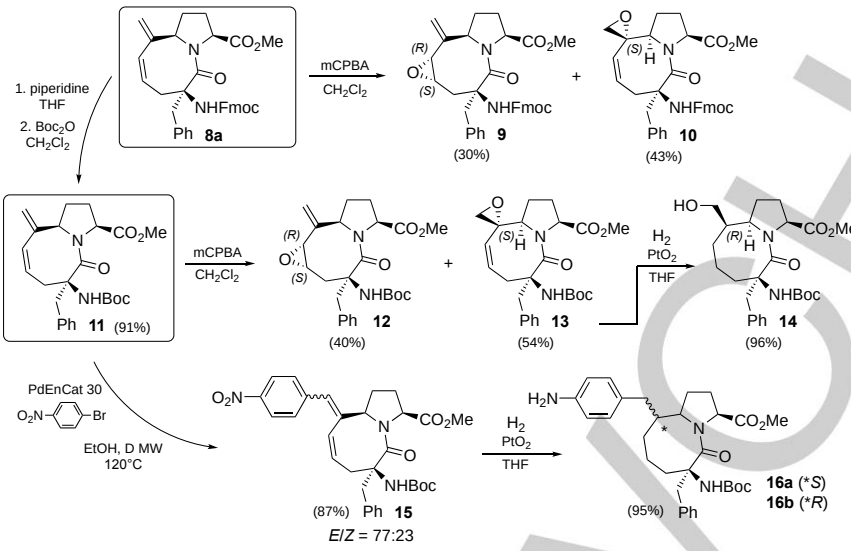


Scheme 2. Synthesis of 8,5-fused azabicycloalkanone derivatives.

In order to optimize the CEYM step, we tested the Grubbs catalysts **G1**, and **G2**. Although both of them proved to be less efficient than **HG2**, giving the trienes in yields not higher than 50%, interestingly the use of **G2** led to isolation of small amounts (13%) of the bicyclic scaffolds **8**. The final compounds **8** were also isolated in low yield (<15%) when the reaction mixture was heated at 40°C in the presence of **HG2**. Their amounts gradually increased with increasing temperature, reaching yields close to 40% at 80 °C, at the expense of formation of trienes **7**. These results, together with the need to reduce the number of synthetic steps and intermediate purifications, prompted us to develop a one-pot protocol for the preparation of the desired 8,5-fused derivatives. Indeed, in our opinion, any new synthetic method for the preparation of active compounds should not only be designed to meet the criteria of atom economy and step economy, but also to be economically viable and environment friendly. In this regard, cascade reactions involving metathesis processes have attracted, over the last years, increasing interest.[15] Although the use of ethylene in metathesis reactions is widely reported, its application in one-pot protocols to synthesize biological and medicinal relevant compounds remains quite unexplored. To the best of our knowledge, apart from our work on 7,5-fused azabicycloalkane derivatives,[5d] only one example of tandem ethylene-mediated CEYM/RCM has been previously described.[16]

In order to standardize as much as possible the reaction conditions, we performed some preliminary CEYM experiments at the concentration required for the subsequent RCM reaction (0.01 M). To our pleasure, the reaction proceeded well, and the triene derivatives **7** were obtained in increased yield (81%) and almost unchanged reaction rate. After careful evaluation of various experimental parameters, such as reaction temperature, time, and catalyst loading, the best conditions to be adopted in the one-pot protocol involved a first CEYM step working at rt in the presence of gaseous ethylene (balloon) and **HG2** (7.5%), followed by a RCM step carried out in nitrogen atmosphere after the addition of further 5% of catalyst at 80 °C. In this way the azabicyclolactam derivatives **8** were prepared in slightly higher yield (78%) if compared with the overall 75% yield of the step-by-step approach. The one-pot CEYM/RCM protocol was then applied to a dipeptide mixture enriched in diastereoisomer **6a** (70% de), for the dual purpose of investigating the influence of the stereochemical nature of the starting material and to assign the final compounds' absolute configuration. The reaction proceeded to completion, affording the cyclic dienes **8** in unchanged yields and distereoisomeric excess.

Finally, to probe the utility of our method in preparative synthesis, a gram-scale reaction of dipeptide **6** was performed, delivering the product **8** with very similar yield (79%).



Scheme 3. Functionalization of 8,5-fused azabicycloalkanone derivatives.

The great importance of 8,5-fused azabicycloalkanone scaffolds is highlighted by the fact they were chosen as privileged structures (three dimensional fragments) to be deployed in a fragment-based discovery approach using diversity-oriented synthesis.[17] The aforementioned study pointed out that subtle changes in functionalities and shape of fragments can result in significant changes to binding affinities. In this regard, Wang and coworkers showed that modifications of the eight-membered ring of the bicyclolactam scaffolds can produce new Smac mimetics with improved in vitro and in vivo properties.[10] In light of these evidences, therefore, the synthesis of functionalized azabicyclo[6.3.0]alkanone amino acids is a key element to increase the chemical diversity of available structures and design more active derivatives. To this aim we decided to explore the reactivity of the diene moiety of the newly synthesized scaffolds. Following our well-established protocol for the derivatization of sterically hindered double bonds,[5b-d, 18] the functionalization of 8,5-fused derivative **8a** has been initially attempted by exploiting a Heck reaction with 1-bromo-4-nitrobenzene in the presence of PdEnCAt 30,[19] a polyurea-encapsulated Palladium(II) acetate catalyst (Scheme 3). Unfortunately, diene **8a** showed to be unreactive and, besides unchanged starting material, only the corresponding *N*-deprotected side-product was recovered. Unaltered starting material was also recovered by submitting **8a** to various typical transformations involving double bonds and diene systems, such as cross metathesis (with 4-nitrostyrene), hydroboration (with 9-BBN or BH_3), and osmilation (with OsO_4), even forcing the conditions by heating at reflux, increasing the amount of reagents, and prolonging the reaction time.

Conversely, by reacting **8a** with 3-chloroperoxybenzoic acid we obtained the epoxides **9** and **10** as single diastereoisomers in 30% and 43% yield, respectively. This last manipulation could then be used as an entry point for further scaffold elaborations, *e.g.* alkylations or substitution reactions of the allylic epoxide moiety.[20]

By reasoning that different protecting groups on the amine function could affect the conformational properties of the bicyclolactam scaffold and, as a consequence, its reactivity, the Fmoc was replaced with *t*-Boc, achieving the *N*-(tert-butoxycarbonyl) derivative **11** in excellent 91% yield. Applying the previously reported epoxidation conditions, we smoothly isolated the epoxides **12** and **13** as single diastereoisomers in improved 94% overall yield. A Pt-catalyzed hydrogenation reaction of **13** allowed the attainment of the corresponding saturated 8,5-fused derivative **14**, endowed with a hydroxymethyl group at C7. Even more indicative of the increased reactivity of the scaffold **11**, if compared with **8a**, was the Heck reaction with 1-bromo-4-nitrobenzene; indeed, the cross-coupled product **15** was obtained in very good 87% yield. The subsequent contemporary reduction of the diene system and the nitro group afforded an equimolar mixture of the diastereoisomer **16** in nearly quantitative yield.

Notably, both the hydroxymethyl group and the para-substituted ethyl aryl chain at C7 could be straightforwardly exploited for further functionalizations. Moreover, the introduction of these side chains should be considered as a proof of concept for the installation of a linker in view of the future synthesis of bioconjugate derivatives that may find application for targeted drug delivery systems, as theranostic agents, or for cell labeling.

Configurational assignments

Configurational assignments (Figure 1) were carried out through 2D-NOESY experiments. In the case of epoxide **9**, the NOE correlation between H_8 and H_b certified the absolute *R*-configuration of the ring fusion carbon, while the strong magnetization transfer with H_{4b} allowed to discriminate between the two diastereoisomeric protons in position 4. Diagnostic for the absolute configuration at C5 and C6 were the NOE correlations of H_5 with H_{4a} and H_6. This data was in agreement with the results obtained by us,[5b-d] and by Lubell et al.[21] on structural correlated 7,5-fused azabicycloalkane scaffolds. Indeed, it has been observed that a magnetization transfer between vicinal protons only occurred when the protons were oriented toward the same side of the lactam ring.

Similar correlations involving H_8 were also observed in compound **10.** The absolute *S*-configuration at C7 was assigned on the basis of the NOE contacts of H_e, one of the protons of the oxirane ring,

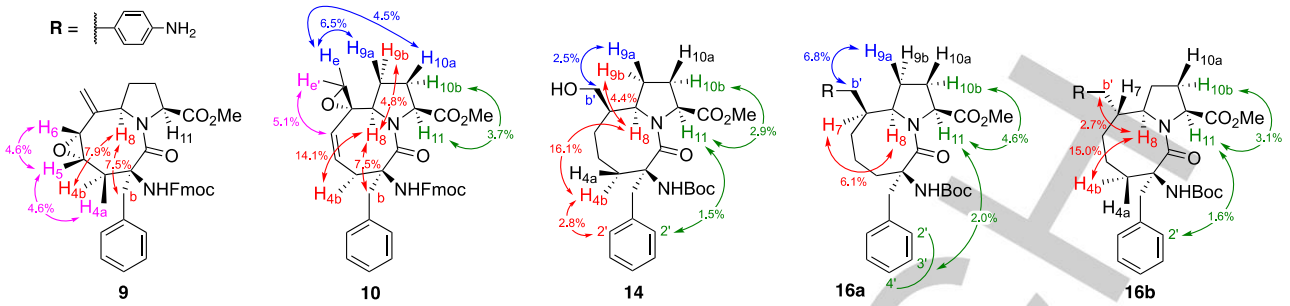


Figure 1. Relevant NOE correlations exhibited by compounds **9, 10, 14, 16a,** and **16b** (curved arrows).

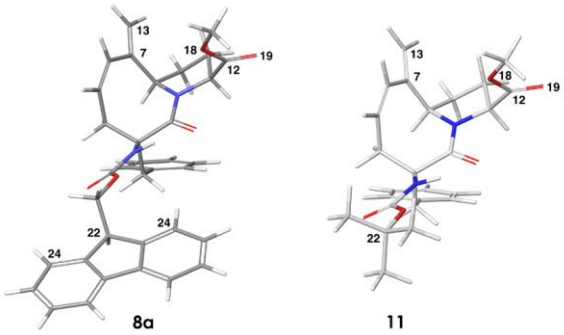
with H_{9a} and H_{10a}. The proton H_{9a} was also essential to deduce the configuration of the stereocenter carrying the hydroxymethyl group in compound **14**. Indeed, the presence of an NOE between H_{9a} and $H_{b'}$ was indicative of the (*R*) configuration at C7. The two diastereoisomers **16a** and **16b**, differing by the orientation of the ethyl aryl chain at C7, were assigned by comparing the NOE contacts of H_8. In compound **16a**, H_8 showed a quite strong NOE with H_7, while this magnetization transfer was not detectable in the NOESY spectrum of **16b**. Conversely, in derivative **16b**, H_8 showed an NOE with $H_{b'}$. As a further confirmation of the C7 absolute configuration, derivative **16a** was characterized by the presence of an NOE correlation between H_{9a} and $H_{b'}$ which was not observable in **16b**. These experiments definitively proved that the stereochemical integrity of the designed compounds at C3, C8, and C11 is maintained throughout the performed chemical transformations.

Computational studies

To get some insight into the dichotomy of reactivity in Heck coupling between derivatives **8a** and **11**, whose only difference lies in the protecting group at the amine in C3, we performed molecular mechanics calculations on both compounds (for details see Supporting Information). In advance, we verified that the choice of force field and calculation parameters would give results in agreement with some experimental results, *e. g.* relevant vicinal coupling constants. As a matter of fact, the theoretical coupling constants calculated according to the Karplus equation on all conformations weighted by their Boltzmann populations, were in good agreement with the experimental data (Table S1 Supporting Information). Our initial hypothesis was that there could be a difference in the conformation of the eight-membered lactam that places, in the case of the N-Fmoc derivative **8a**, the fluorenyl group near the exocyclic double bond thus preventing its coordination with the Pd-complex. The results of calculations showed that stereoelectronic effects cannot explain the different reactivity. Indeed, the distances between the carbons of the exocyclic double bond and C22 of both **8a** and **11** are very similar, while the distances between the nearest benzene ring of the fluorenyl group and the carbons of the exocyclic double bond are too large to justify a steric effect (Table 1).

Another steric effect that could be responsible for the failure of the Heck reaction of **8a** is ascribable to the methylester functions pointing in the same direction of the exocyclic double bond. However, the distances concerning the oxygen atoms and the carbons of the exocyclic double bond differ only by ≤ 0.1 angstrom between the Boc- and the Fmoc-derivatives, thus excluding any intervention of a steric effect in the Heck coupling. Conversely, the methyl ester group probably plays an important role in affecting the stereochemical outcome of the epoxidation reaction. In fact, both in the case of compounds **8a** and **11**, the corresponding epoxides have been isolated as single diastereoisomers, indicating the tendency for the nucleophilic attack to occur from the side of the molecule not encumbered by the methyl ester group.

Table 1. Relevant atomic distances (in angstrom) involving the exocyclic double bond of compounds **8a** and **11**



Cmpd.	C7–O18	C13–018	C7–019	C13–019	C7–C12
8a	4.10	4.40	5.15	5.59	4.13
11	3.97	4.50	5.08	5.52	4.12
Cmpd.	**C13–C12**	**C7–C22**	**C13–C22**	**C7–C24**	**C13–C24**
8a	4.68	6.78	7.85	9.56	10.75
11	4.67	6.57	7.60	-	-

Conclusion

In summary, we have reported an efficient one-pot protocol for the preparation of functionalized 8,5-fused azabicycloalkane derivatives by exploiting an ethylene-mediated CEYM/RCM sequence. The [6.3.0]-fused systems, endowed with a diene moiety, can be obtained in good overall yields starting from an

easily accessible dipeptide precursor. Finally, once we investigated the reactivity of the newly synthesized bicyclolactam scaffolds, we have shown the possibility to prepare the corresponding saturated azabicycloalkanone amino acids carrying further functionalizable side chains on the lactam ring.

Experimental Section

General Remarks: All chemicals were of reagent grade and were used without further purification. Solvents were purified according to the guidelines in Purification of Laboratory Chemicals.[22] All solvents were freshly distilled from the appropriate drying agent. THF, and toluene were distilled from sodium/benzophenone ketyl; TEA and DCM from CaH_2. Reactions requiring anhydrous conditions were performed under N_2. Yields were calculated for compounds purified by flash chromatography and judged homogeneous by thin-layer chromatography, NMR, and mass spectrometry. Thin layer chromatography was performed on Kieselgel 60 F_{254} (Merck) glass Plate eluting with solvents indicated, visualized by a 254 nm UV lamp, and stained with aqueous ceric molybdate solution or iodine and a solution of 4,4'-methylenebis-*N,N*-dimethylaniline, ninhydrin, and KI in an aqueous ethanolic solution of AcOH. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Optical rotations $[\alpha]_D$ were measured in a cell of 5 cm path length and 1 mL capacity with a Jasco DIP-1000 polarimeter. Infrared spectra were recorded on a Perkin–Elmer ATR-FTIR 1600 series spectrometer using neat samples. The HRMS spectra were acquired on a Thermo Finnigan Q Exactive instrument with API-HESI source. Samples were introduced as 0.1 mg/L solutions in MS grade methanol at 5 µL/min flow rate. Unless indicated, an oil bath was used as heat source for conventional heating. Microwave heating was performed with a Biotage Initiator 2.0 instrument (400W). Glassware for all reactions was oven-dried at 110 °C and cooled in a desiccator, or flame-dried and cooled under inert atmosphere prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septa-sealed flasks under an inert atmosphere.

NMR spectroscopic methods: Nuclear magnetic resonance spectra were acquired using a Bruker Avance 400 MHz spectrometer equipped with Bruker's TopSpin 1.3 software package. The abbreviatons s, d, t, q, br s, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, broad singlet, and multiplet, respectively. In the peak listing of ^{13}C spectra abbreviations s and t refer to zero and two protons attached to the carbons, as determined by DEPT-135 experiments. Sample temperatures were controlled with the variable-temperature unit of the instrument. Phase-sensitive 2D-NOESY experiments were performed at 298 K by using noesygpph pulse program from the Bruker library (mixing time of 0.5s or 0.8s). Sample temperatures were controlled with the variable-temperature unit of the instrument.

Synthesis of (2*S*,5*R*)-methyl 1-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-benzylpent-4-enoyl)-5-(buta-1,3-dien-2-yl)pyrrolidine-2-carboxylate (7): Ethylene was bubbled for 10 minutes into a solution of compound **6** (62 mg, 0.11 mmol) in dry toluene (52 mL, 0.01 M). Afterwards, Hoveyda Grubbs II generation catalyst (3 mg, 0.006 mmol) was added and the reaction mixture and ethylene was bubbled for 10 minutes. The reaction was stirred at room temperature, while maintaining ethylene atmosphere (balloon). After 3 hours Hoveyda Grubbs II generation catalyst (2 mg, 0.003 mmol) was added, ethylene was bubbled for 10 minutes and the reaction was stirred at room temperature, while maintaining ethylene atmosphere (balloon). After 3 hours the solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (toluene/AcOEt 80:20) to obtain compound **7** as a mixture of diastereoisomers (249 mg, 81%). White amorphous solids R_f = 0.27; IR (neat, cm^{-1}) 3371, 3028, 2961, 2927, 1726, 1627, 1262, 1080, 1030; mixture of diastereoisomers and rotamers: ^1H NMR ($CDCl_3$, 400 MHz,) δ 1.40 (m, 1H), 1.62 (m, 1H), 1.80–2.04 (m, 2H), 2.13 (m, 0.5H), 2.65 (m, 0.5H), 2.80 (m, 0.5H), 3.00 (m, 1H), 3.18–3.61 (m, 2H), 3.80 (s, 3H), 4.02 (m, 0.5H), 4.13–4.47 (m, 3.5H), 4.59 (m, 0.5H), 4.79–5.33 (m, 5H), 5.52–6.03 (m, 3H), 6.28 (m, 0.5H), 6.98–7.16 (m, 1.5H), 7.17–7.37 (m, 6.5H), 7.40–7.47 (m, 2H), 7.52–7.64 (m, 2H), 7.98 (d, *J* = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 25.5 (t), 25.6 (t), 32.1 (t), 32.6 (t), 40.2 (t), 41.5 (t), 41.9 (t), 42.4 (t), 47.6, 47.7, 52.5, 52.6, 59.0, 59.4, 62.8, 63.5, 66.2 (t), 66.4 (s), 66.7 (t), 67.5 (s), 114.2 (t), 114.8 (t), 118.7 (t), 119.5 (t), 119.8 (t), 120.3, 125.3, 125.4, 125.5, 125.6, 127.2, 127.3, 127.4, 127.5, 128.1, 128.8, 130.3, 130.7, 133.3, 133.5, 136.6, 136.8 (s), 137.5, 137.8 (s), 141.7 (2C, s); 141.8 (s), 141.9 (s), 144.2 (s), 144.3 (s), 144.5 (2C, s), 146.2 (s), 148.4 (s), 154.8 (s), 155.6 (s), 172.5 (s), 172.7 (s), 173.0 (s). HRMS (ESI) calculated for $C_{37}H_{38}N_2O_5Na$ $[M+Na]^+$ 613.26729, found 613.26764 (Δ = –0.6 ppm).

Synthesis of (3*S*,10a*R*,*Z*)-methyl 6-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6-benzyl-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate (8): Compound **7** (130 mg, 0.22 mmol) was dissolved in dry toluene (22 mL, 0.010 M) under nitrogen atmosphere. Hoveyda Grubbs II generation catalyst (6.9 mg, 0.011 mmol) was added and the reaction was heated to 80 °C. After 4 hours the solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (hexane/AcOEt 75:25) to obtain compounds **8a** and **8b** as white amorphous solids (**8a**: 58 mg, 47 %; **8b**: 56 mg, 45 %).

One-pot procedure: Ethylene was bubbled for 10 minutes into a solution of compound **6** (950 mg, 1.69 mmol) in dry toluene (169 mL, 0.01 M). Afterwards, Hoveyda Grubbs II generation catalyst (53 mg, 0.084 mmol) was added and the reaction mixture was further bubbled with ethylene for 10 minutes. The reaction was stirred at room temperature, while maintaining ethylene atmosphere (balloon). After 3 hours Hoveyda Grubbs II generation catalyst (53 mg, 0.084 mmol) was added, ethylene was bubbled for 10 minutes and the reaction was stirred at room temperature, while maintaining ethylene atmosphere (balloon). After 3 hours the solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (hexane/AcOEt 75:25) to obtain compounds 8a and 8b in 79 % overall yield. White amorphous solids (8a: 380 mg, 40 %; 8b: 372 mg, 39 %).

Compound 8a: R*f* = 0.34; $[\alpha]_D^{22}$ +91.1 (c = 0.9, $CHCl_3$) IR (neat, cm^{-1}) 3382, 3026, 2951, 2923, 1756, 1719, 1629, 1488, 1057; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (m, 1H), 1.79 (m, 1H), 2.15–2.29 (m, 2H), 2.95 (m, 1H), 3.39 (AB system, 2H), 3.71 (app s, 4H), 4.27 (t, *J* = 6.9 Hz, 1H), 4.31–4.40 (m, 2H), 4.49 (m, 1H), 4.72 (d, *J* = 3.7 Hz, 1H), 5.07 (s, 1H), 5.14 (s, 1H), 5.77 (m, 1H), 6.26 (d, *J* = 11.0 Hz, 1H), 6.54 (s, 1H), 7.03–7.13 (m, 2H), 7.25–7.31 (m, 3H), 7.32–7.35 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.60–7.69 (m, 2H), 7.80 (d, *J* = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 25,6 (t), 28.5 (t), 31.4 (t), 44.2 (t), 47.3, 52.2, 60.5, 61.8, 66.4 (t), 66.6 (s), 115.3 (t), 120.0, 125.2, 125.3, 127.1, 127.2, 127.7, 128.5, 130.1, 133.6, 135.8 (s), 141.3 (s), 144.0 (2C, s), 154.6 (s), 170.7 (s), 172.4 (s); HRMS (ESI) calculated for $C_{35}H_{34}N_2O_5Na$ $[M+Na]^+$ 585.23599, found 585.23621 (Δ = –0.4 ppm).

Compound 8b: R*f* = 0.24; $[\alpha]_D^{22}$ +6.6 (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 3273, 3029, 2953, 2925, 1754, 1719, 1587, 1449, 1257, 1030; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.91 (m, 1H), 2.07 (m, 1H), 2.17–2.32 (m, 2H), 2.38 (dd, J = 5.8, 12.4 Hz, 1H), 3.18 (d, *J* = 14.2 Hz, 1H), 3.34 (m, 1H), 3.60 (d, *J* = 14.2 Hz, 1H), 3.73 (s, 3H), 4.21 (t, *J* = 7.0 Hz, 1H), 4.37 (d, *J* = 7.0 Hz, 2H), 4.72 (t, *J* = 9.0 Hz, 1H), 5.11 (s, 2H), 5.35 (s, 1H), 5.65 (m, 1H), 5.78 (s, 1H), 6.30 (d, *J* = 11.7 Hz, 1H), 7.26–7.47 (m, 9H), 7.56 (dd, *J* = 2.9, 7.3 Hz, 2H), 7.78 (d, *J* = 7.4 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 26,1 (t), 29.5 (t), 32.5 (t), 42.6 (t), 47.2, 52.0, 59.9, 61.7, 62.7 (s), 66.6 (t), 114.8 (t), 120.0, 123.7, 125.1, 127.1, 127.3, 127.7, 128.8, 130.9, 134.0, 136.2 (s), 141.3 (s), 143.7 (s), 144.6 (s), 154.8 (s), 170.9 (s), 172.7 (s); HRMS (ESI) calculated for $C_{35}H_{34}N_2O_5Na$ $[M+Na]^+$ 585.23599, found 585.23645 (Δ = –0.8 ppm).

Synthesis of (2*S*,3'*S*,6'R,10a'*R*,*Z*)-methyl 6'-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6'-benzyl-5'-oxo-2',3',5',6',7',10a'-hexahydro-1'*H*-spiro[oxirane-2,10'-pyrrolo[1,2-*a*]azocine]-3'-carboxylate (9) and (1a*S*,3*S*,6*S*,8a*R*,9a*R*)-methyl 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl) amino)-3-benzyl-9-methylene-4-oxodecahydrooxireno[2,3-*d*]pyrrolo[1,2-*a*]azocine-6-carboxylate (10): A solution of compound **8a** (80 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL,

0.10 M) under nitrogen atmosphere was cooled to 0 °C and *m*CPBA (74 mg, 0.42 mmol) was added portionwise. The reaction was warmed to room temperature and, after 7 hours, AcOEt was added and the reaction was quenched was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with AcOEt. The organic phases were collected, washed with a NaCl saturated solution, dried with anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/AcOEt 60:40) to obtain **9** and **10** in 73 % overall yield.

Compound 9: White amorphous solid; (24 mg, 30%). R*f* = 0.27; $[\alpha]_D^{22}$ +26.4 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3368, 2928, 2857, 1749, 1715, 1653, 1406, 1374, 1262, 1072; mixture of rotamers, only major rotamer peaks were reported: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (dd, *J* = 11.4, 14.9 Hz, 1H), 1.85 (m, 1H), 2.06 (m, 1H), 2.23–2.35 (m, 2H), 3.14 (d, *J* = 13.7 Hz, 1H), 3.30 (dt, *J* = 3.8, 11.3 Hz, 1H), 3.59 (d, *J* = 13.7 Hz, 1H), 3.74 (s, 3H), 3.79–3.88 (m, 2H), 4.26 (t, *J* = 6.9 Hz, 1H), 4.30–4.40 (m, 2H), 4.57 (dd, *J* = 7.0, 10.5 Hz, 1H), 4.61 (m, 1H), 5.38 (s, 1H), 5.61 (m, 1H), 6.58 (s, 1H), 6.91–6.95 (m, 2H), 7.19–7.27 (m, 3H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 26.3 (t), 32.3 (t), 34.0 (t), 41.9 (t), 47.3, 51.9, 52.3, 56.0, 59.7, 62.3, 63.6 (s), 66.4 (t), 118.6 (t), 120.0, 125.2, 127.1, 127.4, 127.7, 128.5, 129.8, 135.0 (s), 141.3 (s), 143.9 (s), 144.3 (s), 154.4 (s), 170.3 (s), 172.4 (s); HRMS (ESI) calculated for $C_{35}H_{34}N_2O_6Na$ [M+Na]$^+$ 601.23091, found 601.23120 (Δ = –0.5 ppm).

Compound 10: white amorphous solid; (35 mg, 43%). R*f* = 0.22; $[\alpha]_D^{22}$ +59.9 (c = 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3374, 2962, 2924, 1742, 1717, 1631, 1478, 1412, 1261, 1082, 1021; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42–1.59 (m, 2H), 1.68 (m, 1H), 2.26 (m, 1H), 2.85 (d, *J* = 3.8 Hz, 1H), 2.88 (d, *J* = 3.8 Hz, 1H), 3.16 (dd, *J* = 9.6, 14.2 Hz, 1H), 3.40 (s, 2H), 3.75 (s, 3H), 3.82 (m, 1H), 4.26 (t, *J* = 6.9 Hz, 1H), 4.32–4.44 (m, 2H), 4.50 (m, 1H), 4.57 (d, *J* = 5.6 Hz, 1H), 5.52 (d, *J* = 10.9 Hz, 1H), 6.11 (m, 1H), 6.48 (s, 1H), 7.00–7.11 (m, 2H), 7.23–7.26 (m, 3H), 7.32–7.37 (m, 2H); 7.43 (t, *J* = 7.4 Hz, 2H), 7.60–7.66 (m, 2H), 7.80 (d, *J* = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 26.7 (t), 26.8 (t), 44.3 (t), 47.7, 52.7, 55.2 (t), 56.8 (s), 59.6, 60.8 (t), 61.8, 66.7 (t), 67.1 (s), 120.4, 125.6, 127.5, 127.7, 128.1, 129.0, 130.4, 130.9, 133.3, 135.8 (s), 141.7 (s), 144.4 (s), 154.9 (s), 171.3 (s), 173.3 (s); HRMS (ESI) calculated for $C_{35}H_{34}N_2O_6Na$ [M+Na]$^+$ 601.23091, found 601.23108 (Δ = –0.3 ppm).

Synthesis of (3*S*,6*R*,10a*R*,*Z*)-methyl 6-benzyl-6-((*tert*-butoxycarbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate (11): To a solution of compound **8a** (270 mg, 0.48 mmol) in dry THF (0.47 mL, 0.09 M) under nitrogen atmosphere, piperidine (142 µl, 1.44 mmol) was added. Formation of the product was monitored by TLC, R_f = 0.35 (AcOEt/MeOH 95:05). After 5 hours the solvent was evaporated under reduced pressure and the residue was recovered with a HCl 2 N solution and washed with Et_2O. The pH of the aqueous phase was adjusted to 9 with a saturated aqueous solution of Na_2CO_3 and extracted three times with AcOEt. The organic phase was dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude mixture was dissolved in dry CH_2Cl_2 (4.8 mL, 0.10 M) under nitrogen atmosphere and was added with Boc_2O (136 mg, 0.62 mmol). The formation of the product was monitored by TLC, R_f = 0.25 (hexane/AcOEt 70:30). After 12 hour the solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (hexane/AcOEt 70:30) to obtain compound **11**. White amorphous solid (192 mg, 91% over two steps). R_f = 0.25; $[\alpha]_D^{22}$ +14.5 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3387, 2977, 1755, 1708, 1614, 1482, 1412, 1162, 1056; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.55 (m, 1H), 1.75 (m, 1H), 2.11–2.25 (m, 2H), 2.89 (dd, *J* = 9.4, 14.9 Hz, 1H), 3.32 (d, *J* = 13.2 Hz, 1H), 3.40 (d, *J* = 13.2 Hz, 1H), 3.68 (s, 3H), 3.70 (m, 1H), 4.34 (dd, *J* = 8.6, 9.5 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 5.04 (s, 1H), 5.11 (s, 1H), 5.77 (m, 1H), 6.17–6.25 (m, 2H), 7.06–7.11 (m, 2H), 7.23–7.28 (m, 2H), 7.30 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 26.0 (t), 28.9 (t), 31.6 (t), 44.6 (t), 52.5, 60.8, 62.1, 66.8 (s), 79.4 (s), 115.5 (t), 126.1, 127.5, 128.8, 130.6, 133.7, 144.6 (s), 154.8 (s), 171.4 (s), 172.9 (s); HRMS (ESI) calculated for $C_{25}H_{32}N_2O_5Na$ [M+Na]$^+$ 463.22034, found 463.22055 (Δ = –0.5 ppm).

Synthesis of (1a*S*,3*S*,6*S*,8a*R*,9a*R*)-methyl 3-benzyl-3-((*tert*-butoxycarbonyl)amino)-9-methylene-4-oxodecahydrooxireno[2,3-*d*]pyrrolo[1,2-*a*]azocine-6-carboxylate (12) and (2*S*,3'*S*,6'*R*,10a'*R*,*Z*)-methyl 6'-benzyl-6'-((*tert*-butoxycarbonyl)amino)-5'-oxo-2',3',5',6',7',10a'-hexahydro-1'*H*-spiro[oxirane-2,10'-pyrrolo[1,2-*a*]azocine]-3'-carboxylate (13): A solution of compound **8a** (98 mg, 0.22 mmol) in dry CH_2Cl_2 (2.2 mL, 0.10 M) under nitrogen atmosphere was cooled to 0 °C and *m*CPBA (87 mg, 0.26 mmol) was added portionwise. The reaction was warmed to room temperature and, after 7 hours, AcOEt was added and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with AcOEt. The organic phases were collected, washed with a NaCl saturated solution, dried with anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/AcOEt 60:40) to obtain **12** and **13** in 94 % overall yield.

Compound 12: White amorphous solid; (40 mg, 40%). R*f* = 0.28 (hexane/AcOEt 60:40); $[\alpha]_D^{22}$ +12.4 (c = 1.7, $CHCl_3$); IR (neat, cm^{-1}) 3383, 3028, 2976, 1748, 1707, 1629, 1467, 1404, 1163, 1071; 80:20 mixture of (3*S*)/(3*R*) diastereoisomers, only major diastereoisomer peaks were reported: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.52 (m, 1H), 1.82 (m, 1H), 2.00 (m, 1H), 2.21–2.31 (m, 2H), 3.13 (d, *J* = 13.6 Hz, 1H), 3.33 (dt, *J* = 3.7, 11.0 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.71 (s, 3H), 3.78–3.87 (m, 2H), 4.36 (dd, *J* = 7.8, 10.1 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 5.35 (t, = 1.9 Hz, 1H), 5.59 (t, *J* = 1.9 Hz, 1H), 6.27 (s, 1H), 6.97–7.01 (m, 2H), 7.24–7.28 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 26.2 (t), 28.5, 32.2 (t), 33.9 (t), 42.0 (t), 52.2 (2C), 56.1, 59.6, 62.3, 63.4 (s), 79.2 (s), 118.5 (t), 127.3, 128.4, 129.9, 135.3 (s), 144.4 (s), 154.1 (s), 170.6 (s), 172.4 (s); HRMS (ESI) calculated for $C_{25}H_{32}N_2O_6Na$ [M+Na]$^+$ 479.21526, found 479.21548 (Δ = –0.5 ppm).

Compound 13: white amorphous solid; (54 mg, 54%). R*f* = 0.23 (hexane/AcOEt 60:40); $[\alpha]_D^{22}$ +85.4 (c = 1.6, $CHCl_3$); IR (neat, cm^{-1}) 3382, 3029, 2969, 2930, 1747, 1709, 1635, 1365, 1262, 1168, 1030; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (m, 1H), 1.48 (s, 9H), 1.54 (m, 1H), 1.67 (m, 1H), 2.22 (dt, *J* = 8.4, 12.9 Hz, 1H), 2.82 (d, *J* = 3.8 Hz, 1H), 2.86 (d, *J* = 3.8 Hz, 1H), 3.11 (dd, *J* = 9.7, 14.8 Hz, 1H), 3.36 (d, *J* = 13.4 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.71 (s, 3H), 3.81 (dd, *J* = 8.4, 14.8 Hz, 1H), 4.39 (t, *J* = 8.9 Hz, 1H), 4.52 (d, *J* = 6.7 Hz, 1H), 5.48 (d, *J* = 10.9 Hz, 1H), 6.08–6.18 (m, 2H), 7.08 (d, *J* = 6.6 Hz, 2H), 7.24–7.32 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 26.6 (t), 26.8 (t), 28.9, 31.7 (t), 44.4 (t), 52.6, 55.2, 56.9 (s), 59.5, 61.8, 66.9 (s), 79.6 (s), 127.6, 128.8, 130.5, 130.6, 133.7, 136.1 (s), 154.7 (s), 171.6 (s), 173.3 (s); HRMS (ESI) calculated for $C_{25}H_{32}N_2O_6Na$ [M+Na]$^+$ 479.21526, found 479.21564 (Δ = –0.8 ppm).

Synthesis of (3*S*,6*R*,10*R*,10a*R*)-methyl 6-benzyl-6-((*tert*-butoxycarbonyl)amino)-10-(hydroxymethyl)-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylate (14): To a solution of **12** (42 mg, 0.092 mmol) in dry THF (1.8 mL, 0.05 M), under H_2 (balloon), PtO_2 was added (6 mg, 15% weight). The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of Celite, and the organic phase was evaporated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/AcOEt 40:60) to obtain pure compound **14** in 96 % overall yield.

Compound 14: White amorphous solid; (41 mg, 96%). R*f* = 0.29 (hexane/AcOEt 40:60); $[\alpha]_D^{22}$ –64.2 (c = 1.0, CHCl3); IR (neat, cm^{-1}) 3396 (broad) 3027, 2979, 2930, 1749, 1715, 1164; 90:10 mixture of rotamers, only major rotamer peaks were reported; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (m, 1H), 1.47 (s, 9H), 1.56–1.77 (m, 5H, 1H exchanges with D_2O), 1.90 (dd, *J* = 7.1, 13.1 Hz, 1H), 1.95–2.09 (m, 3H), 2.30 (m, 1H), 3.12 (d, = 12.8 Hz, 1H), 3.17 (m, 1H), 3.52–3.60 (m, 3H), 3.78 (s, 3H), 3.96 (dd, *J* = 5.4, 8.0 Hz, 1H), 4.21 (dd, *J* = 8.7, 10.0 Hz, 1H), 6.08 (s, 1H), 7-08–7.15 (m, 2H), 7.21–7.32 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 22.8 (t), 24.6 (t), 26.3 (t), 28.5, 28.9 (t), 30.0 (t), 45.4, 47.2 (t), 52.3, 58.1, 62.4, 63.0 (t), 65.4 (s), 79.0 (s), 127.0, 128.1, 130.3, 136.3 (s), 154.4 (s), 173.3 (s), 173.7 (s); HRMS (ESI) calculated for $C_{25}H_{36}N_2O_6Na$ [M+Na]$^+$ 483.24656, found 483.24673 (Δ = –0.4 ppm).

(3*S*,6*R*,8*Z*,10a*R*)-methyl 6-benzyl-6-((*tert*-butoxycarbonyl)amino)-10-(4-nitrobenzylidene)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate (15): To a solution of compound **11** (44 mg, 0.10 mmol) in dry MeOH (1.0 mL, 0.10 M), under nitrogen atmosphere, 4-bromo-nitrobenzene (22 mg, 0.11 mmol), PdEnCat 30 (12 mg, 0.005 mmol) and Bu_4NOAc (90 mg, 0.30 mmol) were added. The reaction was heated to 120 °C through microwave irradiation for 2 hours and 30 minutes (sealed vessel, external surface sensor). The reaction mixture was filtered through a Gooch apparatus and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography (toluene/AcOEt 70:30) to obtain compound **15** as a mixture of diastereoisomers. Yellow amorphous solid (49 mg, 87 %). R*f* = 0.30; $[\alpha]_D^{22}$ +457.7 (c = 0.9, CHCl3); IR (neat, cm^{-1}) 3390, 3026, 2979, 1750, 1708, 1624, 1409, 1341, 1166, 1056; 77:23 mixture of diastereoisomers, only major diastereoisomer peaks were reported: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.74–1.84 (m, 2H), 2.26 (m, 1H), 2.48 (m, 1H) 2.87 (dd, *J* = 10.2, 14.5 Hz, 1H), 3.37 (d, *J* = 13.3 Hz, 1H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.63 (s, 3H), 3.80 (dd, *J* = 7.8, 14.6 Hz, 1H), 4.40 (app t, *J* = 8.4, 1H), 4.85 (d, *J* = 3.9 Hz, 1H), 6.05 (ddd, *J* = 8.0, 10.2, 10.7 Hz, 1H), 6.21 (s, 1H), 6.27 (d, *J* = 10.8 Hz, 1H), 6.45 (s, 1H), 7.07–7.12 (m, 2H), 7.26–7.33 (m, 3H), 7.48 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 26.2 (t), 28.9, 29.6 (t), 32.7 (t), 43.8 (t), 52.5, 62.1, 62.2, 66.6 (s), 79.5 (s), 123.8, 125.1, 127.6, 128.9, 129.5, 130.2, 130.6, 130.8, 136.2 (s), 141.4 (s), 143.6 (s), 147.0 (s), 154.7 (s), 171.5 (s), 172.7 (s); HRMS (ESI) calculated for $C_{31}H_{35}N_3O_7Na$ $[M+Na]^+$ 584.23672, found 584.23730 (Δ = –1.0 ppm).

Synthesis of (3*S*,6*R*,10*R*,10a*R*)-methyl 10-(4-aminobenzyl)-6-benzyl-6-((*tert*-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylate (16): To a solution of **15** (48 mg, 0.085 mmol) in dry THF (1.7 mL, 0.05 M), under H_2 (balloon), PtO_2 was added (5 mg, 10% weight). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite, and the organic phase was evaporated under reduced pressure. The crude mixture was purified by flash chromatography (toluene/AcOEt 83:17). to obtain pure compounds **16a** and **16b** in 94% overall yield.

Compound 16a: White amorphous solid; (22 mg, 48%). R*f* = 0.28 (toluene/AcOEt 83:17); $[\alpha]_D^{22}$ –35.8 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3368, 2961, 2924, 1744, 1709, 1608, 1410, 1264, 1163, 1063; 77:23 mixture of diastereoisomers, only major diastereoisomer peaks were reported: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.38 (m, 3H), 1.39–1.51 (m, 11H), 1.60–1.87 (m, 4H), 2.06 (m, 1H), 2.24–2.35 (m, 2H), 2.38 (s, 1H, exchanges with D_2O), 2.52 (d, *J* = 12.4 Hz, 1H), 3.08 (m, 1H), 3.13 (d, *J* = 12.7 Hz, 1H), 3.55 (d, *J* = 12.7 Hz, 1H), 3.82 (s, 3H), 4.04 (t, *J* = 6.9 Hz, 1H), 4.26 (t, *J* = 9.3 Hz, 1H), 6.10 (s, 1H), 6.60 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 7.9 Hz, 2H), 7.11–7.16 (m, 2H), 7.24–7.31 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 23.4 (t), 25.5 (t), 26.8 (t), 28.8, 29.6 (t), 30.5 (t), 35.4 (t), 46.0, 47.6 (t), 52.4, 59.5, 62.8, 65.8 (s), 79.3 (s), 115.6, 127.3, 128.5, 130.3, 130.7, 131.6 (s), 136.9 (s), 144.6 (s), 154.8 (s), 173.3 (s), 173.7 (s); HRMS (ESI) calculated for $C_{31}H_{42}N_3O_5Na$ $[M+Na]^+$ 536.31190, found 536.31219 (Δ = –0.5 ppm).

Compound 16b: white amorphous solid; (21 mg, 46%). R*f* = 0.24 (toluene/AcOEt 83:17); $[\alpha]_D^{22}$ +9.3 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3376, 2962, 2924, 1743, 1708, 1610, 1413, 1262, 1096, 1027; 77:23 mixture of rotamers, only major rotamer peaks were reported: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.52 (m, 14 H, 1H exchanges with D_2O), 1.68–1.89 (m, 4H, 1H exchanges with D_2O), 2.01 (m, 1H), 2.19 (m, 1H), 2.31–2.45 (m, 3H), 3.10–3.19 (two signals overlapped: m, 1H and d, *J* = 12.8 Hz, 1H), 3.28 (m, 1H), 3.52 (d, *J* = 12.8 Hz, 1H), 3.74 (s, 3H), 4.24 (dd, *J* = 8.1, 9.5 Hz, 1H), 6.18 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 6.5 Hz, 2H), 7.26–7.32 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 19.4 (t), 22.7 (t), 25.7 (t), 28.9, 30.1 (t), 31.6 (t), 35.5 (t), 44.7, 46.9 (t), 52.5, 62.2, 63.0, 65.3 (s), 79.2 (s), 115.7, 127.3, 128.4, 129.8, 130.5 (s), 130.8, 136.7 (s), 144.8 (s), 154.7 (s), 173.2 (s), 173.5 (s); HRMS (ESI) calculated for $C_{31}H_{42}N_3O_5Na$ $[M+Na]^+$ 536.31190, found 536.31238 (Δ = –0.9 ppm).

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Keywords: Tandem Metathesis • One-pot • Azabicycloalkanone • Amino acids • Ruthenium • Heterocycles

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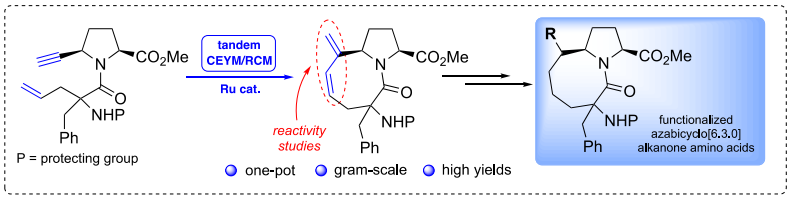
Entry for the Table of Contents

Key Topics: Constrained Peptidomimetics



Azabicyclo[X.Y.0]alkanone amino acids are one of the most attractive classes of rigid dipeptide surrogates employed to study conformation-activity relationships of biologically active peptides. Here we report an efficient one-pot synthetic approach for the preparation of 8,5-fused azabicycloalkane derivatives. These scaffolds, characterized by the presence of a conjugate diene system, could be exploited to design compounds with improved activity.

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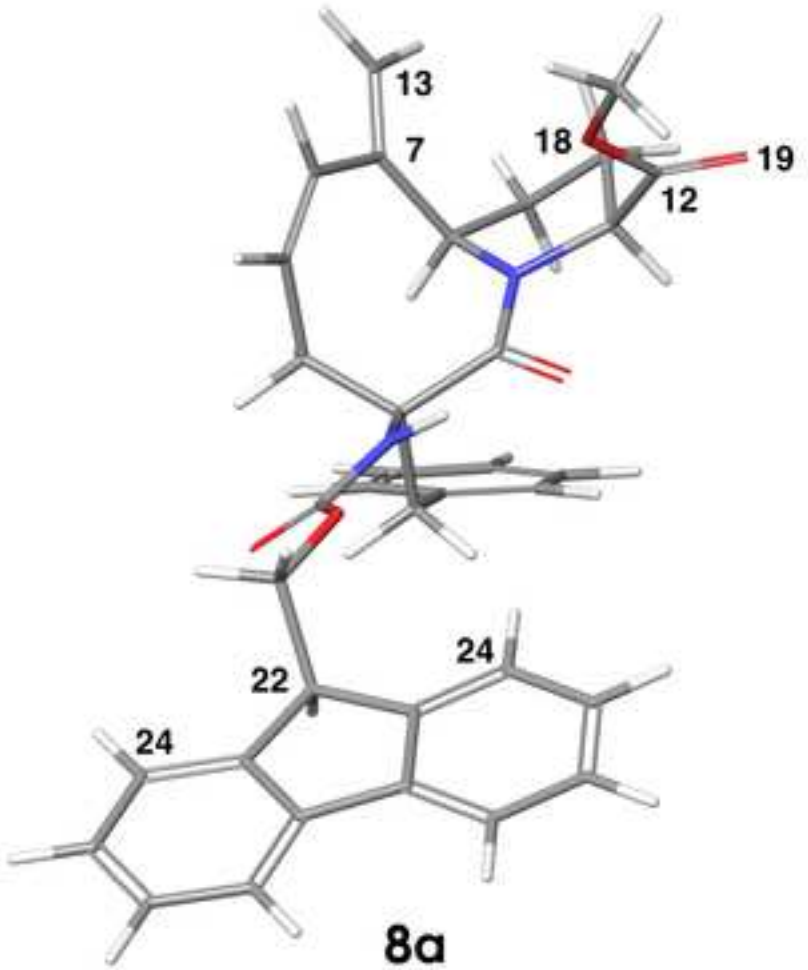

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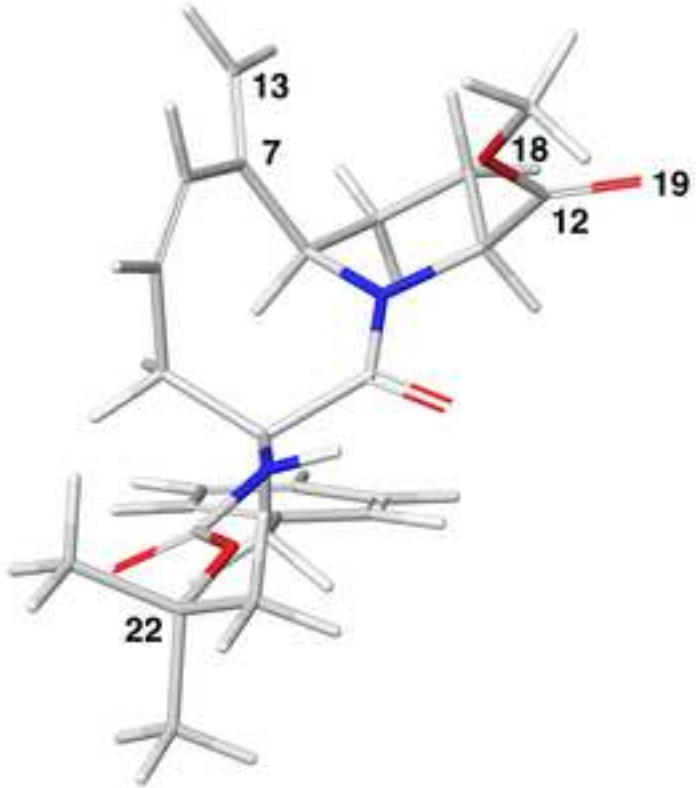

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TOC graphic