EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201501003

Synthesis of Easy-to-Functionalize Azabicycloalkane Scaffolds as Dipeptide Turn Mimics en Route to cRGD-Based Bioconjugates

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Keywords: RGD integrin antagonists / Peptidomimetics / Amino acids / Lactams / Antitumor agents

In this paper we report the synthesis of new azabicycloalkane scaffolds, which could be exploited to obtain cRGD-based bioconjugates that may find promising application for targeted drug delivery, theranostic, and general cancer-cell labeling. By exploiting a Hosomi–Sakurai intramolecular allylation reaction we efficiently converted a silylated aldehyde precursor into 7,5-fused lactam scaffolds endowed with an exocyclic double bond. The presence of the vinyl function should make it possible to conjugate bioactive compounds to selectively carry them to tumor sites. The optimized synthetic sequence allows the gram-scale preparation of the target scaffolds in a few steps and good 39 % overall yield from readily accessible materials. The high reactivity of the exocyclic olefin moiety was ascertained by performing a Heck coupling reaction with 1-bromo-4-nitrobenzene, which gave the corresponding functionalized derivatives in good (80–91 %) yields.

Introduction

A key issue related to cancer therapy is the control of tumor-cell proliferation and aggressive behavior. Neoplastic growth is a complex process that results from interactions among different cell types present in the tumor mass, such as tumor cells, and cells present in the tumoral niche, such as fibroblast and endothelial cells, that contribute to the composition of the extracellular matrix (ECM). ECM proteins, such as fibronectin, laminin and collagen, regulate cellular processes like cell migration, proliferation, and differentiation, and exert their effect by binding cell surface receptors, the integrins.[1] The most interesting feature of integrins in oncology comes from the observation that changes in the adhesion properties in cancer cells are deeply involved in the early and final steps of metastasis formation.[2] Moreover, integrins represent an excellent target in cancer therapy, because in some cancer cells they are overexpressed relative to their non-cancer cell counterpart.

The αvβ3 and αvβ5 integrins appear to regulate metastasic processes in different cancer types like colon cancer, melanoma, breast cancer, and brain cancer, such as glioblastoma (GBM).[3] The αvβ3 and αvβ5 recognize endogenous ECM proteins and synthetic molecules that contain the tripeptide sequence Arg-Gly-Asp (RGD) that is therefore used as a binding motif in the design and synthesis of integrin antagonists.[4]

Some previous studies have investigated the functional effects of small RGD-like molecules as integrin antagonists. A prototype RGD-like molecule, Cilengitide, has been mainly tested for treatment of GBM.[5] Despite promising preliminary data, its use as an anticancer therapeutic has been discontinued as a result of failure in phase-III clinical trials.[6] As a consequence, in the last years, the use of RGD-based antagonists alone as anticancer agents has been set aside. Nevertheless, the availability of high-affinity ligands, and the well-known biological roles of αvβ3 integrin subtypes, has placed RGD-based αvβ3 antagonists under extensive studies for tumor targeting.[7]

Azabicyclolactam derivatives of type **1** can be viewed as conformationally constrained mimics of dipeptide Phe-Pro (Scheme 1). These 7,5-fused bicyclic scaffolds, which can be structurally characterized by the presence of a quaternary stereocenter at position 3 of the lactam ring, are useful intermediates in the synthesis of RGD-based cyclopentapeptides that are effective integrin inhibitors.[8] The most active compound of the series, **1a-RGD**, was shown to be a nanomolar inhibitor of integrin receptors $\alpha_v\beta_3$ and $\alpha_v\beta_5$, which are overexpressed on the cancer-cell surface and reported to be involved in tumor-induced neoangiogenesis.[9] Moreover, cyclopentapeptide **1a-RGD** is one of the few RGD-like antagonists that proved to be effective at inhibiting cell mi-

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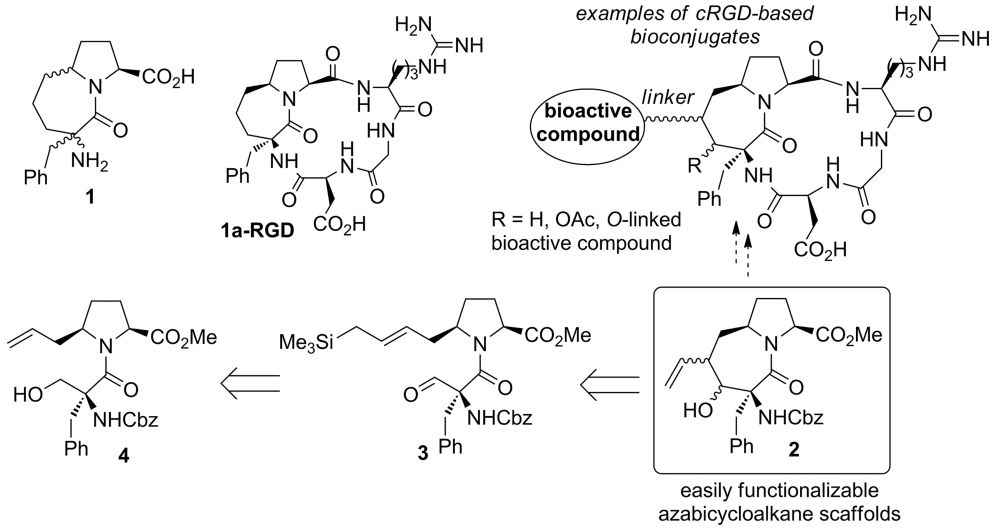


Scheme 1.

gration and attachment, and inducing anoikis in glioblastoma cell lines.[10]

In recent years, many efforts have been directed towards the development of integrin ligands that can provide advanced tools for drug delivery, imaging, or theranostics.[11] Along these lines, and taking into account the relevant affinity of **1a-RGD** towards αvβ3 and αvβ5 receptors, we are pursuing the idea to develop a synthetic strategy that would allow the synthesis of conjugate derivatives with potential use in cancer therapy. To this aim, the introduction onto bicyclolactam scaffolds **1** of a functional group to be exploited as an attachment point for the conjugation of bioactive compounds is mandatory. Indeed, through the use of an appropriate linker, it would be possible to covalently conjugate these RGD-based cyclopentapeptides to either therapeutic (cytotoxic) or imaging agents, such that they could be selectively carried on the tumor-induced neovascularization (Scheme 1). Because such a structural modification could lead to an unpredictable influence on the conformational properties of the cyclic peptide moiety, we assumed that the most appropriate position to be functionalized would be the one that resides on a carbon atom away from both the RGD sequence and the proline ring. A vinyl function seemed the most appropriate choice on grounds of its ample synthetic versatility, robustness of the C–C bond, and limited steric requirements.

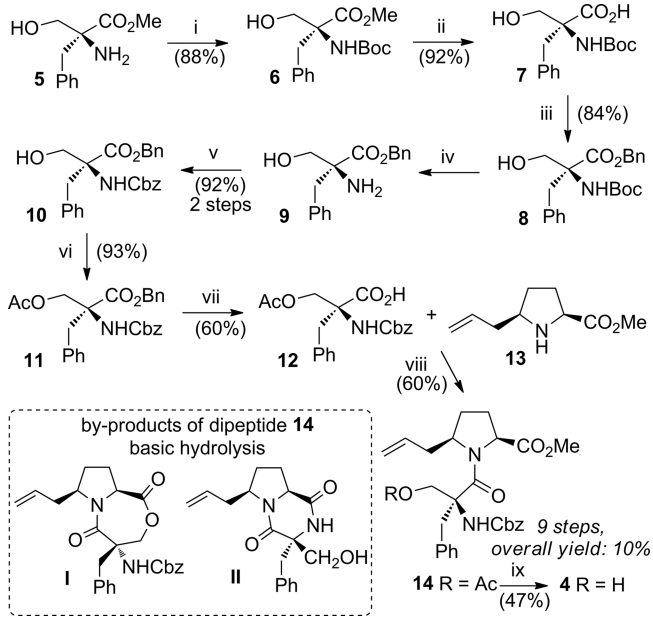
This new synthetic approach uses, as a key reaction, an intramolecular Sakurai allylation reaction of aldehyde **3**. This Lewis acid catalyzed cyclization reaction would allow us to obtain, in one operation, the seven-membered lactam ring and introduce an exocyclic vinyl unit.

Results and Discussion

First-Generation Synthesis of Dipeptide 4

The retrosynthetic analysis (Scheme 1) shows that dipeptide **4** is a key intermediate to obtain new bicyclolactam scaffolds of type **2**. Indeed, alcohol **4** could be converted into aldehyde **3** through oxidation of the alcoholic function followed by introduction of the trimethylsilyl moiety.

To obtain **4**, we initially decided to explore the feasibility of the synthetic route depicted in Scheme 2, which exploits the condensation reaction between (*S*)-*N*-carboxybenzyl-(Cbz)-*O*-acetylbenzylserine **12** and *cis*-5-allylproline methyl ester **13**.



Scheme 2. Reagents and conditions: (i) $(Boc)_2O$, THF, 0 °C then r.t., 24 h; (ii) LiOH, THF/H_2O/MeOH, r.t., 2.5 h; (iii) $PhCH_2Br$., $CsCO_3$, 50 °C, 1 h; (iv) HCl/MeOH, 0 °C, 3 h; (v) $(Cbz)_2O$, THF, 0 °C then r.t., 1 h; (vi) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 1 h; (vii) H_2, Pd/C(en) (en = ethylenediamine), EtOH, r.t., 3 h; (viii) PyBroP, DIEA, DMAP, CH_2Cl_2, r.t., 24 h; (ix) HCl/MeOH, 0 °C, 5 h.

This choice was mainly dictated by the easy accessibility of amino acidic precursors **5** and **13**, the stereoselective

(asymmetric) synthesis of which was reported previously by us.[12,13] Compound **5** is readily obtained from L-serine through stereoselective alkylation reaction of Seebach's oxazolidine, whereas (2*S*,5*R*)-5-allylproline methyl ester **13** could be synthesized in a few steps from L-pyroglutamic acid.

The unacceptable length of this seemingly trivial synthesis resulted, because the condensation reaction between either *N*-*tert*-butoxycarbonyl- (Boc-) or *N*-Cbz-protected 2-benzylserine and *cis*-5-allylproline methyl ester was unsuccessful. Despite an extensive screen for condensing agents, such as *N*,*N*′-dicyclohexylcarbodiimide, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, 1-hydroxy-7-azabenzotriazole, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, isobutyl chloroformate, PyBroP, and bis(2-oxo-3-oxazolidinyl)phosphinic chloride, at both room and reflux temperatures, we isolated only unreacted starting materials along with traces of a by-product with a structure consistent with (4-benzyl-2-oxo-4-oxazolidine)carboxylic acid.[14] This compound arises probably through nucleophilic attack of the free hydroxy group to the carbamate carbonyl group.

The low nucleophilicity of the nitrogen atom in proline derivative **13** and the unavoidable steric requirements of the α-benzylserine derivative hamper the formation of the dipeptide. To the best of our knowledge, only one similar dipeptide has been reported in the literature, Boc-NH-α-methyl-Ser-ProCO_2Me, but neither experimental procedure for its preparation nor spectroscopic data are detailed.[15] Moreover, only one example of condensation between *N*-protected serine and 5-substituted proline esters is known, whereas proline or 4-substituted proline esters were shown to couple in good yields under standard conditions.

To avoid side reactions (vide supra), the hydroxy group of quaternary amino acid **6** was protected either as the trimethylsilyl ether or *tert*-butyldiphenylsilyl ether. Unfortunately, any attempt of methyl ester saponification gave only starting material contaminated with trace amounts of desilylated products.

By assuming that the very low hydrolysis rate was mainly due to steric factors, we tried to change the *N*-protecting group by replacing *t*Boc with Cbz, but attempts to perform the ester basic hydrolysis were unsuccessful. To further reduce the steric hindrance around the quaternary stereocenter, we thought to adopt a less bulky protective group on the alcohol function by converting **6** into its corresponding *O*-acetyl derivative. Surprisingly, the acetylation reaction with acetic anhydride or acetyl chloride did not provide the desired product; similar results were obtained for attempts to acetylate benzylserine **7**. However, by starting from *N*-Cbz-benzylserine, the acetylation reaction proceeded smoothly, but the acetyl group cleaved easily during the subsequent saponification step. Attempts to restore the protection on the hydroxy group met with failure, as reported for *N*-Boc analogue **7**. To circumvent these drawbacks, mainly ester hydrolysis, we decided to synthesize benzyl ester **8**, which was *O*-acetylated and, after hydrogenolysis, converted into the corresponding free acid. Unfortunately, the following reaction with 5-allylproline methyl ester gave the desired dipeptide in yields not higher than 10% despite a thorough screen of the most common condensing agents. It was therefore necessary to add an additional step, to switch the *N*-protecting group of derivative **8** from Boc to Cbz, to obtain intermediate **10**. To obtain (*S*)-*N*-Cbz-*O*-acetylbenzylserine **12** we had to develop a selective benzyl ester hydrogenolysis reaction that would preserve the Cbz protecting group. By performing the reaction in the presence of a Pd/C–ethylenediamine complex catalyst,[16] after careful optimization work, we were able to isolate free amino acid **12** in 50–60% yields. By exploiting PyBroP as a condensing agent for the amide bond formation, we obtained dipeptide **14**, which, after removal of the acetyl group, was converted into desired dipeptide **4**. The final deprotection step proved rather troublesome. Attempts to selectively cleave the acetate whilst keeping the methyl ester intact, e.g. by using a methanolic solution of potassium carbonate, led to the isolation of lactone by-product **I**, which arises from intramolecular attack of the alcoholic function on the methyl ester carbonyl group. Under more basic reaction conditions, it was possible to isolate only diketopiperazine **II**, possibly arising from previous hydrolysis of the benzyl carbamate followed by intramolecular attack of the amino group on the methyl ester.

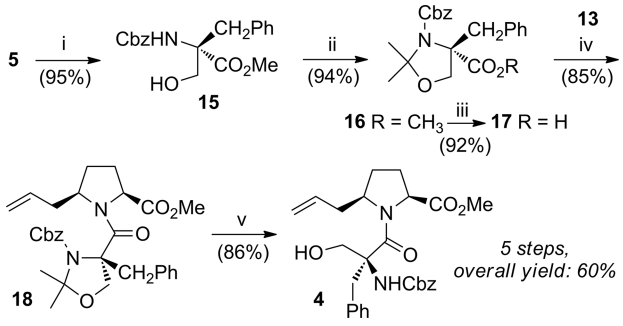
The difficulties encountered to restore the hydroxy group by saponification of the corresponding acetate, led us to attempt a transesterification reaction with methanolic HCl. This reaction made it possible to obtain desired dipeptide **4** with yields close to 50%, but again we isolated significant amounts of the previously described lactone by-product.

As clearly highlighted by the experimental results described so far, this first-generation synthesis was awkward and suffers from several weak points. In particular the selective benzyl ester cleavage and the final hydrolysis, which involves rather advanced and synthetically precious intermediates, required carefully controlled experimental conditions. Moreover, the 9 linear steps necessary to obtain key intermediate **4**, and the low 10% overall yield, do not meet with our needs to synthesize final bicyclolactam scaffolds of type **2** on a gram scale.

Second-Generation Synthesis of Dipeptide 4

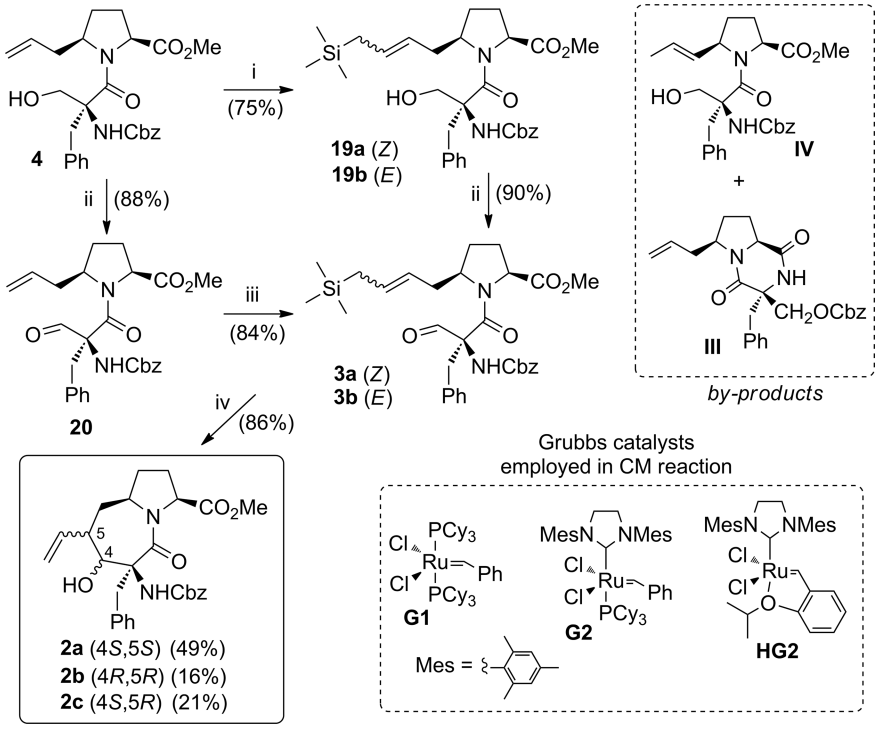
Efforts to reduce the length of the synthetic route and raise the overall yield that leads to **4**, prompted us to explore a second approach that involved the contemporary protection of the alcoholic and amino group of quaternary α-amino ester **5** (Scheme 3). The synthetic sequence started with protection of the amino group of compound **5** as its Cbz derivative, followed by the almost quantitative conversion of obtained (*S*)-*N*-Cbz-α-benzylserine methyl ester **15** into the corresponding N,O-aminal **16** by treatment with 2,2-dimethoxypropane (DMP). Methyl ester saponification with LiOH afforded carboxylic acid intermediate **17**, which was coupled with *cis*-5-allylproline methyl ester to give dipeptide **18** in up to 85% yield. The last step, i.e. cleavage of

the oxazolidine ring, turned out to be very arduous and required careful investigation. The first attempts, performed with mixtures of MeOH/HCl (12 N) in different ratios, gave dipeptide **4** in low yields with long reaction times (about 96 h); moreover, in addition to the desired product, we isolated similar amounts of by-product **I**. All methods for the selective cleavage of N,O-aminals, such as a catalytic amount of *p*-toluensulfonic acid,[17] camphorsulfonic acid,[18] and scandium triflate,[19] led to low conversion.



Scheme 3. Reagents and conditions: (i) $(Cbz)_2O$, THF, 0 °C, 15 min; (ii) DMP, TsOH, benzene, reflux, 4 h; (iii) LiOH, THF/H_2O/MeOH, r.t., 24 h; (*iv*) PyBroP, DIEA, DMAP, CH_2Cl_2, r.t., 24 h; (v) $Bi(OTf)_3$, CH_3CN, r.t., 10 min.

The first encouraging result was obtained by employing $BiBr_3$,[20] which catalyzed the hydrolysis of dipeptide **18** (100 mg; 0.2 mmol) in less than 4 h in 85–90% yields. Unfortunately, our attempts to scale-up the reaction by tripling the amount of starting material and keeping the other parameters unchanged, gave disappointing results. Indeed, the reaction proceeded slowly (24–48 h), and alcohol **4** was obtained in low yields (40–50%) along with significant amounts of undesired products. Specifically, we isolated lactone **I** and new side-product **III** (Scheme 4), analogous to **II**, but characterized by the presence of a benzyl carbonate instead of a free hydroxy group. This compound could arise either by nucleophilic attack of the dipeptide **4** *N*-protected amino group on the methyl ester, followed by migration of the Cbz group on the alcohol moiety, or by an unconventional first migration of the Cbz group from the nitrogen atom to the oxygen atom of the primary alcohol, followed by attack of the resulting free amino group on the methyl ester. Despite thorough experimentation, that included screens of various solvents [CH_3CN, CH_2Cl_2, $(CH_3)_2CO$, tetrahydrofuran (THF)], various amounts of Lewis acid (0.1–0.5 equiv.), different reaction concentrations (0.05–0.3 M) and temperatures (from room temperature to 60 °C), and conventional and microwave-assisted heating, we have never been able to repeat the results obtained even with small amounts of compound **18**. Although these results were difficult to rationalize, we thought that by accelerating the oxazolidine ring-opening step, it might be possible to minimize the formation of the side-products and, as a consequence, increase the yield of desired alcohol **4**. On the basis of this consideration, we took into account the use of bismuth(III) triflate, already employed in the catalytic deprotection of acetals and ketals.[21] It is known that metal centers of metal triflates are more cationic than those of metal halides;[22] we therefore expected that bismuth(III) triflate, which is a stronger Lewis acid than bismuth(III) bromide, would lead to more efficient activation



Scheme 4. Reagents and conditions: (i) allyltrimethylsilane, G2, DBBQ, ethylene, CH_2Cl_2, reflux, 6 h; (ii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, –60 °C then 0 °C, 2 h; (iii) allyltrimethylsilane, HG2, DBBQ, CH_2Cl_2, reflux, 8 h; (iv) $Sc(OTf)_3$, CH_2Cl_2, –10 °C then r.t., 5 h.

of the hemiaminal basic sites and consequently to a faster opening of the oxazolidine ring. In fact, by using commercial bismuth(III) triflate, the hydrolysis of the N,O-aminal was complete in only 10 min, with yields close to 90%, even on a gram scale.

The synthesis of target compound **4** was thus accomplished in 60% overall yield from benzylserine methyl ester **5**, which is significantly higher than the yield obtained with the first-generation approach. Moreover, the new protocol is characterized by a limited number of steps and can be easily applied to a multi-gram scale synthesis.

With good amounts of alcohol **4** in hand, we decided to introduce the allylsilane unit by exploiting a cross metathesis (CM) reaction with allyltrimethylsilane. The experiment was performed by applying typical metathesis reaction conditions, with the use of aprotic solvents, such as dichloromethane, dichloroethane, or toluene, and the Grubbs catalyst highlighted in Scheme 4.

In preliminary experiments, the Ru complex that turned out to be the most effective was **G2**, but the CM reaction was sluggish and resulted in low conversion yields (<30%) even if the temperature was raised and the reaction time extended. In addition, we isolated desired product **19** along with the expected 1,4-bis(trimethylsilyl)but-2-ene, which arises from homocoupling of allyltrimethylsilane, diketopiperazine **III**, and compound **IV**, which are generated by double-bond migration of the allyl moiety of alcohol **4**. The isomerization of terminal alkenes to internal alkenes promoted by ruthenium–carbene complexes is well known[23] and has found various synthetic applications.[24] It was proposed that the ruthenium species responsible for isomerization was a ruthenium hydride generated in situ either by impurities[25] or decomposition of the Grubbs catalysts, e.g. by silyl enol ethers,[26] hydrogen,[27] inorganic hydrides,[28] and traces of alcohols.[29]

A possible way to suppress the unwanted olefin isomerization reaction is by addition of a moderate pK_a acid, such as acetic acid, or quinone-type compounds, such as 1,4-benzoquinone.[30] These additives are able to prevent the formation of ruthenium hydride by reacting with hydride species generated under metathesis conditions. Among various benzoquinones, we decided to exploit the use of 2,6-dichloro-1,4-benzoquinone (DBBQ), an electron-deficient derivative reported to be highly effective in the prevention of olefin migration in reactions catalyzed by **G2**. Moreover, with the aim to reduce the amount of bis(silane) side product that arises from self-metathesis of allyltrimethylsilane, we thought to take advantage of an ethenolysis, namely a CM reaction of an olefinic compound and ethene. By carrying out the reaction under gaseous ethylene and in the presence of a catalytic amount of DBBQ we obtained **19** as a 7:3 mixture of (*E*)/(*Z*) isomers in a satisfactory 75% yield. Subsequent Swern oxidation of dipeptide **19** gave aldehyde **3**, the starting material for our intramolecular Sakurai reaction studies, in 90% yield.

The formation of diketopiperazine side product **III**, in which the free hydroxy group of dipeptide **4** is strongly involved, remained one of the unresolved issues of this synthetic approach. To further optimize the synthetic protocol and minimize collateral reactions of alcohol **4**, we decided to anticipate the oxidation step. The Swern reaction to give **20** proceeded in a yield very similar to that previously reported for the synthesis of **3**, whereas the introduction of the allylsilane moiety required a different experiment. The best CM catalyst proved to be **HG2**, which converted **20** into trimethylsilyl derivative **3**, as a 7:3 mixture of (*E*)/(*Z*) isomers, in 84% yield. It is worthy to note that, in this case, the use of ethylene did not lead to any benefit; it can therefore be omitted, with significant cost savings and synthetic protocol simplification.

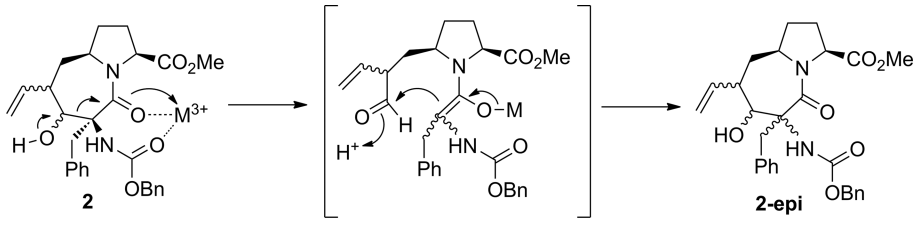
From the outset it was only possible to obtain a few milligrams of diastereoisomeric pure compounds **3a** and **3b**, the chromatographic separation of which proved to be very difficult; therefore, the final cyclization was performed with the (*E*)/(*Z*) mixture of the two diastereoisomers. After an extensive investigation of various Lewis acids able to promote this intramolecular Sakurai allylation, we found that scandium triflate was the best one in terms of yield and mild reaction conditions. Among the Lewis acids tested, CuCl, $ZnCl_2$, $NiCl_2$, $CeCl_3$, $InCl_3$, and $BiBr_3$ gave exclusively proto-desilylation of dipeptide **3**, whereas the use of $BF_3{\cdot}Et_2O$, $TiCl_4$, and $NbCl_5$ also gave traces of three diastereoisomeric alcohols **2a**–**2c**. By employing $In(OTf)_3$ it was possible to isolate alcohols **2** in 35% overall yield, whereas lanthanide triflates, such as $La(OTf)_3$, $Yb(OTf)_3$, and $Eu(OTf)_3$, were unable to catalyze the cyclization reaction.

The use of a stoichiometric amount of $Sc(OTf)_3$ afforded desired alcohols **2**, as a mixture of 3 out of the potential 4 diastereoisomers that arise from the generation of the seven-membered lactam ring, with an overall yield of 86%. Attempts to reduce the amount of the Lewis acid resulted in lower conversion rates. By performing the reaction in the presence of protic acids such as trifluoroacetic or methanesulfonic acid, rapid proto-desilylation of dipeptide **3** occurred, which led to conversion of the (trimethylsilyl)allyl moiety into a butenyl group. Finally, by employing molecular iodine, which is also reported to catalyze similar transformations, we obtained the same previously described diastereoisomeric mixture of alcohols **2**, but in yields not higher than 15%.

Configurational Assignments

Configurational assignments were performed by 2D-NOESY experiments. Analysis of NOE correlations between relevant hydrogen atoms clearly evidenced that the configuration of the C3 and C7 stereocenters was not affected by the cyclization reaction. The quaternary C3 stereocenter of the final products could, in principle, epimerize through an acid-catalyzed retro-aldol reaction of the β-hydroxy amide group, followed by a subsequent aldol reaction between the amide enol and the newly created aldehyde function (Scheme 5).

All the diastereoisomers showed an evident NOE correlation between H_7 and Hb (Figure 1), which suggests that



Scheme 5. Possible mechanism for the acid-catalyzed epimerization of the C3 stereocenter.

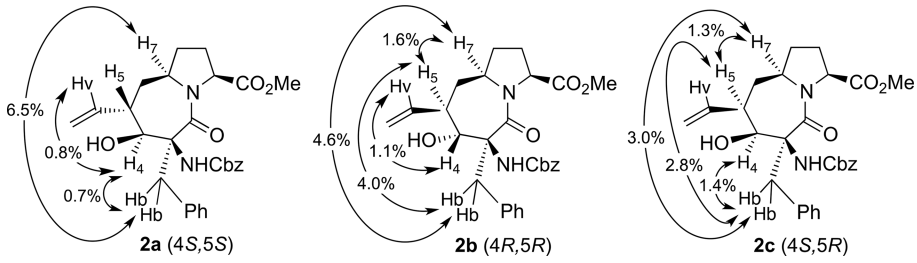


Figure 1. Relevant NOE correlations exhibited by compounds **2a**, **2b**, and **2c** (curved arrows).

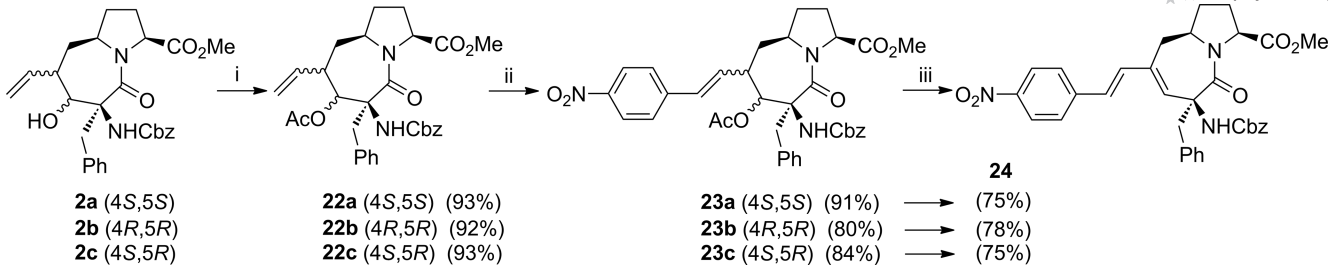
the seven-membered ring has some favored conformations in which the benzyl moiety is folded into the inner side of the lactam.

For alcohol **2a**, NOEs of H_4 with Hb and Hv are particularly diagnostic for the (*S*) absolute configuration of the C4 stereocenter. The opposite C5 configuration of alcohol **2b** was deduced by the presence of an NOE between H_5 and H_7, whereas an NOE of H_4 with Hv and the lack of a correlation signal between H_4 and Hb are indicative of the (*R*) configuration at C4. Further experimental evidence of the (*R*) absolute configuration at C5 is the NOE between H_5 and Hb. The fact that both, the H_5 and the benzyl moiety, are oriented towards the same side of the bicyclic scaffold, is confirmed in the ^{1}H NMR spectrum of **2b**. Indeed, the H_5 resonance is shifted to higher frequency (δ = 2.8 versus 2.3 ppm for **2b** and **2a**, respectively), which suggests that in alcohol **2b** the H_5 proton is affected by the anisotropic deshielding effect of the aromatic ring. This effect is clearly evident in alcohol **2c**, in which the absolute configuration of the C5 stereocenter is the same as in **2b**. Finally, the (*S*) configuration at C4 of the last diastereoisomer **2c** was attributed on the basis of an NOE signal correlating H_4 and Hb.

By following the hypothesis that scandium triflate could be involved in the stereochemistry-determining step, we were curious to see whether the use of chiral scandium(III) bis(oxazoline) (box) or pyridyl-bis(oxazoline) (pybox) complexes could be exploited as valuable stereocontrolling agents, which could enhance the low diastereoselection exerted by the Lewis acid alone. Among the various commercially available ligands tested, only (–)-2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine furnished alcohol **2a** as a single diastereoisomer, albeit in low yield (20%) and reduced reaction rate. The use of other box or pybox derivatives had a strong detrimental effect on the catalytic activity of scandium(III) triflate, and only traces of diastereoisomer **2a** along with unreacted starting material were recovered.

Functionalization of the C5 Exocyclic Vinyl Group

Because the following objective of the project was the attachment to the exocyclic vinyl function of a suitable linker necessary to the obtainment of conjugate derivatives, it seemed mandatory to ascertain the reactivity of the exocyclic double bond. To this end, we decided to couple the less-substituted position of the vinyl function with a *p*-nitrophenyl moiety through a Heck reaction with 1-bromo-4-nitrobenzene. The introduction of this aromatic moiety can be regarded as a model of "adaptable linker". Indeed, the *p*-nitro group could be exploited to directly conjugate the bioactive compound, e.g. through reduction of the nitro group followed by formation of an amide bond. Alternatively, the aromatic amine that derives from reduction could be efficiently converted into an azide, and treated in a one-pot "click" reaction with an alkynyl moiety.[31] To avoid the formation of possible side products, the presence of the free C4 hydroxy group must be considered with caution, because it could be reactive towards the adjacent Cbz-protected amino group. Indeed, the basic conditions needed for the coupling reaction could increase the nucleophilicity of the alcoholic function and lead to the formation of tricyclic oxazolidinone side-products generated by intramolecular attack on the carbamate carbonyl group. On the basis of these assumptions, we decided to convert alcohols **2a**–**2c** into the corresponding acetate esters **22a**–**22c** that were then separately submitted to Heck coupling experiments (Scheme 6). We were particularly interested in the use of immobilized transition metal catalysts as the palladium source, which offer the promise of easy handling, straightforward separation from the reaction mixture, and decreased product contamination as a result of metal leaching. The latter issue is particularly important in the field of active pharmaceutical ingredients, in which the reduction of palladium content at the ppm level is required. The best results were obtained in the presence of commercially avail-



Scheme 6. Reagents and conditions: (i) Ac_2O, DMAP, CH_2Cl_2, 60 °C (microwave), 1 h; (ii) 4-bromo-nitrobenzene, PdEnCat 30, Bu_4NOAc, EtOH, 120 °C (microwave); (iii) DBU, THF, 80 °C (microwave).

able PdEnCat 30, a polyurea-encapsulated $Pd(OAc)_2$ catalyst reported to be applicable to a variety of cross-coupling reactions, including the Heck coupling reaction.[32] By performing the reaction with microwave heating, we synthesized the desired functionalized scaffolds **23a**–**23c** without the need of any phosphine ligands in high yields (80–91%) and relatively short reaction times (<1 h), thus confirming the high reactivity of the exocyclic double bonds.

For the sake of completeness, we tested whether functionalized scaffolds **23a**–**23c** could be converted into the same diene derivative **24**, which allowed further optimization of our synthetic strategy. The elimination reaction, realized by heating each compound in the presence of DBU, afforded **24** in satisfactory yields (75–78%). The same procedure could also be performed with comparable yields by starting from a diastereoisomeric mixture of derivatives **23a**–**23c**.

Computational Studies

Computational studies designed to investigate the ability of the new azabicycloalkane scaffolds to adopt reverse-turn conformations were performed on *N*-acetyl-*N*′-methylamide dipeptide analogues **25a**–**25c** (Supporting Information, Figure S3), featuring capping groups on the N- and C-termini suitable for the definition of the various turn and H-bond parameters. The preferred conformations of each stereoisomeric scaffold were analyzed relative to the structures of the parent 7,5-fused azabicyclolactam derivative **25**. The turn propensity was quantitatively assessed by computing the percentage of conformations for which the aforementioned parameters assume typical turn values. A summary of the reverse-turn mimetic properties of the calculated structures is reported in Table S1.

The quantitative characterization of the turn propensity of the functionalized azabicycloalkane amino acid scaffolds suggests that these systems are more effective as reverse-turn mimetics than as β- or γ-turn mimics, in agreement with the results obtained for the unsubstituted bicyclic lactam. In fact, the percentages of conformers with a torsion angle β (absolute value) of less than 60° are within a range of 71–94%, whereas the percentages of conformers that form intramolecular hydrogen bonds (by stabilizing either a γ-turn or a β-turn) are significantly lower (20–37% for γ-turn, 0% for β-turn, see Table S1). The analysis of the $C\alpha_i$-$C\alpha_{i+3}$ distance ($d\alpha$) confirms that the reverse-turn mimetic scaffolds induce rather "open" turns. Accordingly, the lowest-energy conformer of **25** and **25a**–**25c** features an open turn, which induces the peptide backbone to reverse direction (Figure S4).

Conclusions

We have reported a new synthetic strategy to obtain 7,5-fused 2-oxo-1-azabicycloalkane scaffolds characterized by the presence of a vinyl moiety and a hydroxy group on the seven-membered lactam ring at C5 and C4 positions, respectively. These scaffolds are useful intermediates for the synthesis of cRGD-based bioconjugates, which could find potential applications in anticancer therapy. The key reaction in the synthetic scheme is an intramolecular Hosomi–Sakurai reaction, which allows the simultaneous generation of both the lactam ring and the exocyclic double bond. The synthetic sequence allows the gram-scale preparation of scaffolds **2** in 8 steps and good 39% overall yield starting from readily accessible materials. Even if the C5 exocyclic double bond was designed as the privileged attachment point for the conjugation of bioactive compounds, the hydroxy group at C4 could be either a suitable conjugation alternative, or a further conjugation site. In the case of exclusive functionalization of the vinyl appendage, the OH group should also be protected or eliminated, e.g. through its conversion into an acetate or the formation of a C=C double bond, by applying the reported functionalization strategy. Finally, the C5 vinyl moiety has shown to be easily functionalizable through a Heck-coupling reaction, thus demonstrating it could be exploited as a point of attachment for the synthesis of conjugate derivatives.

Experimental Section

General: All chemicals were of reagent grade and were used without further purification. Solvents were purified in accordance with the guidelines in Purification of Laboratory Chemicals.[33] All solvents were freshly distilled from the appropriate drying agent. THF and toluene were distilled from sodium/benzophenone ketyl, and triethylamine (TEA) and CH_2Cl_2 from CaH_2. Reactions that required anhydrous conditions were performed under N_2. Yields were calculated for compounds purified by flash chromatography and judged homogeneous by thin-layer chromatography, NMR spectroscopy,

and mass spectrometry. Thin layer chromatography was performed with Kieselgel 60 F_{254} (Merck) glass plates, and compounds were 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 with 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. IR spectra were recorded with a Perkin–Elmer ATR-FTIR 1600 series spectrometer by using neat samples. Mass spectra were recorded with a Finnigan LCQ-DECA mass spectrometer. Elemental analyses were performed with a Carlo Erba Elemental Analyzer Mod. 1106. Glassware for all reactions was oven-dried at 110 °C and cooled in a desiccator, or flame-dried and cooled under an inert gas prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septum-sealed flasks under an inert gas.

Spectroscopic Methods: NMR spectra were acquired at 400 MHz for ^{1}H and 100 MHz for ^{13}C with 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. The coupling constant values of complex multiplets (e.g. dddd, ddddd) were confirmed by using multiplet simulation procedures. In the peak listing of ^{13}C spectra abbreviations s and t refer to zero and two protons attached to the carbon atoms, respectively, as determined by DEPT-135 experiments. Phase-sensitive 2D-NOESY experiments were performed at 298 K by using the noesygpph pulse program from the Bruker library (mixing time of 0.5 s). Sample temperatures were controlled with the variable-temperature unit of the instrument.

Synthesis of Methyl (*S*)-2-Benzyl-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (6): To a solution of Boc_2O (6.8 g, 31.1 mmol) in dry THF (95 mL) under nitrogen and at 0 °C compound **5** (23.9 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 24 h. A saturated solution of NaCl (100 mL) was added to quench the reaction, and the aqueous phase was extracted with Et_2O and CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 6:4) to obtain pure compound **6** as a pale yellow oil (88%). R_f = 0.4 (hexane/EtOAc, 60:40). $[\alpha]_D^{22}$ –50.6 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3423 (br.), 1741, 1710, 1495, 1159 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 1.44 (s, 9 H), 3.16 (d, J = 13.5 Hz, 1 H), 3.25 (d, J = 13.5 Hz, 1 H), 3.60 (dd, J = 5.2, 10.8 Hz, 1 H), 3.63–3.67 (m, 4 H), 4.64 (app t, 1 H, exchanges with D_2O), 5.97 (s, 1 H), 7.10–7.17 (m, 2 H), 7.18–7.30 (m, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 29.1, 37.5 (t), 52.4, 63.7 (t), 65.4 (s), 79.4 (s), 127.2, 128.6, 131.0, 137.3 (s), 155.1 (s), 173.2 (s) ppm. MS (ESI): m/z = 332.4 [M + Na]$^+$. $C_{16}H_{23}NO_5$ (309.36): calcd. C 62.12, H 7.49, N 4.53; found C 62.33, H 7.27, N 4.42.

Synthesis of (*S*)-2-Benzyl-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoic Acid (7): To a solution of **6** (350 mg, 1.13 mmol) in THF (11.3 mL) were added sequentially a solution of $LiOH{\cdot}H_2O$ (2.26 mmol) in water (5.3 mL) and MeOH until a homogeneous solution was obtained. The reaction mixture was stirred at room temperature for 2.5 h. After the reaction was complete (TLC analysis), THF and MeOH were removed under reduced pressure, and aqueous $NaHCO_3$ was added. The aqueous phase was washed twice with EtOAc, acidified with HCl (1 N) to pH = 1 and extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo to obtain compound **7** as an amorphous solid, without further purification (92%). R_f = 0.30 (EtOAc). $[\alpha]_D^{22}$ –37.1 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3402 (br.), 1706, 1683, 1495, 1158 cm^{-1}. ^{1}H NMR ([D$_6$]-DMSO, 90 °C, 400 MHz): δ = 1.44 (s, 9 H), 3.16 (d, J = 13.5 Hz, 1 H), 3.22 (d, J = 13.4 Hz, 1 H), 3.66 (d, J = 10.6 Hz, 1 H), 3.79 (d, J = 10.6 Hz, 1 H), 4.82–5.18 (br. s, 1 H, exchanges with D_2O), 5.72 (s, 1 H), 7.13–7.30 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 29.2, 37.4 (t), 64.1 (t), 65.5 (s), 79.2 (s), 127.1, 128.6, 131.0, 137.6 (s), 154.9 (s), 173.9 (s) ppm. MS (ESI): m/z = 296.3 [M + H]$^+$, 318.3 [M + Na]$^+$. $C_{15}H_{21}NO_5$ (295.33): calcd. C 61.00, H 7.17, N 4.74; found C 60.84, H 7.23, N 4.65.

Synthesis of Benzyl (*S*)-2-Benzyl-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (8): To a solution of **7** (5 g, 16.9 mmol) in dry CH_3CN (170 mL) under nitrogen were added sequentially $CsCO_3$ (20.3 mmol) and benzyl bromide (20.3 mmol). The reaction mixture was warmed to 50 °C and stirred for 1 h. After the reaction was complete (TLC analysis), the CH_3CN was removed under reduced pressure. Deionized water was added, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography to obtain pure compound **8** as an amorphous solid (84%). R_f = 0.34 (hexane/EtOAc, 75:25). $[\alpha]_D^{22}$ = +4.0 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3415, 1738, 1710, 1495, 1163 cm^{-1}. ^{1}H NMR ([D$_6$]-DMSO, 90 °C, 400 MHz): δ = 1.42 (s, 9 H), 3.18 (d, J = 13.5 Hz, 1 H), 3.31 (d, J = 13.5 Hz, 1 H), 3.64 (d, J = 13.5 Hz, 1 H), 3.67 (d, J = 13.5 Hz, 1 H), 4.51–4.89 (br. s, 1 H, exchanges with D_2O), 5.11 (d, J = 12.7 Hz, 1 H), 5.15 (d, J = 12.6 Hz, 2 H), 6.07 (s, 1 H), 7.09–7.16 (m, 2 H), 7.17–7.27 (m, 3 H), 7.29–7.40 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 29.1, 37.5 (t), 63.7 (t), 65.3 (s), 67.0 (t), 79.4 (s), 127.2, 128.6 (2 C), 128.7, 129.1, 131.1, 136.9 (s), 137.2 (s), 155.1 (s), 172.6 (s) ppm. MS (ESI): m/z = 408.4 [M + Na]$^+$. $C_{22}H_{27}NO_5$ (385.46): calcd. C 68.55, H 7.06, N 3.63; found C 68.78, H 7.22, N 3.68.

Synthesis of Benzyl (*S*)-2-Amino-2-benzyl-3-hydroxypropanoate (9): A solution of compound **8** (1 g, 2.60 mmol), in saturated HCl methanol (5 mL) was stirred at 0 °C for 3 h. After the reaction was complete (TLC analysis), the MeOH was removed under reduced pressure. The crude mixture was dissolved in deionized water (15 mL) and washed with Et_2O (3 × 5 mL). After basification with solid K_2CO_3, the aqueous phase was carefully extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo to obtain compound **9** as an amorphous solid without further purification. R_f = 0.31 (EtOAc/hexane, 7:3). $[\alpha]_D^{22}$ = +35.4 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3336, 3294, 3163 (br.), 1734, 1494, 1172 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 1.62–2.30 (br., 2 H, exchanges with D_2O), 2.77 (d, J = 13.3 Hz, 1 H), 2.98 (d, J = 13.3 Hz, 1 H), 3.45 (d, J = 10.3 Hz, 1 H), 3.75 (d, J = 10.3 Hz, 1 H), 4.38–4.89 (br., 1 H, exchanges with D_2O), 5.10 (s, *2* H), 7.11–7.16 (m, 2 H), 7.18–7.24 (m, 3 H), 7.31–7.39 (m, 5 H) ppm. ^{13}C NMR ([D$_6$] DMSO, 90 °C, 100 MHz): δ = 42.7 (t), 64.4 (s), 66.8 (t), 68.5 (t), 127.2, 128.6, 128.7 (2 C), 129.1, 130.9, 137.0 (s), 137.4 (s), 175.5 (s) ppm. MS (ESI): m/z = 286.3 [M + H]$^+$, 308.3 [M + Na]$^+$. $C_{17}H_{19}NO_3$ (285.34): calcd. C 71.56, H 6.71, N 4.91; found C 71.41, H 6.54, N 4.82.

Synthesis of Benzyl (*S*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoate (10): To a solution of Cbz_2O (920 mg, 3.21 mmol) in dry THF (10.5 mL) under nitrogen at 0 °C, compound **9** (705 mg, 2.47 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 1 h. After the

reaction was complete (TLC analysis), a saturated NaCl solution was added to quench the reaction, and the aqueous phase was extracted once with Et_2O and twice with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 60:40) to obtain the pure compound as a yellow oil (92%, 2 steps). R_f = 0.28 (hexane/EtOAc, 60:40). $[\alpha]_D^{22}$ –10.1 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3409 (br.), 1712, 1495, 1213 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 3.19 (d, J = 13.5 Hz, 1 H), 3.31 (d, J = 13.5 Hz, 1 H), 3.68 (d, J = 5.2, 11.2 Hz, 1 H), 3.71 (d, J = 5.2, 11.2 Hz, 1 H), 4.76 (app t, J = 5.2 Hz, 1 H, exchanges with D_2O), 5.06 (d, J = 12.6 Hz, 1 H), 5.09 (d, J = 12.6 Hz, 1 H), 5.11 (s, 2 H), 6.61 (s, 1 H), 7.04–7.12 (m, 2 H), 7.15–7.23 (m, 3 H), 7.22–7.42 (m, 10 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 37.5 (t), 63.4 (t), 65.6 (s), 66.4 (t), 67.1 (t), 127.2, 128.5, (3 C), 128.6 (3 C), 128.7 (2 C), 129.1 (2 C), 131.1, 136.8 (s), 136.9 (s), 137.9 (s), 155.7 (s), 172.4 (s) ppm. MS (ESI): m/z = 442.5 $[M + Na]^+$. $C_{25}H_{25}NO_5$ (419.48): calcd. C 71.58, H 6.01, N 3.34; found C 71.82, H 6.08, N 3.42.

Synthesis of Benzyl (*S*)-3-Acetoxy-2-benzyl-2-(benzyloxycarbonylamino)propanoate (11): To a solution of **10** (1.98 g, 4.30 mmol) in dry CH_2Cl_2 (17.2 mL) under nitrogen were added sequentially Et_3N (4.30 mmol), Ac_2O (12.87 mmol) and 4-(dimethylamino)pyridine (DMAP; 0.86 mmol). The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete (TLC analysis), a saturated solution of NH_4Cl was added to quench the reaction, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 75:25) to obtain pure compound **11** as an oil (93%). R_f = 0.40 (hexane/EtOAc, 75:25). $[\alpha]_D^{22}$ –38.8 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3419, 1741, 1718, 1495, 1214 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 2.00 (s, 3 H), 3.18 (d, J = 13.7 Hz, 1 H), 3.29 (d, J = 13.7 Hz, 1 H), 4.22 (d, J = 11.3 Hz, 1 H), 4.37 (d, J = 11.3 Hz, 1 H), 5.06 (d, J = 12.6 Hz, 1 H), 5.09 (d, J = 12.4 Hz, 1 H), 5.10 (d, J = 12.6 Hz, 1 H), 5.12 (d, J = 12.4 Hz, 1 H), 7.01–7.07 (m, 2 H), 7.15 (br. s, 1 H), 7.20–7.25 (m, 3 H), 7.29–7.41 (m, 10 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 21.1, 38.7 (t), 63.4 (s), 64.0 (t), 66.6 (t), 67.5 (t), 127.7, 128.5, 128.6, 128.9 (3 C), 129.1, 129.2, 131.0, 135.8 (s), 136.5 (s), 137.8 (s), 155.6 (s), 170.4 (s), 171.2 (s) ppm. MS (ESI): m/z = 462.5 $[M + H]^+$, 484.5 $[M + Na]^+$. $C_{27}H_{27}NO_6$ (461.51): calcd. C 70.27, H 5.90, N 3.03; found C 70.39, H 5.83, N 2.97.

Synthesis of (*S*)-3-Acetoxy-2-benzyl-2-(benzyloxycarbonylamino)-propanoic Acid (12): To a solution of **11** (961 mg, 2.08 mmol) in absolute EtOH (8.3 mL), under H_2 (balloon), was added Pd/C(en) (en = ethylenediamine) (961 mg). The reaction mixture was stirred at room temperature for 3 h. After complete consumption of the starting material, the reaction mixture was filtered through a pad of Celite, and the organic phase was removed under reduced pressure. The residue was taken up with a saturated aqueous solution of $NaHCO_3$ and washed with Et_2O. The aqueous phase was cooled to 0 °C, acidified to pH = 1 with HCl (12 N), and extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo to obtain the pure compound as an amorphous solid without further purification (60%). R_f = 0.44 (EtOAc/MeOH, 80:20). $[\alpha]_D^{22}$ –43.4 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3412 (br.), 1738, 1714, 1495, 1214 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 2.02 (s, 3 H), 3.19 (d, J = 13.6 Hz, 1 H), 3.25 (d, J = 13.6 Hz, 1 H), 4.37 (AB system, J = 11.3 Hz, 2 H), 5.09 (AB system, J = 13.2 Hz, 2 H), 6.63 (br. s, 1 H), 7.07–7.16 (m, 2 H), 7.18–7.29 (m, 3 H), 7.30–7.49 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 21.2, 38.4 (t), 63.4 (s), 64.6 (t), 66.5 (t), 127.6, 128.5, 128.6, 128.8, 129.1, 130.8, 136.2 (s), 137.9 (s), 155.3 (s), 170.4 (s), 172.4 (s) ppm. MS (ESI): m/z = 372.4 $[M + H]^+$, 394.4 $[M + Na]^+$. $C_{20}H_{21}NO_6$ (371.39): calcd. C 64.68, H 5.70, N 3.77; found C 64.81, H 5.65, N 3.89.

Synthesis of Methyl (2*S*,5*R*)-1-[(*S*)-3-Acetoxy-2-benzyl-2-(benzyloxycarbonylamino)propanoyl]-5-allylpyrrolidine-2-carboxylate (14): To a solution of **12** (150 mg, 0.40 mmol) in dry CH_2Cl_2 (1.6 mL) under nitrogen were added sequentially *N*,*N*-diisopropylethylamine (DIEA; 0.44 mmol) and PyBroP (0.44 mmol). The reaction mixture was stirred at room temperature for 2 h; then a solution of **13** (68 mg, 0.40 mmol) in dry CH_2Cl_2 (1.6 mL) and DMAP (0.04 mmol) were added. After 24 h, the organic phase was concentrated under reduced pressure, and the crude mixture was purified by flash chromatography (hexane/EtOAc, 70:30) to obtain compound **14** as a pale yellow oil (60%). R_f = 0.37 (hexane/EtOAc, 70:30). $[\alpha]_D^{22}$ –59.1 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3308, 1790, 1742, 1633, 1214 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 1.66 (m, 1 H), 1.79 (m, 1 H), 1.88–2.02 (m, 2 H), 2.03 (s, 3 H), 2.25 (m, 1 H), 2.64 (m, 1 H), 3.23 (s, 2 H), 3.66 (s, 3 H), 4.08 (d, J = 11.5 Hz, 1 H), 4.38 (m, 1 H), 4.48 (d, J = 11.5 Hz, 1 H), 4.64 (app t, J = 6.3 Hz, 1 H), 4.98–5.12 (m, 4 H), 5.81 (m, 1 H), 7.10–7.19 (m, 3 H), 7.20–7.28 (m, 3 H), 7.29–7.41 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 21.2, 28.4 (t), 29.1 (t), 39.0 (t), 39.2 (t), 52.4, 59.5, 61.2, 63.4 (s), 64.0 (t), 66.8 (t), 117.4 (t), 127.6, 128.6, 128.8, 129.0, 131.0, 131.2, 136.0 (s), 136.2, 137.7 (s), 155.3 (s), 169.6 (s), 170.4 (s), 173.3 (s) ppm. MS (ESI): m/z = 523.6 $[M + H]^+$, 545.6 $[M + Na]^+$. $C_{29}H_{34}N_2O_7$ (522.60): calcd. C 66.65, H 6.56, N 5.36; found C 66.79, H 6.44, N 5.29.

Synthesis of Methyl (2*S*,5*R*)-5-Allyl-1-[(*S*)-2-benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoyl]pyrrolidine-2-carboxylate (4). Starting from Compound 14: A solution of **14** (100 mg, 0.19 mmol), in HCl-saturated methanol (0.5 mL) was stirred at 0 °C for 5 h. After complete consumption of the starting material, the reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ until neutralized, and extracted with EtOAc. The organic phases were collected, dried with Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 6:4) to obtain **4** as an oil (47%). **Starting from Compound 18:** To compound **18** (2.15 g, 4.13 mmol) solubilized in dry CH_3CN under nitrogen was added bismuth triflate (1.35 g, 2.06 mmol). After 10 min, a saturated solution of $NaHCO_3$ was added to quench the reaction, until neutral pH was reached; then the mixture was quickly extracted with CH_2Cl_2. The organic phases were collected, dried with Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (CH_2Cl_2/Et_2O, 9:1) to obtain **4** as an oil (86%). R_f = 0.36 (hexane/EtOAc, 6:4), R_f = 0.30 (CH_2Cl_2/Et_2O, 9:1). $[\alpha]_D^{22}$ –10.4 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3376 (br.), 1720, 1621, 1495, 1395 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 90 °C, 400 MHz): δ = 1.64 (m, 1 H), 1.78 (m, 1 H), 1.90 (m, 1 H), 2.01 (m, 1 H), 2.22 (m, 1 H), 2.65 (m, 1 H), 3.17 (d, J = 13.8 Hz, 1 H), 3.25 (d, J = 13.8 Hz, 1 H), 3.62 (dd, J = 5.3, 11.3 Hz, 1 H), 3.64 (s, 3 H), 3.73 (dd, J = 5.3, 11.3 Hz, 1 H), 4.31–4.41 (br., 1 H), 4.42 (app t, J = 5.3 Hz, 1 H, exchanges with D_2O), 4.64 (m, 1 H), 4.96–5.11 (m, 4 H), 5.79 (m, 1 H), 6.78 (s, 1 H), 7.12–7.25 (m, 5 H), 7.29–7.42 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 90 °C, 100 MHz): δ = 28.2 (t), 29.1 (t), 38.1 (t), 39.1 (t), 52.4, 59.4, 61.2, 62.5 (t), 65.3 (s), 66.5 (t), 117.3 (t), 127.1, 128.6 (2 C), 128.7, 129.1, 131.4, 136.5, 137.2 (s), 137.8 (s), 155.4 (s), 170.8 (s), 173.6 (s) ppm. MS (ESI): m/z = 481.5 $[M + H]^+$, 503.5 $[M + Na]^+$. $C_{27}H_{32}N_2O_6$ (480.56): calcd. C 67.48, H 6.71, N 5.83; found C 67.24, H 6.73, N 5.91.

Synthesis of 3-Benzyl 4-Methyl (*S*)-4-Benzyl-2,2-dimethyloxazolidine-3,4-dicarboxylate (16): To compound **15** (307 mg, 0.89 mmol) solubilized in dry benzene (10.2 mL) under nitrogen were sequentially added 2,2-dimethoxypropane (4.47 mmol) and *p*-toluensulfonic acid (PTSA·H_2O; 0.06 mmol). The reaction mixture was heated to reflux with a Dean–Stark apparatus for 2 h to remove H_2O. After the reaction was complete (TLC analysis), a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous phase was extracted with EtOAc, and the organic phases were collected, dried with anhydrous Na_2SO_4 filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 8:2) to obtain **16** as a pale yellow oil (94%). R_f = 0.36 (hexane/EtOAc, 8:2). $[\alpha]_D^{22}$ = +91.6 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 1739, 1696, 1399, 1380, 1343, 1244, 1068 cm^{-1}. ^1H NMR ([D_6]DMSO, 120 °C, 400 MHz): δ = 0.83 (s, 3 H), 1.49 (s, 3 H), 3.13 (d, J = 13.9 Hz, 1 H), 3.49 (d, J = 13.8 Hz, 1 H), 3.65 (s, 3 H), 4.04 (d, J = 9.4 Hz, 1 H), 4.15 (d, J = 9.4 Hz, 1 H), 5.11 (d, J = 12.3 Hz, 1 H), 5.20 (d, J = 12.3 Hz, 1 H), 7.10–7.16 (m, 2 H), 7.19–7.27 (m, 3 H), 7.33–7.44 (m, 5 H) ppm. ^{13}C NMR ([D_6]DMSO, 100 °C, 100 MHz): δ = 25.0, 25.5, 38.6 (t), 53.2, 67.3 (t), 69.6 (s), 71.5 (t), 96.9 (s), 127.5, 128.6, 128.8, 128.9, 129.2, 131.7, 136.9 (s), 137.3 (s), 152.5 (s), 173.0 (s) ppm. MS (ESI): m/z = 384.4 $[M + H]^+$, 406.4 $[M + Na]^+$. $C_{22}H_{25}NO_5$ (383.44): calcd. C 68.91, H 6.57, N 3.65; found C 69.07, H 6.45, N 3.60.

Synthesis of (*S*)-4-Benzyl-3-(benzyloxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic Acid (17): To a solution of **16** (316 mg, 0.82 mmol) in THF (9 mL) were added sequentially a solution of LiOH·H_2O (3.29 mmol) in water (2 mL) and MeOH until a homogeneous solution was obtained. The reaction mixture was stirred at room temperature for 24 h. After the reaction was complete (TLC analysis), THF and MeOH were removed under reduced pressure, and a saturated solution of $NaHCO_3$ was added. The aqueous phase was washed with Et_2O, acidified with HCl (1 N) to pH = 1, and extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo to obtain compound **17** as an amorphous solid without further purification (92%). R_f = 0.3 (CH_2Cl_2/MeOH, 9:1, 0.1% AcOH). $[\alpha]_D^{22}$ = +96.3 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3172 (br.), 1740, 1699, 1346 cm^{-1}. ^1H NMR ([D_6]DMSO, 120 °C, 400 MHz): δ = 0.87 (s, 3 H), 1.50 (s, 3 H), 3.13 (d, J = 13.9 Hz, 1 H), 3.53 (d, J = 13.9 Hz, 1 H), 4.07 (d, J = 9.2 Hz, 1 H), 4.14 (d, J = 9.2 Hz, 1 H), 5.17 (AB system, 2 H), 7.11–7.16 (m, 2 H), 7.17–7.25 (m, 3 H), 7.30–7.46 (m, 5 H) ppm. ^{13}C NMR ([D_6]DMSO, 120 °C, 100 MHz): δ = 25.1, 25.6, 38.8 (t), 67.2 (t), 69.6 (s), 71.8 (t), 96.8 (s), 127.3, 128.5, 128.7 (2 C), 129.1, 131.6, 137.4 (s, 2 C), 152.7, (s), 173.8, (s) ppm. MS (ESI): m/z = 370.4, $[M + H]^+$, 392.4, $[M + Na]^+$. $C_{21}H_{23}NO_5$ (369.42): calcd. C 68.28, H 6.28, N 3.79; found C 68.53, H 6.18, N 3.87.

Synthesis of Benzyl (*S*)-4-[(2*R*,5*S*)-2-Allyl-5-(methoxycarbonyl)-pyrrolidine-1-carbonyl]-4-benzyl-2,2-dimethyloxazolidine-3-carboxylate (18): Compounds **17** (1.78 g, 4.84 mmol) and **13** (1 g, 5.91 mmol) were solubilized in dry CH_2Cl_2 (52.8 mL) under nitrogen. After 5 min, DIEA (5 mmol), PyBroP (5 mmol), and DMAP (1.82 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 24 h. After the reaction was complete (TLC analysis), the solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography (hexane/EtOAc, 75:25) to obtain compound **18** as a pale yellow oil (85%). R_f = 0.36 (hexane/EtOAc, 75:25). $[\alpha]_D^{22}$ = +20.5 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 1748, 1703, 1638, 1341 cm^{-1}. ^1H NMR ([D_6]-DMSO, 120 °C, 400 MHz): δ = 0.86 (s, 3 H), 1.45 (s, 3 H), 1.62 (m, 1 H), 1.92–2.14 (m, 3 H), 2.23 (m, 1 H), 2.68 (m, 1 H), 3.15 (d, J = 13.4 Hz, 1 H), 3.56 (d, J = 13.4 Hz, 1 H), 3.68 (s, 3 H), 4.04 (d, J = 9.3 Hz, 1 H), 4.23 (m, 1 H), 4.32 (d, J = 9.3 Hz, 1 H), 4.71 (dd, J = 4.0, 7.8 Hz, 1 H), 4.99–5.16 (m, 4 H), 5.82 (m, 1 H), 7.11–7.28 (m, 5 H), 7.29–7.53 (m, 5 H) ppm. ^{13}C NMR ([D_6] DMSO, 120 °C, 100 MHz): δ = 24.7, 25.6, 29.1 (t), 29.7 (t), 39.4 (t), 39.8 (t), 52.7, 60.4, 61.8, 67.1 (t), 71.3 (t), 72.2 (s), 96.6 (s), 117.2 (t), 127.3, 128.5, 128.6, 128.8, 129.1, 131.6, 136.2, 137.4 (s), 137.5 (s), 153.1 (s), 170.5 (s), 173.3 (s) ppm. MS (ESI): m/z = 521.6 $[M + H]^+$, 543.6 $[M + Na]^+$. $C_{30}H_{36}N_2O_6$ (520.62): calcd. C 69.21, H 6.97, N 5.38; found C 69.33, H 7.08, N 5.42.

Synthesis of Methyl (2*S*,5*R*)-1-[(*S*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoyl]-5-[4-(trimethylsilyl)but-2-enyl]pyrrolidine-2-carboxylate (19): G2 catalyst (18 mg, 0.02 mmol) was loaded in a round-bottomed flask under argon. Compound **4** (100 mg, 0.21 mmol), solubilized in dry CH_2Cl_2 (2.1 mL), 2,6-dichloro-1,4-benzoquinone (0.02 mmol), and allyltrimethylsilane (1.05 mmol) were sequentially added, and the reaction mixture was heated to reflux. Ethylene was bubbled into the reaction flask for 15 min, and then a balloon was filled to maintain an atmosphere of ethylene. After 2 h, a second portion of **G2** (0.006 mmol) was added, and the reaction mixture was heated to reflux for a further 6 h. After the reaction was complete (TLC analysis), the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (100% hexane to remove the excess of allyltrimethylsilane, then hexane/EtOAc, 65:35 to recover **19**) to obtain compound **19** (oil) as a 7:3 mixture of (*E*) and (*Z*) isomers (75%). R_f = 0.36 (hexane/EtOAc, 65:35). $[\alpha]_D^{22}$ = +5.3 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3375.8 (br.), 1722, 1621, 1495, 1395 cm^{-1}. ^1H NMR ([D_6]DMSO, 120 °C, 400 MHz, mixture of diastereoisomers): δ = (–0.03)–0.07 (m, 9 H), 1.43 (d, J = 7.9 Hz, 1.35 H), 1.50 (d, J = 8.5 Hz, 0.55 H), 1.56–1.82 (m, 2 H), 1.88 (m, 1 H), 2.00 (m, 1 H), 2.07–2.19 (m, 0.67 H), 2.22–2.35 (m, 0.33 H), 2.64 (m, 1 H), 3.13–3.30 (m, 2 H), 3.59–3.68 (m, 4 H), 3.73 (m, 1 H), 4.25–4.46 (br., 1 H), 4.63 (m, 1 H), 5.02 (d, J = 12.6 Hz, 1 H), 5.07 (d, J = 12.6 Hz, 1 H), 5.24 (m, 1 H), 5.46 (m, 1 H), 6.75 (br. s, 1 H), 7.10–7.25 (m, 5 H), 7.27–7.43 (m, 5 H) ppm. ^{13}C NMR ([D_6]DMSO, 120 °C, 100 MHz mixture of diastereoisomers): δ = –1.0, –0.9, –0.3, 19.2 (t), 23.2 (t), 29.1 (t), 29.3 (t), 32.5 (t), 38.0 (t), 38.1 (t), 38.2 (t), 52.3, 52.4, 60.1, 61.2, 61.3, 62.5 (t), 65.3 (s), 65.4 (s), 66.5 (t), 124.7, 126.1, 127.1, 128.0, 128.5 (2 C), 128.6 (2 C), 129.0 (2 C), 129.2, 131.3 (2 C), 131.4; 137.1 (s), 137.2 (s), 137.8 (s, 2 C), 155.3 (s), 170.8 (s, 2 C), 173.6 (s), 173.7 (s) ppm. MS (ESI): m/z = 567.8 $[M + H]^+$, 589.8 $[M + Na]^+$. $C_{31}H_{42}N_2O_6Si$ (566.77): calcd. C 65.69, H 7.47, N 4.94; found C 65.47, H 7.50, N 4.86.

Synthesis of Methyl (2*S*,5*R*)-5-Allyl-1-[(*S*)-2-benzyl-2-(benzyloxycarbonylamino)-3-oxopropanoyl]pyrrolidine-2-carboxylate (20): Oxalyl chloride (2 M) in CH_2Cl_2 (4.23 mL) was cooled to –60 °C under nitrogen, and a solution of freshly distilled DMSO (0.8 mL, 11.28 mmol) in dry CH_2Cl_2 (3.76 mL) was added dropwise. After 30 min, a solution of **4** (1.36 g, 2.82 mmol) in dry CH_2Cl_2 (17.1 mL) was added, and the reaction mixture was stirred for a further 30 min. Then, a solution of Et_3N (2.28 mL, 22.56 mmol) in dry CH_2Cl_2 (6.8 mL) was added, and the reaction mixture was slowly warmed to 0 °C. After the reaction was complete (TLC analysis, CH_2Cl_2/Et_2O, 95:05), phosphate buffer (pH = 7) was added to quench the reaction, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (CH_2Cl_2/Et_2O, 95:05) to obtain **20** as an oil (88%). R_f = 0.38 (CH_2Cl_2/Et_2O, 95:05). $[\alpha]_D^{22}$ –21.1 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3373, 3316, 1734, 1715, 1634, 996, 915 cm^{-1}. ^1H NMR ([D_6]DMSO, 120 °C, 400 MHz): δ = 1.62 (m, 1 H), 1.81 (m, 1 H), 1.88–2.01 (m, 2 H), 2.18 (m, 1 H), 2.53–2.65 (br., 1 H), 3.37 (d, J = 14.2 Hz, 1 H), 3.42

(d, J = 14.2 Hz, 1 H), 3.64 (s, 3 H), 4.13 (m, 1 H), 4.58 (app t, J = 6.3 Hz, 1 H), 4.99–5.10 (m, 2 H), 5.04 (d, J = 12.5 Hz, 1 H), 5.10 (d, J = 12.5 Hz, 1 H), 5.78 (dddd, J = 6.4, 7.6, 10.3, 17.2 Hz, 1 H), 7.05–7.15 (m, 3 H), 7.19–7.28 (m, 3 H), 7.29–7.41 (m, 5 H), 9.80 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 120 °C, 100 MHz): δ = 28.8 (t, 2 C), 38.9 (t), 39.1 (t), 52.5, 59.9, 60.9, 67.3 (t), 70.9 (s), 117.4 (t), 127.8, 128.7 (2 C), 128.9, 129.1, 131.2, 135.2 (s), 136.0, 137.3 (s), 155.6 (s), 166.9 (s), 172.9 (s), 197.8 ppm. MS (ESI): m/z = 501.3 [M + Na]$^+$. $C_{27}H_{30}N_2O_6$ (478.54): calcd. C 67.77, H 6.32, N 5.85; found C 67.93, H 6.42, N 5.85.

Synthesis of Methyl (2*S*,5*R*)-1-[(*S*)-2-Benzyl-2-(benzyloxycarbonylamino)-3-oxopropanoyl]-5-[4-(trimethylsilyl)but-2-enyl]pyrrolidine-2-carboxylate [3, (*E*) + (*Z*) Mixture). Starting from Compound 19: Oxalyl chloride (2 M) in CH_2Cl_2 (0.32 mL, 0.64 mmol) was cooled to –60 °C under nitrogen, and a solution of freshly distilled DMSO (0.06 mL, 0.85 mmol) in dry CH_2Cl_2 (0.25 mL) was added dropwise. After 30 min, a solution of **19** (121 mg, 0.21 mmol) in dry CH_2Cl_2 (1.27 mL) was added, and the reaction mixture was stirred for a further 30 min. Then, a solution of Et_3N (0.23 mL, 1.71 mmol) in dry CH_2Cl_2 (0.51 mL) was added, and the reaction mixture was slowly warmed to 0 °C. After the reaction was complete (TLC analysis, hexane/EtOAc, 6:4), phosphate buffer (pH = 7) was added to quench the reaction, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 85:15) to obtain **3** (pale yellow oil) as a 7:3 mixture of (*E*)/(*Z*) isomers (90%). **Starting from Compound 20: HG2** catalyst (0.04 mmol) was loaded in a dry round-bottomed flask under argon. Compound **20** (200 mg, 0.42 mmol), solubilized in dry CH_2Cl_2 (4.2 mL), 2,6-dichloro-1,4-benzoquinone (0.042 mmol), and allyltrimethylsilane (2.09 mmol) were then sequentially added, and the reaction mixture was heated to reflux. After 3 h, a second portion of **HG2** (0.021 mmol) was added, and the reaction mixture was heated to reflux for a further 8 h. After the reaction was complete (TLC analysis), CH_2Cl_2 was removed under reduced pressure. The crude mixture was purified by flash chromatography (hexane/EtOAc, 85:15) to obtain compound **3** as a 7:3 mixture of (*E*)/(*Z*) isomers (84%). **Compound 3a:** R_f = 0.33 (hexane/EtOAc, 85:15). ^{1}H NMR ([D$_6$]DMSO, 120 °C, 400 MHz): δ = 0.02 (s, 9 H), 1.51 (app d, J = 8.5 Hz, 2 H), 1.59 (m, 1 H), 1.80 (m, 1 H), 1.87–1.99 (m, 2 H), 2.20 (m, 1 H), 2.55 (m, 1 H), 3.38 (AB system, 2 H), 3.63 (s, 3 H), 4.08 (m, 1 H), 4.58 (app t, J = 6.2 Hz, 1 H), 5.04 (d, J = 12.6 Hz, 1 H), 5.08 (d, J = 12.6 Hz, 1 H), 5.24 (ddddd, J_1 = J_2 = 1.5, J_3 = 6.3 Hz, J_4 = 7.9 Hz, J_5 = 10.2 Hz, 1 H), 5.49 (ddddd, J_1 = J_2 = 1.7, J_3 = J_4 = 8.5 Hz, J_5 = 10.2 Hz, 1 H), 7.04–7.14 (m, 3 H), 7.19–7.27 (m, 3 H), 7.30–7.41 (m, 5 H), 9.79 (s, 1 H) ppm. MS (ESI): m/z = 565.7 [M + H]$^+$, 587.7 [M + Na]$^+$. **Compound 3b:** R_f = 0.31 (hexane/EtOAc, 85:15). $[a]_D^{22}$ –12.4 (c = 1.0, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3380, 2840, 2720, 1736, 1716, 1635 cm^{-1}. ^{1}H NMR ([D$_6$]-DMSO, 120 °C, 400 MHz): δ = 0.18 (m, 9 H), 1.44 (app d, J = 7.9 Hz, 2 H), 1.57–1.69 (m, 1 H), 1.70–1.82 (m, 1 H), 1.85–2.00 (m, 2 H), 2.02–2.14 (m, 1 H), 2.50–2.58 (m, 1 H), 3.36 (d, J = 14.3 Hz, 1 H), 3.41 (d, J = 14.3 Hz, 1 H), 3.63 (s, 3 H), 4.00–4.09 (m, 1 H), 4.54 (app t, J = 6.6 Hz, 1 H), 5.04 (d, J = 12.5 Hz, 1 H), 5.09 (d, J = 12.5 Hz, 1 H), 5.16–5.26 (ddddd, J_1 = J_2 = 1.3 Hz, J_3 = 7.6 Hz, J_4 = 9.0 Hz, J_5 = 15.4 Hz, 1 H), 5.41–5.51 (ddddd, J_1 = J_2 = 1.3, J_3 = J_4 = 7.9 Hz, J_5 = 15.4 Hz, 1 H), 7.01–7.12 (m, 3 H), 7.17–7.27 (m, 3 H), 7.29–7.41 (m, 5 H), 9.77 (s, 1 H) ppm. MS (ESI): m/z = 565.7 [M + H]$^+$, 587.7 [M + Na]$^+$. ^{13}C NMR ([D$_6$]DMSO, 120 °C, 100 MHz mixture of diastereoisomers): δ = –1.1, –0.9, –0.3, 19.2 (t), 23.3 (t), 28.8 (t), 32.2 (t), 37.8 (t), 39.0 (t), 39.1 (t) 52.6 (3 C), 60.5, 60.8, 67.2 (t, 2 C), 70.7 (s, 2 C), 124.2, 125.6, 127.8 (2 C), 128.3, 128.6, 128.7 (2 C), 128.9 (2 C), 129.1, 129.5, 131.2, 135.1 (s), 137.3 (s), 155.6 (s, 2 C), 166.7 (s), 167.0 (s), 172.9 (s, 2 C), 198.0, 198.1 ppm. $C_{31}H_{40}N_2O_6Si$ (564.75): calcd. C 65.93, H 7.14, N 4.96; found C 66.08, H 7.23, N 5.01.

Synthesis of Methyl (3*S*,6*S*,9a*R*)-6-Benzyl-6-(benzyloxycarbonylamino)-7-hydroxy-5-oxo-8-vinyloctahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (2): Compound **3** [mixture of (*E*)/(*Z*) isomers, 1.01 g, 1.79 mmol] was solubilized in dry CH_2Cl_2 (17.9 mL) under nitrogen and cooled to –10 °C. $Sc(OTf)_3$ (2.15 mmol) was added; after 30 min, the reaction mixture was warmed to room temperature. After 5 h, the reaction mixture was filtered through a pad of Celite. CH_2Cl_2 was removed under reduced pressure. The crude mixture was purified by flash chromatography (hexane/EtOAc, 65:35) to obtain compounds **2a** (49%), **2b** (16%), and **2c** (21%) as foamy solids. **Compound 2a:** R_f = 0.36 (hexane/EtOAc, 65:35). $[a]_D^{22}$ –34.9 (c = 0.5, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3364, 3361 (br.), 1745, 1700, 1637 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.57 (m, 1 H, H$_6$), 1.69 (m, 1 H, H$_6$), 1.79 (m, 1 H, H$_8$), 1.91 (m, 1 H, H$_9$), 2.22–2.38 (m, 3 H, H$_5$, H$_8$, H$_9$), 2.99 (d, J = 14.0 Hz, 1 H, H$_b$), 3.51 (d, J = 14.0 Hz, 1 H, H$_b$), 3.57 (s, 3 H, CO_2CH_3), 4.18 (t, J = 7.6 Hz, 1 H, H$_{10}$), 4.28 (d, J = 5.7 Hz, 1 H, H$_4$, singlet after exchange with D_2O), 4.59 (m, 1 H, H$_7$), 4.92–5.06 (m, 3 H, OCH_2Ph, H$_C$, H$_T$), 5.21 (d, J = 12.5 Hz, 1 H, OCH_2Ph), 5.90 (ddd, J = 7.8, 10.2, 17.7 Hz, 1 H, H$_V$), 5.98 (d, J = 5.7 Hz, 1 H, OH, exchanges with D_2O), 6.19 (s, 1 H, NH), 6.73 (app d, J = 6.7 Hz, 2 H, ArH), 7.04–7.16 (m, 3 H, ArH), 7.32–7.46 (m, 5 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 26.5 (t), 30.7 (t), 33.3 (t), 34.7 (t), 42.9, 51.8, 53.9, 60.8, 65.4 (t), 68.4 (s), 73.7, 114.0 (t), 126.2, 127.7, 128.0 (2 C), 128.4, 129.9, 136.4 (s), 136.9 (s), 141.6, 153.8 (s), 168.3 (s), 172.3 (s) ppm. MS (ESI): m/z = 493.6 [M + H]$^+$, 515.6 [M + Na]$^+$. MS (ESI): m/z = 501.3 [M + Na]$^+$. $C_{28}H_{32}N_2O_6$ (492.57): calcd. C 68.28, H 6.55, N 5.69; found C 68.41, H 6.49, N 5.57. **Compound 2b:** R_f = 0.30 (hexane/EtOAc, 65:35). $[a]_D^{22}$ –55.8 (c = 0.6, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3415, 3296 (br.), 1735, 1687, 1625 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.57–1.76 (m, 2 H, H$_6$, H$_8$), 1.82–1.96 (m, 2 H, H$_6$, H$_9$), 2.07 (m, 1 H, H$_9$), 2.24 (m, 1 H, H$_8$), 2.76 (m, 1 H, H$_5$), 3.34 (d, J = 14.1 Hz, 1 H, H$_b$), 3.41 (d, J = 14.1 Hz, 1 H, H$_b$) 3.59 (s, 3 H, CO_2CH_3), 4.06 (dd, J = 5.7, 10.1 Hz, 1 H, H$_4$, doublet after exchange with D_2O), 4.16 (d, J = 8.7 Hz, 1 H, H$_{10}$), 4.32 (m, 1 H, H$_7$), 4.93 (d, J = 12.5 Hz, 1 H, OCH_2Ph), 4.97–5.18 (m, 4 H, OH, OCH_2Ph, H$_C$, H$_T$, 1 H exchanges with D_2O), 5.86–6.09 (m, 2 H, H$_V$, NH), 6.94–7.08 (m, 2 H, ArH), 7.15–7.26 (m, 3 H, ArH), 7.28–7.41 (m, 5 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 27.5 (t), 32.9 (t), 34.3 (t), 39.2 (t), 46.3, 52.7, 57.4, 63.4, 66.2 (t), 70.2 (s), 74.3, 114.9 (t), 127.6, 128.6 (2 C), 129.1 (2 C), 130.7, 136.5 (s), 137.8 (s), 143.3, 156.1 (s), 168.9 (s), 173.0 (s) ppm. MS (ESI): m/z = 493.6 [M + H]$^+$, 515.6 [M + Na]$^+$. $C_{28}H_{32}N_2O_6$ (492.57): calcd. C 68.28, H 6.55, N 5.69; found C 68.34, H 6.43, N 5.61. **Compound 2c:** R_f = 0.27 (hexane/EtOAc, 65:35). $[a]_D^{22}$ –81.9 (c = 1.4, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3349 (br.), 1738, 1700, 1623 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.62 (br. d, J = 13.0 Hz, 1 H, H$_6$), 1.78 (m, 1 H, H$_8$), 1.90 (m, 1 H, H$_9$), 2.05–2.21 (m, 2 H, H$_6$, H$_9$), 2.26 (m, 1 H, H$_8$), 2.82 (br. t, J = 9.6 Hz, 1 H, H$_5$), 3.35 (d, J = 13.6 Hz, 1 H, H$_b$), 3.40 (d, J = 13.6 Hz, 1 H, H$_b$), 3.58 (s, 3 H, CO_2CH_3), 4.28 (d, J = 8.9 Hz, 1 H, H$_{10}$), 4.38 (m, 1 H, H$_7$), 4.48 (d, J = 5.3 Hz, 1 H, H$_4$, singlet after exchange with D_2O), 4.90 (d, J = 12.6 Hz, 1 H, OCH_2Ph), 5.05 (dd, J = 1.5, 10.3 Hz, 1 H, H$_C$), 5.11–5.23 (m, 2 H, OCH_2Ph, H$_T$), 5.30 (d, J = 5.3 Hz, 1 H, OH, exchanges with D_2O), 5.94 (ddd, J = 7.5, 10.3, 17.5 Hz, 1 H, H$_V$), 6.31 (s, 1 H, NH), 6.73–6.83 (m, 2 H, ArH), 7.07–7.19 (m, 3 H, ArH), 7.30–7.44 (m, 5 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 27.5 (t), 33.6 (t), 33.8 (t), 34.5 (t), 43.9, 52.6, 58.6, 63.5, 65.8 (t), 69.6 (s), 70.6, 115.1 (t),

127.3, 128.6, 128.7 128.8, 129.2, 130.3, 136.9 (s), 138.0 (s), 143.1, 153.9 (s), 169.7 (s), 172.9 (s) ppm. MS (ESI): *m*/*z* = 493.6 [M + H]$^+$, 515.6 [M + Na]$^+$. $C_{28}H_{32}N_2O_6$ (492.57): calcd. C 68.28, H 6.55, N 5.69; found C 68.13, H 6.51, N 5.76.

Synthesis of Methyl (3*S*,6*S*,9a*R*)-7-Acetoxy-6-benzyl-6-(benzyloxycarbonylamino)-5-oxo-8-vinyloctahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (22). General Procedure: To a solution of compounds **2a**–**2c** in dry CH_2Cl_2 (0.1 M), Ac_2O (5 equiv.) was added dropwise, followed by DMAP (1 equiv.). The pH was monitored (litmus test) and, if necessary, Et_3N was added to basify the solution. The reaction mixture was heated by using microwaves and, after the reaction was complete (TLC analysis), a saturated solution of NH_4Cl was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2, and the organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography. **Compound 22a:** Compound **22a** was synthesized from **2a** (100 mg, 0.2 mmol) by applying the above general procedure. After 30 min of microwave heating at 60 °C, additional Ac_2O (5 equiv.) was added, and the reaction mixture was irradiated at 60 °C for 1 h. The crude mixture was purified by flash chromatography (hexane/EtOAc, 60:40) to obtain **22a** as a foamy solid (93%). R_f = 0.34 (hexane/EtOAc, 6:4). $[\alpha]_D^{22}$ –50 (*c* = 1.5, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3363, 1744, 1719, 1639, 1421, 1198, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.78 (m, 1 H), 1.89 (m, 1 H), 2.00 (m, 1 H), 2.10 (m, 1 H), 2.24 (s, 3 H), 2.29–2.48 (m, 2 H), 2.83 (m, 1 H), 3.06 (d, *J* = 13.9 Hz, 1 H), 3.62 (d, *J* = 13.9 Hz, 1 H), 3.70 (s, 3 H), 4.38 (t, *J* = 7.5 Hz, 1 H), 4.64 (m, 1 H), 5.03 (d, *J* = 12.2 Hz, 1 H), 5.06 (d, *J* = 10.2 Hz, 1 H), 5.10 (d, *J* = 17.0 Hz, 1 H), 5.36 (d, *J* = 12.2 Hz, 1 H), 5.87 (ddd, *J* = 6.9, 10.2, 17.1 Hz, 1 H), 5.91 (s, 1 H), 6.47 (s, 1 H), 6.79 (d, *J* = 7.1 Hz, 2 H), 7.07–7.23 (m, 3 H), 7.30–7.45 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 27.3 (t), 32.2 (t), 34.1 (t), 35.6 (t), 42.8, 52.7, 54.7, 61.7, 66.6 (t), 68.1 (s), 76.4, 115.5 (t), 127.5, 128.4, 128.5, 128.6, 128.8, 130.3, 135.5 (s), 137.1 (s), 139.5, 154.9 (s), 168.2 (s), 169.4 (s), 173.0 (s) ppm. MS (ESI): *m*/*z* = 557.4 [M + Na]$^+$. $C_{30}H_{34}N_2O_7$ (534.61): calcd. C 67.40, H 6.41, N 5.24; found C 67.59, H 6.47, N 5.31. **Compound 22b:** Compound **22b** was synthesized from **2b** (100 mg, 0.2 mmol) by applying the general procedure. After 30 min of microwave heating at 60 °C, additional Ac_2O (5 equiv.) was added, and then the solution was irradiated at 60 °C for 30 min. The crude mixture was purified by flash chromatography (CH_2Cl_2/Et_2O, 94:06) to obtain **22b** as a foamy solid (92%). R_f = 0.36 (CH_2Cl_2/Et_2O, 94:06). $[\alpha]_D^{22}$ –79 (*c* = 1.75, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3314, 1752, 1737, 1725, 1635, 1491, 1197, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.91 (m, 1 H), 1.89 (s, 3 H), 1.97–2.08 (m, 4 H), 2.32 (m, 1 H), 2.92 (m, 1 H), 3.35 (d, *J* = 14.5 Hz, 1 H), 3.73 (s, 3 H), 4.26–4.37 (m, 2 H), 4.38 (d, *J* = 14.5 Hz, 1 H), 4.99 (d, *J* = 12.7 Hz, 1 H), 5.05 (dd, *J* = 1.3, 10.1 Hz, 1 H), 5.10 (d, *J* = 12.7 Hz, 1 H), 5.15 (d, *J* = 17.0 Hz, 1 H), 5.20 (d, *J* = 10.6 Hz, 1 H), 5.63 (ddd, *J* = 8.8, 10.1, 17.0 Hz, 1 H), 6.64 (s, 1 H), 6.97–7.05 (m, 2 H), 7.10–7.22 (m, 3 H), 7.26–7.38 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.2, 27.5 (t), 30.8 (t), 34.3 (t), 39.6 (t), 46.9, 52.8, 57.7, 63.7, 66.2 (t), 67.8 (s), 76.3, 117.0 (t), 127.4, 128.0 (2 C), 128.7 (2 C), 129.7, 135.6 (s), 137.7 (s), 139.5, 155.2 (s), 168.6 (s), 170.6 (s), 172.7 (s) ppm. MS (ESI): *m*/*z* = 557.4 [M + Na]$^+$. $C_{30}H_{34}N_2O_7$ (534.61): calcd. C 67.40, H 6.41, N 5.24; found C 67.32, H 6.46, N 5.19. **Compound 22c:** Compound **22c** was synthesized from **2c** (100 mg, 0.2 mmol) by applying the general procedure. After 30 min of microwave heating at 60 °C, additional Ac_2O (5 equiv.) was added, and then the solution was irradiated at 60 °C for 30 min. The crude mixture was purified by flash chromatography (CH_2Cl_2/Et_2O, 93:07) to obtain **22c** as a foamy solid (93%). R_f = 0.36 (CH_2Cl_2/Et_2O, 93:07); $PhCH_3$/EtOAc, 80:20; R_f = 0.35. $[\alpha]_D^{22}$ –73 (*c* = 0.75, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3376, 1740, 1720, 1630, 1483, 1424, 1198, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.91 (m, 1 H), 2.03 (s, 3 H), 2.06–2.32 (m, 4 H), 2.38 (m, 1 H), 2.98 (m, 1 H), 3.28 (d, *J* = 13.6 Hz, 1 H), 3.74 (s, 3 H), 3.87 (d, *J* = 13.6 Hz, 1 H), 4.36 (m, 1 H), 4.59 (app d, *J* = 7.5 Hz, 1 H), 5.00 (d, *J* = 12.4 Hz, 1 H), 5.13 (d, *J* = 10.4 Hz, 1 H), 5.17 (d, *J* = 17.0 Hz, 1 H), 5.27 (d, *J* = 12.4 Hz, 1 H), 5.87 (ddd, *J* = 6.1, 10.5, 17.0 Hz, 1 H), 6.21 (s, 1 H), 6.45 (s, 1 H), 6.79–6.85 (m, 2 H), 7.09–7.15 (m, 2 H), 7.15–7.22 (m, 1 H), 7.30–7.41 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.0, 27.7 (t), 33.6 (t), 33.9 (t), 34.5 (t), 42.1, 52.6, 58.5, 63.4, 66.4 (t), 67.6 (s), 72.1, 116.1 (t), 127.4, 128.2, 128.5, 128.7 (2 C), 129.9, 135.3 (s),137.5 (s), 139.3, 154.5 (s), 168.6 (s), 170.3 (s), 172.6 (s) ppm. MS (ESI): *m*/*z* = 557.4 [M + Na]$^+$. $C_{30}H_{34}N_2O_7$ (534.61): calcd. C 67.40, H 6.41, N 5.24; found C 67.29, H 6.44, N 5.33.

Synthesis of Methyl (3*S*,6*S*,9a*R*)-7-Acetoxy-6-benzyl-6-(benzyloxycarbonylamino)-8-(4-nitrostyryl)-5-oxooctahydro-1*H*-pyrrolo-[1,2-*a*]azepine-3-carboxylate (23). General Procedure: To a solution of **22a**–**22c** in EtOH 99% (0.1 M) under nitrogen were added sequentially 1-bromo-4-nitrobenzene (1.1 equiv.), PdEnCat 30 (0.05 equiv.) and Bu_4NOAc (3 equiv.). The reaction mixture was heated in a microwave oven; after the reaction was complete (TLC analysis), the reaction mixture was separated by filtration and washed with EtOH. The crude mixture was purified by flash chromatography. **Compound 23a (*E*):** Compound **22a** (*E*) was synthesized from **22a** (50 mg, 0.09 mmol) by applying the general procedure. After 30 min of microwave heating at 120 °C, the reaction was complete. The crude mixture was purified by flash chromatography to obtain **23a** as an amorphous solid (91%). R_f = 0.37 (hexane/EtOAc, 65:35). $[\alpha]_D^{22}$ –8.5 (*c* = 0.50, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 2923, 2852, 2690, 1756, 1716, 1649, 1482, 1340, 1193, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.85 (m, 1 H), 1.94–2.20 (m, 3 H), 2.29 (s, 3 H), 2.35–2.53 (m, 2 H), 3.04–3.15 (m, 2 H), 3.64 (d, *J* = 13.6 Hz, 1 H), 3.73 (s, 3 H), 4.43 (app t, *J* = 7.5 Hz, 1 H), 4.71 (m, 1 H), 5.01 (d, *J* = 12.3 Hz, 1 H), 5.36 (d, *J* = 12.3 Hz, 1 H), 5.98 (s, 1 H), 6.40 (dd, *J* = 7.1, 16.0 Hz, 1 H), 6.48 (s, 1 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 6.79 (d, *J* = 7.2 Hz, 2 H), 7.08–7.24 (m, 3 H), 7.30–7.44 (m, 5 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 8.16 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4, 27.2 (t), 32.0 (t), 34.3 (t), 35.5 (t), 42.6, 52.7, 54.5, 61.5, 66.6 (t), 67.9 (s), 76.1, 124.1, 127.2, 127.4, 128.3, 128.4, 128.6, 128.7, 129.9, 130.1, 135.1 (s), 136.4, 136.8 (s), 144.0 (s), 147.0 (s), 154.8 (s), 167.9 (s), 169.5 (s), 173.1 (s) ppm. MS (ESI): *m*/*z* = 678.4 [M + Na]$^+$. $C_{36}H_{37}N_3O_9$ (655.70): calcd. C 65.94, H 5.69, N 6.41; found C 65.72, H 5.62, N 6.44. **Compound 23b (*E*):** Compound **23b** (*E*) was synthesized from **22b** (50 mg, 0.09 mmol) by applying the general procedure. After 1 h of microwave heating at 120 °C, the reaction was complete. The crude mixture was purified by flash chromatography to obtain **23b** as an amorphous solid (80%). R_f = 0.28 (hexane/EtOAc, 60:40). $[\alpha]_D^{22}$ = +27.7 (*c* = 1.4, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3341, 1738, 1636, 1596, 1492.6, 1415 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.79 (s, 3 H), 1.93 (m, 1 H), 2.03–2.18 (m, 4 H), 2.37 (m, 1 H), 3.17 (m, 1 H), 3.39 (d, *J* = 14.4 Hz, 1 H), 3.75 (s, 3 H), 4.31–4.48 (m, 3 H), 4.99 (d, *J* = 12.7 Hz, 1 H), 5.09 (d, *J* = 12.6 Hz, 1 H), 5.35 (m, 1 H), 6.22 (dd, *J* = 9.0, 15.8 Hz, 1 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 6.62 (s, 1 H), 6.99–7.05 (m, 2 H), 7.12–7.23 (m, 3 H), 7.27–7.36 (m, 5 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 8.17 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.5, 27.0 (t), 29.6 (t), 33.7 (t), 38.6 (t), 45.7, 52.3, 56.9, 63.1, 65.8 (t), 67.1 (s), 75.8, 124.0, 126.7, 127.0, 127.6 (2 C), 128.2, 129.2, 129.8, 134.9 (s), 135.5, 137.0 (s), 143.1 (s), 146.9 (s), 154.7 (s), 168.0 (s), 169.9 (s), 172.1 (s) ppm. MS (ESI): *m*/*z* = 678.4 [M + Na]$^+$. $C_{36}H_{37}N_3O_9$ (655.70): calcd. C 65.94, H

5.69, N 6.41; found C 65.76, H 5.75, N 6.49. **Compound 23c (*E*):** Compound **23c** (*E*) was synthesized from **22c** (50 mg, 0.09 mmol) by applying the general procedure. After 1 h of microwave heating at 120 °C, the reaction was complete. The crude mixture was purified by flash chromatography to obtain **23c** as an amorphous solid (84%). R_f = 0.28 (CH_2Cl_2/Et_2O, 95:5). R_f = 0.32 (toluene/EtOAc, 85:15). $[a]_D^{22}$ –36 (*c* = 1.7, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3361, 1739, 1713, 1630, 1594, 1480, 1421 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.03 (s, 3 H), 2.04–2.28 (m, 4 H), 2.33–2.50 (m, 2 H), 3.22 (m, 1 H), 3.33 (d, *J* = 13.5 Hz, 1 H), 3.75 (s, 3 H), 3.90 (d, *J* = 13.5 Hz, 1 H), 4.43 (m, 1 H), 4.64 (app d, *J* = 7.3 Hz, 1 H), 5.01 (d, *J* = 12.4 Hz, 1 H), 5.25 (d, *J* = 12.4 Hz, 1 H), 6.31 (s, 1 H), 6.39 (dd, *J* = 6.4, 16.1 Hz, 1 H), 6.47 (s, 1 H), 6.58 (d, *J* = 16.1 Hz, 1 H), 6.80–6.87 (m, 2 H), 7.09–7.16 (m, 2 H), 7.20 (m, 1 H), 7.30–7.42 (m, 5 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 8.19 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.1, 27.7 (t), 34.0 (t), 34.5 (t), 41.9, 52.7, 58.3, 63.4, 66.5 (t), 67.6 (s), 72.0, 124.4, 127.3, 127.6, 128.3, 128.5, 128.8 (2 C), 129.2, 129.9, 135.1 (s), 136.1, 137.4 (s), 143.9 (s), 147.4 (s), 154.6 (s), 168.4 (s), 170.3 (s), 172.6 (s) ppm. MS (ESI): *m*/*z* = 678.4 $[M + Na]^+$. $C_{36}H_{37}N_3O_9$ (655.70): calcd. C 65.94, H 5.69, N 6.41; found C 66.05, H 5.76, N 6.54.

Synthesis of Methyl (3*S*,6*S*,9a*R*)-6-Benzyl-6-(benzyloxycarbonylamino)-8-(4-nitrostyryl)-5-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (24): To a solution of **23a**–**23c** (50 mg, 0.076 mmol) in dry THF (0.1 M) under nitrogen DBU (0.15 mmol) was added dropwise. The reaction mixture was heated in a microwave oven at 80 °C for 1 h, then additional DBU (0.15 mmol) was added, and the reaction mixture was irradiated at 80 °C for 1 h. After the reaction was complete, a solution of HCl (1 M) was added to quench the reaction. The aqueous phase was extracted with EtOAc, the organic phases were collected, dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude mixture was purified by flash chromatography to obtain **24** as an amorphous solid. Yield: 75% starting from **23a**, 75% starting from **23b**, and 78% starting from **23c**. R_f = 0.36 (CH_2Cl_2/Et_2O, 90:10). $[a]_D^{22}$ = +4 (*c* = 1.4, $CDCl_3$). IR (neat): $\tilde{\nu}$ = 3365, 1740, 1713, 1634, 1591, 1480, 1428 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.01 (m, 1 H), 2.09–2.25 (m, 2 H), 2.41 (m, 1 H), 2.65–2.88 (m, 2 H), 3.27 (d, *J* = 13.9 Hz, 1 H), 3.73 (s, 3 H), 3.91 (d, *J* = 13.9 Hz, 1 H), 4.22–4.41 (br., 1 H), 4.54 (dd, *J* = 3.0, 7.8 Hz, 1 H), 5.12 (d, *J* = 12.4 Hz, 1 H), 5.26 (d, *J* = 12.4 Hz, 1 H), 6.57 (d, *J* = 16.2 Hz, 1 H), 6.58–6.65 (br., 1 H), 6.69 (s, 1 H), 6.90–6.96 (m, 2 H), 7.00 (d, *J* = 16.2 Hz, 1 H), 7.16–7.27 (m, 3 H), 7.31–7.45 (m, 5 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 8.21 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.9 (t), 33.2 (t), 34.7 (t), 52.9, 55.8, 62.8, 65.0 (s), 66.7 (t), 124.6, 125.8, 127.2, 127.8, 128.4 (2 C), 128.7, 128.9, 130.1, 133.9, 135.1 (s), 135.3 (s), 137.2 (s), 138.3, 144.1 (s), 147.2 (s), 155.0 (s), 168.9 (s), 172.8 (s) ppm. MS (ESI): *m*/*z* = 618.2 $[M + Na]^+$. $C_{34}H_{33}N_3O_7$ (595.65): calcd. C 68.56, H 5.58, N 7.05; found C 68.79, H 5.68, N 7.13.

Acknowledgments

Financial support from the Italian Ministry of Education, University and Research (Ministero dell'Università e della Ricerca, MIUR) is gratefully acknowledged (PRIN project 2010NRREPL). We thank Dr. Donatella Potenza for her valuable NMR advice.

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Received: July 30, 2015
Published Online: October 23, 2015

