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Stereoselective Synthesis of Aza Analogues of Isoaltholactone and Goniothalesdiol – New Applications of the Heck–Matsuda Reaction

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The stereoselective synthesis of nitrogen analogues of biologically active isoaltholactone and goniothalesdiol are described. The successful strategy employed a Heck–Matsuda reaction between a chiral endocyclic enecarbamate bearing an ester functionality and arenediazonium tetrafluoroborates in a divergent approach at an early stage of the synthesis. Several aspects related to this critical arylation reaction are discussed to highlight structural features that affect the outcome of the arylation process. The synthesis of (–)-aza-isoaltholactone **6** was successfully accomplished in nine steps from the starting enecarbamate. We also performed the synthesis of the new fully substituted pyrrolidine (–)-(2*R*,3*R*,4*S*,5*S*)-1-(*tert*-butoxycarbonyl)-3,4-dihydroxy-5-phenylpyrrolidin-2-ylacrylic acid **28**, which is a potential advanced intermediate in the route to aza-altholactone. Moreover, the synthesis of a new nitrogen analogue of goniothalesdiol (+)-**33** was accomplished from the protected dihydroxypyrrolidine (–)-**27**, obtained from an attempted synthesis of aza-altholactone.

Introduction

Throughout history, Nature has supplied the basic needs of human beings, one of which is the provision of medication to treat a broad spectrum of diseases. Nature provides valuable contributions, not only as a source of potentially chemotherapeutic agents, but also prototype compounds, which function as inspiration for the total synthesis or semisynthesis of new drugs.

Natural products can be considered as prevalidated biological structures, which were selected by evolution to interact with biological systems such as enzymes and protein receptors. Moreover, during their biogenesis natural compounds are recognized and undergo structural modifications through interactions with many different enzymatic systems. These bioprocesses are relevant for the development of new drugs as most are intended to interact with some type of protein target.[1] However, quite often the original structure of the natural product has to undergo several changes in order to achieve therapeutic application as they were not originally intended as drugs by the producing organisms. Therefore, structure refinement through the synthesis of analogues occupies a central role in optimizing efficiency of action, bioavailability, stability, interaction with the target, pharmacokinetic, and pharmacodynamic properties.[2]

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In this context, a class of natural compounds that has received increased attention are the styryllactones, a diverse group of secondary metabolites, which show high toxicity to a broad spectrum of human tumor cells, including breast, colon, kidney, and pancreas.[3] Several of these compounds also have anti-inflammatory and antibiotic activity, as well as activity as immunosuppressants and antifertility agents.[4]

There are over 30 different styryllactones with different structural patterns (Figure 1). Among them, isoaltholactone and altholactone display an α,β-unsaturated furanopyranone unit and a central tetrasubstituted tetrahydrofuran ring bearing four consecutive stereogenic centers. These molecules have a common structural unit dif-

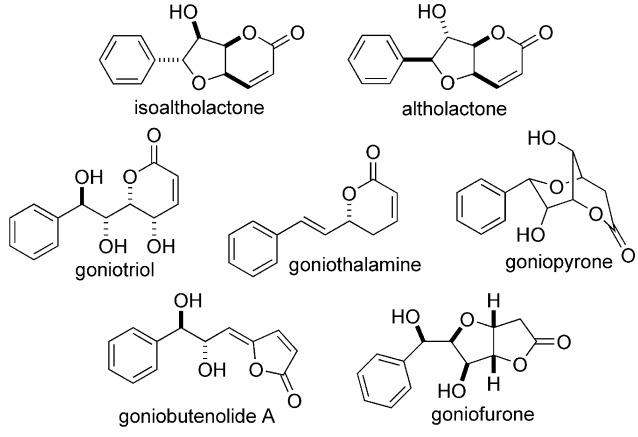
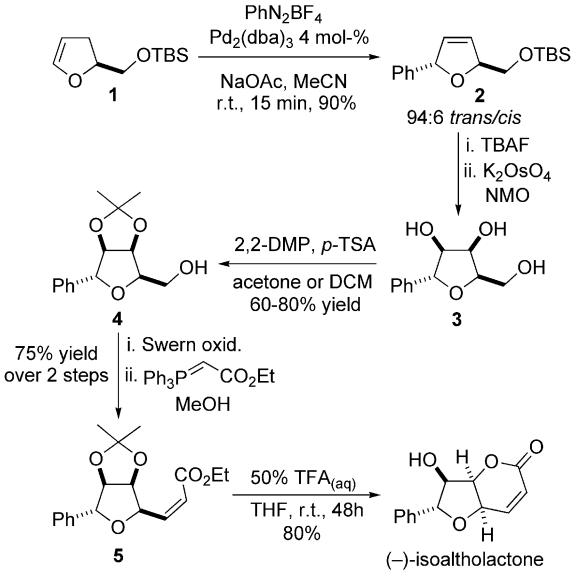


Figure 1. Examples of natural styryllactones.

fering only in the configuration of the stereogenic centers at C-2 and C-3. This configurational difference has driven the development of flexible, stereoselective routes towards the syntheses of both diastereomers.

Due to the broad spectrum of biological activity of this class of compounds, several groups have devoted efforts towards the total synthesis of styryllactones.[5] We recently reported the synthesis of isoaltholactone using the Heck reaction of dihydrofuran **1** with benzenediazonium tetrafluoroborate as the key step (Scheme 1).[6] The reaction, catalyzed by $Pd_2(dba)_3$, occurred rapidly at room temperature, providing the arylated product with high stereoselectivity in favor of the *trans* isomer. Successive deprotection reactions, dihydroxylation, acetonide formation, Swern oxidation, Horner–Wadsworth–Emmons (HWE) olefination, and deprotection/lactonization led to isoaltholactone in 25% overall yield.



Scheme 1. Synthesis of (–)-isoaltholactone.

Given the biological importance of this class of compounds and the synthesis of analogues, we report herein the synthesis of the nitrogen analogue of isoaltholactone, aza-isoaltholactone **6**, as well as studies towards the synthesis of other aza analogues **7** and **8** (Figure 2). It should be noted that, to the best of our knowledge, this is the first time that studies on the syntheses of these unnatural compounds have been described. For reasons of practicality and cost, studies were directed towards the synthesis of the nitrogen analogues as their unnatural enantiomers.

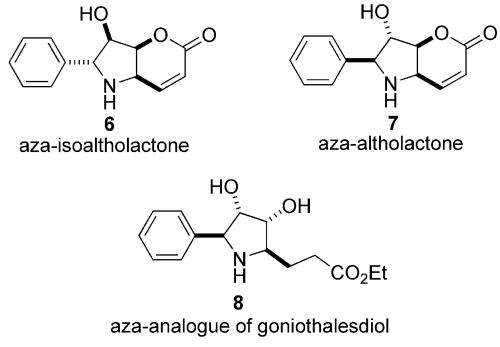
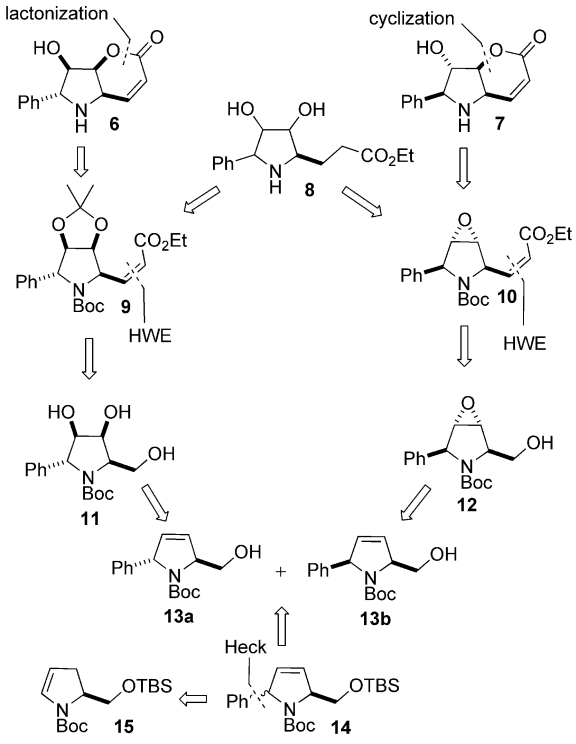


Figure 2. Aza-styryllactones and aza analogue of goniothalesdiol.

Synthetic Plan

Initially, our proposed synthesis was aimed at the preparation of nitrogen analogues of both isoaltholactone and altholactone through a common route (Scheme 2). The convergence of the two synthetic routes would be linked to the Heck reaction between benzenediazonium tetrafluoroborate and endocyclic enecarbamate **15**. Based on our previous results, we predicted that a Heck reaction would provide the *cis* and *trans* isomers in similar amounts.[7] Therefore, the aza-styryllactones **6** and **7** would be accessible from the *trans* and *cis* Heck adducts **13a** and **13b** using distinct routes, whereas aza-goniothalesdiol analogues could be obtained from both routes.



Scheme 2. Synthetic plan.

In our synthetic plan the pyranone ring of the aza-isoaltholactone **6** would be obtained by lactonization after deprotection of acetonide **9** (Scheme 2). On the other hand, the pyranone ring of aza-altholactone **7** would be obtained from **10** in a more challenging manner involving a selective ester hydrolysis with concomitant intramolecular epoxide opening. In both routes, *Z*-α,β-unsaturated esters **9** and **10** would be generated by HWE olefination of the transient aldehydes produced by the oxidation of alcohols **11** and **12**. Diol **11** should be easily accessible from the *trans* Heck adduct **13a** by dihydroxylation, whereas epoxidation of the *cis* isomer **13b** should provide the *anti* epoxide **12**. The arylated

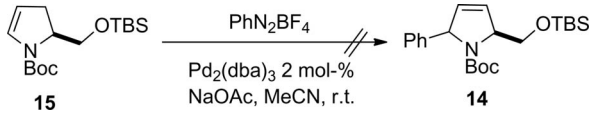
3-pyrrolines **14** can be obtained by a Heck reaction between benzenediazonium tetrafluoroborate and the chiral endocyclic enecarbamate **15** (synthesized from L-pyroglutamic acid). Completing the synthetic strategy, the aza-goniothalesdiol analogues could be synthesized from unsaturated esters **9** and/or **10**.

Results and Discussion

Heck–Matsuda Arylation of Endocyclic Enecarbamates

The palladium-catalyzed Heck–Matsuda reaction of arenediazonium salts with different olefins has been an important tool in the synthesis of natural products and biologically important compounds.[8,9] Arenediazonium salts offer several advantages over the more conventionally employed aryl halides; arylations are usually milder, easier to manipulate, faster, and more economic.[10] Even more important is the fact that they undergo an extremely facile oxidative addition with Pd^0, operating under ligand-free conditions, to generate a highly reactive cationic $ArPd^{II}$ species.[11]

The Heck–Matsuda arylation of endocyclic enecarbamates with arenediazonium salts has been studied extensively by our group.[7] However, the specific arylation of olefin **15** with benzenediazonium tetrafluoroborate has not been previously performed. In analogy to the synthesis of isoaltholactone, this was the olefin of choice for the synthesis of the aza analogues (Scheme 3). Surprisingly, when the conditions described above [$Pd_2(dba)_3$, sodium acetate in acetonitrile] were applied to enecarbamate **15**, the expected Heck adduct **14** was not obtained, and olefin **15** was recovered almost quantitatively.



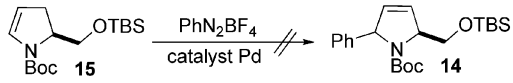
Scheme 3. Unsuccessful Heck–Matsuda arylation.

Faced with this intriguing outcome, other experiments were designed to arylate the endocyclic enecarbamate **15** with benzenediazonium tetrafluoroborate. Changes in the nature of the catalyst, temperature, and ratio of olefin to arenediazonium salts were all evaluated (Table 1). Initially the amount of palladium catalyst was doubled, but again there was no consumption of **15**. Different ratios of the reactants, the use of other palladium catalysts, and changes in the temperature proved fruitless.

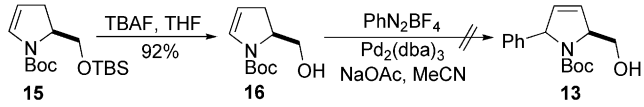
Aiming to remove any potential steric interference, the silicon protecting group of **15** was removed to yield the hydroxy enecarbamate **16** (Scheme 4). Attempts to arylate **16** led to the recovery of the starting material.

These results were even more intriguing when compared to the successful arylation of **16** with arenediazonium salts **17b** and **17c** as previously reported (Table 2).[7] In view of these surprising results, we briefly evaluated the scope of this reaction, and the results seemed to indicate that arylation is highly dependent on the substituent on the arenediazonium salt and on the nature of the group at C-5 on the enecarbamate. Arylation of **16** was only feasible with salts bearing electron-donating substituents (Table 2).

Table 1. Conditions for attempted Heck arylation of **15**.

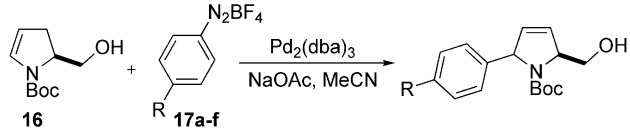


Entry	Cat. (mol-%)	Solvent	Equiv. PhN_2BF_4	*T* [°C]
1	$Pd_2(dba)_3$ (2)	MeCN	1	25
2	$Pd_2(dba)_3$ (4)	MeCN	1	25
3	$Pd_2(dba)_3$ (4)	MeCN	0.85	25
4	$Pd_2(dba)_3$ (4)	MeCN	1.5	25
5	$Pd_2(dba)_3$ (4)	MeCN	1	40
6	$Pd_2(dba)_3$ (4)	MeCN	1	50
7	$Pd(OAc)_2$ (10)	MeOH	1	25
8	$Pd(OAc)_2$ (10)	MeOH	1	40
9	$Pd(OAc)_2$/CO (10)	MeCN	1	25



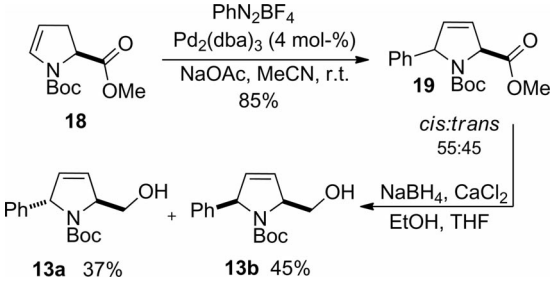
Scheme 4. Attempted arylation of **16**.

Table 2. Heck–Matsuda arylation of **16** with **17a**–**f**.



Entry	R	*trans*/*cis*	Yield [%]
1	H (**17a**)	–	–
2	OMe (**17b**)	48:52	95
3	$NHCO_2Me$ (**17c**)	40:60	80
4	Cl (**17d**)	–	–
5	Br (**17e**)	–	–
6	NO_2 (**17f**)	–	–

Given the unexpected behavior of **15** and **16** with benzenediazonium tetrafluoroborate, we decided to replace these with enecarbamate **18** containing an ester group at C-5 (Scheme 5). Enecarbamate **18** was then subjected to the Heck reaction with benzenediazonium tetrafluoroborate under $Pd_2(dba)_3$ catalysis, as described previously.[7] Gratifyingly, Heck arylation occurred rapidly, which provided Heck product **19** in 85% yield in a diastereoisomeric ratio of 55:45 (*cis*:*trans*), evaluated by gas chromatography. As it was not possible to separate the stereoisomers by column chromatography, they were reduced to the corresponding alcohols by treatment with sodium borohydride in the presence of calcium chloride. At this stage we could efficiently separate the two stereoisomers by flash chromatography. The *trans* adduct **13a** was obtained in 37% isolated yield, and *cis* adduct **13b** in 45% yield.



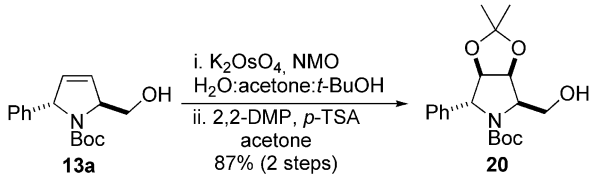
Scheme 5. Heck–Matsuda arylation of **18**.

From this point on, each stereoisomer was treated separately in the synthesis of the corresponding aza-styryllactones. The *trans* isomer **13a** was used for the synthesis of aza-isoaltholactone **6**, and the *cis* isomer **13b** was used for the synthesis of aza-altholactone **7**.

The reasons for the effectiveness of the Heck–Matsuda reaction towards **18** seem to be related to the coordinating power of the nearby carbonyl group and the nature of the reactive cationic arylpalladium intermediate. A more detailed investigation of the mechanism of these arylation reactions is underway.

Synthesis of Aza-isoaltholactone 6

With the *trans* isomer **13a** in hand, it was dihydroxylated using catalytic amounts of potassium osmate (K_2OsO_4) and *N*-methylmorpholine *N*-oxide (NMO) as cooxidants in a ternary mixture of solvents (water, acetone, and *tert*-butyl alcohol, Scheme 6). The corresponding diol was obtained with high yield and purity and was used in the next step without further purification. The diol was protected as an acetonide using 2,2-dimethoxypropane (2,2-DMP) and catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) in acetone. Under these conditions the five-membered acetonide **20** was selectively obtained in 87% yield over two steps.



Scheme 6. Dihydroxylation and protection reactions.

The stereoselectivity observed for the dihydroxylation reaction is in agreement with previous reports.[12] It is believed to be controlled by the steric hindrance of the phenyl group combined with the coordinating effect of the primary hydroxyl group to the osmium reagent. This interaction probably occurs through a hydrogen bond (**A**) or by a direct interaction of the oxygen with the osmium atom (**B**), which leads to the selective formation of the *cis* triol. These two plausible rationalizations are shown in Figure 3.

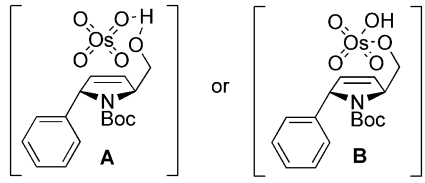
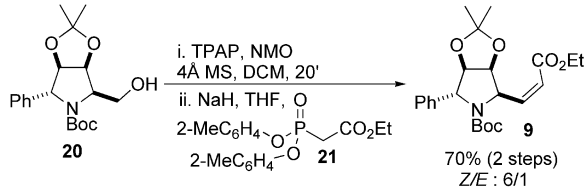


Figure 3. Two plausible rationalizations for stereoselective dihydroxylation.

The exclusive formation of the five-membered ring was unambiguously confirmed by ^{13}C NMR spectroscopy, where the methyl groups of **20** are observed at 24.7 and 26.1 ppm (six-membered ring acetonides display chemical shifts for the methyl groups at approximately 19 and 25 ppm).[13] The difference in chemical shifts between the two methyl groups is due to stereoeletronic effects, which are more prevalent in a six-membered ring.

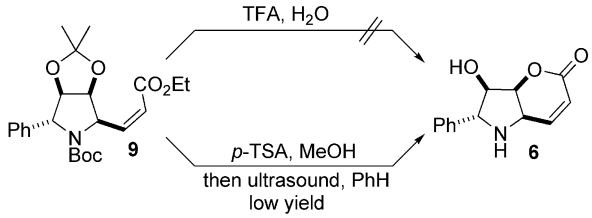
The hydroxy acetonide **20** was oxidized to its corresponding aldehyde with catalytic amounts of tetrapropylammonium perruthenate (TPAP) in the presence of NMO (Scheme 7).[14] The oxidation reaction occurred rapidly and cleanly at room temperature. Therefore, simple filtration through a short pad of silica gel followed by removal of the solvent allowed the product to be used directly in the next step. The intermediate aldehyde was then subjected to a HWE olefination reaction, using Ando's phosphonate **21**.[15] This was the reagent of choice as it provides high stereoselectivity favoring the *Z* isomer. Olefination was performed, using sodium hydride as the base, to generate the desired *Z*-α,β-unsaturated ester **9** in 70% yield (*Z*:*E* ratio of 6:1) over two steps.



Scheme 7. Oxidation with TPAP followed by HWE olefination.

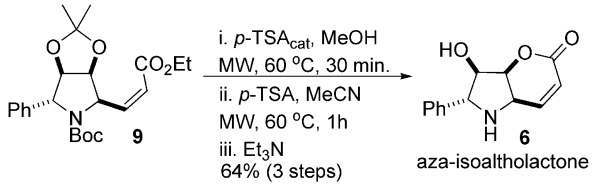
To obtain aza-isoaltholactone **6**, the ester acetonide **9** was treated with trifluoroacetic acid (TFA) in water under the same conditions previously described for the synthesis of (–)-isoaltholactone (Scheme 8).[6] However, under these conditions the starting material was completely consumed, but no formation of the expected unsaturated lactone **6** was observed. Treatment of **9** with a catalytic amount of *p*-TSA in methanol and subsequent use of ultrasound in benzene resulted in **6** in low yield, together with several byproducts.

We then decided to subject **9** to an alternative protocol for the removal of the protecting groups and formation of the lactone (Scheme 9). Therefore, initial treatment of **9** with a catalytic amount of *p*-TSA in methanol under microwave irradiation (60 °C for 30 min) resulted in the removal of the acetonide and lactonization. Subsequently, another microwave-assisted reaction (60 °C for 1 h) using 5 equiv. of



Scheme 8. Deprotection and lactonization of **9**.

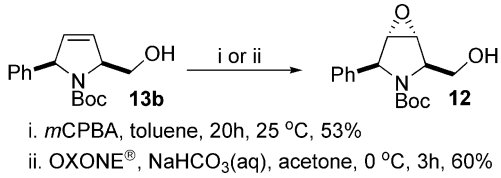
p-TSA in acetonitrile led to the removal of the Boc group. Neutralization of the salt with triethylamine led to aza-isoaltholactone **6** in 64% yield over three steps.



Scheme 9. Completion of the synthesis of **6**.

Attempted Synthesis of Aza-altholactone 7

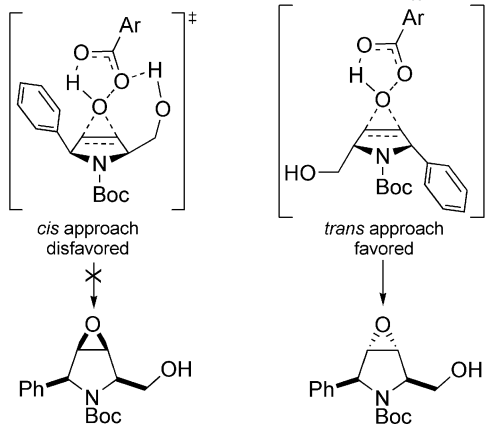
As presented in the synthetic plan, the strategy for the synthesis of aza-altholactone **7** should start from the *cis* diastereoisomer generated in the Heck reaction. Therefore, **13b** was oxidized with *m*-chloroperoxybenzoic acid (*m*CPBA) in toluene to furnish epoxide **12** in a moderate 53% yield (Scheme 10). An alternative method employing dimethyldioxirane as the epoxidation agent was also tested and proved equally effective (60% yield). Dimethyldioxirane was generated in situ from the reaction between OXONE® and acetone in the presence of an aqueous buffer solution of $NaHCO_3$.[16]



Scheme 10. Epoxidation of **13b**.

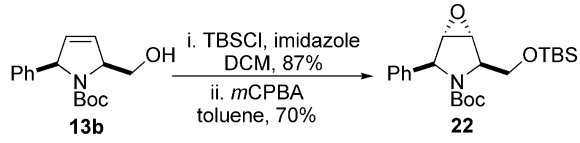
There are several precedents for epoxidations directed by coordinating neighboring groups.[12] However, in our case, hydrogen bond coordination of the hydroxy group with the epoxidation agent might be easily disrupted or prevented because of steric congestion by the phenyl group *cis* to the hydroxymethyl group (Scheme 11).

In order to verify this hypothesis, **13b** was treated with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in dichloromethane to yield the corresponding silyloxy derivative in 87% yield (Scheme 12). Coordination of this silyloxy substrate with the epoxidation agent should



Scheme 11. Stereochemical model for epoxidation.

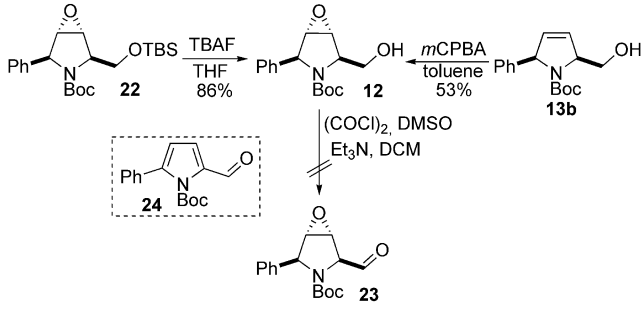
be prevented, which should lead to oxidant approach from the least hindered face of the double bond. Epoxidation of the intermediate silyloxy compound with *m*CPBA provided epoxide **22** in 70% isolated yield.



Scheme 12. Synthesis of **22**.

As expected, deprotection of **22** with tetrabutylammonium fluoride (TBAF) in THF gave the epoxy alcohol **12** previously prepared from **13b**. This result confirms our initial assumption that substrate control during epoxidation is prevented in the case of the *cis* alcohol **13b**.

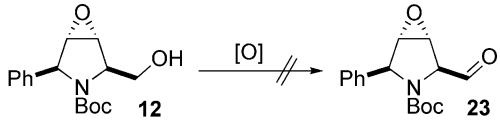
With the desired epoxide **12** in hand, it was subjected to oxidation to aldehyde **23** (Scheme 13) using standard procedures. To our surprise, Swern oxidation [oxalyl chloride, dimethyl sulfoxide (DMSO), and triethylamine in dichloromethane][17] did not provide the desired aldehyde **23**, but 2-formylpyrrole **24** in a typical overoxidation reaction. Attempts to minimize pyrrole formation by conducting the reaction in shorter times were unsuccessful.



Scheme 13. Proof of the stereochemistry of **12**.

Bearing in mind the successful oxidation of alcohol **20** during the synthesis of aza-isoaltholactone **6** employing TPAP,[14] we also tested this mild reagent for the oxidation of **12** (Scheme 14). Unfortunately, even after 12 hours, the

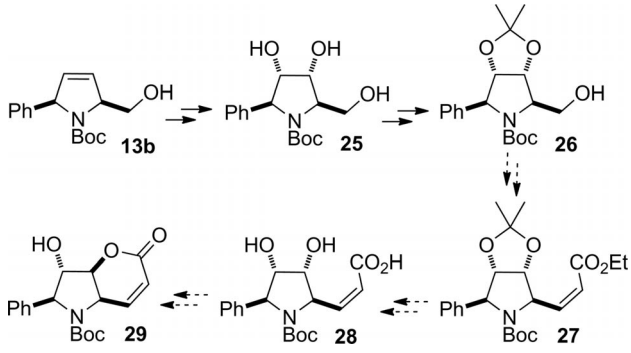
formation of the desired aldehyde **23** was not observed. Other oxidants such py·SO_3/DMSO,[18] PCC/NaOAc,[19] and 2-iodoxybenzoic acid[20] were also examined but all attempts proved fruitless. With the Dess–Martin periodinane (DMP)[21] the starting material **12** was quickly consumed, however, a complex mixture of unidentified products was obtained.



Conditions tested:
py.SO_3, DMSO, Et_3N, DCM, 25 °C, 10h
PCC, NaOAc, DCM, 25 °C, 10h
TPAP, 4Å MS, NMO, DCM, 25 °C, 12h
IBX, EtOAc, 80 °C, 12h
DMP, py, DCM, 25 °C, 1h

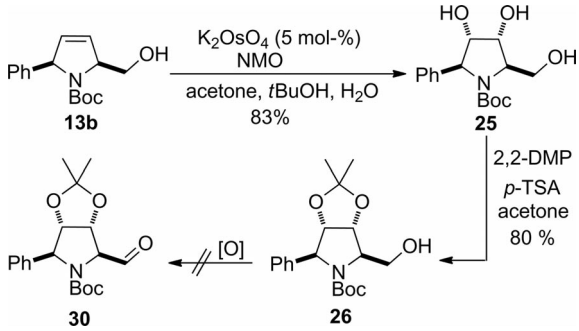
Scheme 14. Attempted oxidation of **12**.

In view of these surprising and disappointing results, a new approach was evaluated (Scheme 15). In this revised strategy we planned the diastereoselective synthesis of triol **25** from *cis* alcohol **13b**, and regioselective protection of the secondary hydroxy groups of **25** in the form of acetonide **26** followed by oxidation of the primary alcohol, thus avoiding the aromatization problems encountered in previous oxidation attempts. The aldehyde formed would be subjected to HWE olefination, and the ester **27** hydrolyzed to the corresponding carboxylic acid. The acetonide protecting group would be removed and an intramolecular Mitsunobu reaction would lead to the desired six-membered lactone **29**.



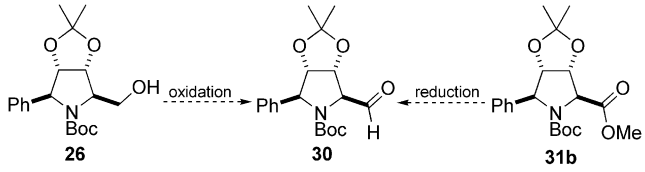
Scheme 15. New synthetic plan.

Putting this plan into practice, **25** was obtained in an efficient and selective manner using catalytic amounts of potassium osmate in the presence of NMO (83% yield) (Scheme 16). Acetalization of **25** occurred uneventfully using 2,2-DMP in acetone, in the presence of *p*-TSA to furnish acetonide **26** in 80% yield. Intriguingly, alcohol **26** also proved very resistant to oxidation to aldehyde **30** (DMP, TPAP, and PCC). In all cases, no consumption of starting material was observed, even after long reaction times. TPAP oxidation of **26** under microwave irradiation (300 W, 30 min, 70 °C) was also unsuccessful.



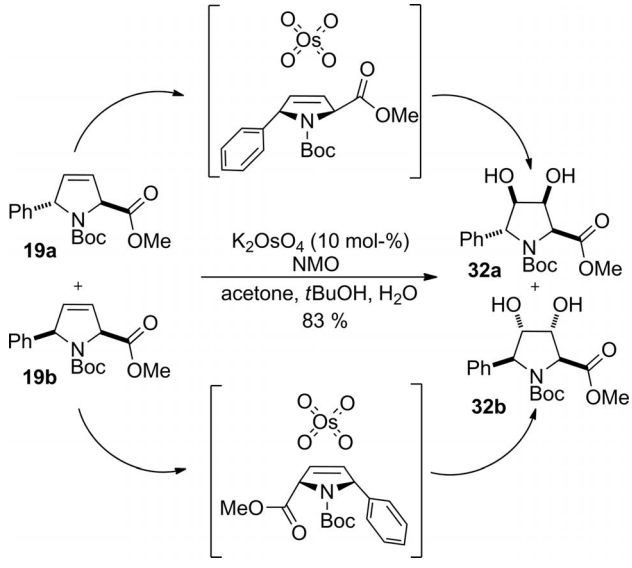
Scheme 16. Attempted oxidation of **26**.

As oxidation of the primary alcohol could not be achieved by the above approach, we chose another pathway for the preparation of aldehyde **30**. The desired aldehyde could, in principle, be achieved by controlled reduction of the ester **31b** with diisobutylaluminium hydride (DIBAL-H) at low temperature (Scheme 17).



Scheme 17. Revised strategy for the synthesis of **30**.

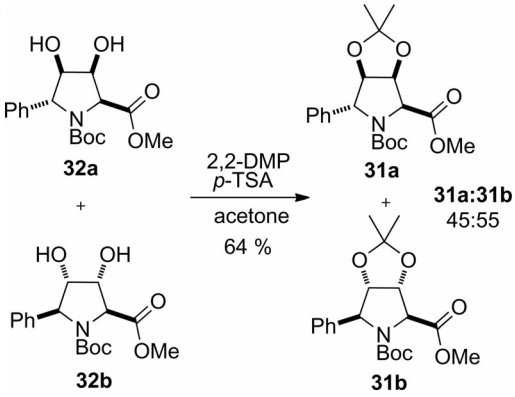
The methylester **31b** was obtained in two steps starting from the mixture of diastereoisomers **19** obtained from the Heck reaction. Initially, the mixture of stereoisomers **19a**/**19b** was dihydroxylated affording the corresponding dia-



Scheme 18. Preparation of **32a** and **32b**.

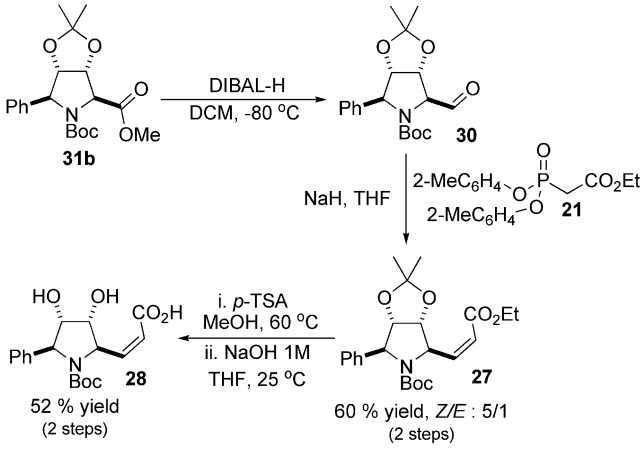
stereoisomeric mixture of diols **32a** and **32b** in 83% yield (Scheme 18). As chromatographic separation was difficult at this stage, the mixture of **32a/32b** was used in the next step.

The mixture of **32a/32b** was converted into the corresponding diastereomeric acetonides **31a/31b** in 64% yield (Scheme 19), which were separated by flash chromatography.



Scheme 19. Preparation and separation of **31a** and **31b**.

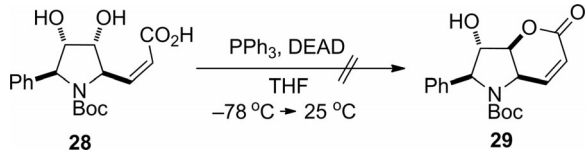
The next step involved reduction of **31b** in a controlled manner to aldehyde **30** (Scheme 20). This reaction was successfully performed by slow and cautious addition of DIBAL-H to a solution of **31b** in dichloromethane at –80 °C. Gratifyingly, the reduction occurred cleanly providing **30**, which was immediately used in HWE olefination using **21**.[15] The desired α,β-unsaturated ester **27** was obtained in a *Z*:*E* ratio of 5:1 in 60% yield from **31b**. The synthesis of **30** by reduction of **31b** circumvented one of the biggest problems faced so far: the oxidation step, and even removed a synthetic step. In spite of not being carried out in this work, the *trans* ester **31a** may also be subjected to same reduction with DIBAL-H, followed by HWE olefination to give intermediate **9**, which was used for the synthesis of aza-isoaltholactone **6**.



Scheme 20. Synthesis of **28**.

After olefination, **27** was treated with catalytic amounts of *p*-TSA in methanol, for the removal of the acetonide, and the α,β-unsaturated ester was hydrolyzed to the corresponding carboxylic acid **28** by treatment with a 1 M solution of sodium hydroxide (52% yield over two steps). The ester diol **28** constitutes an acyclic analogue of aza-altholactone **7**, except for the stereochemistry at C-3.

To form the lactone moiety and invert the stereochemistry at C-3, an intramolecular Mitsunobu reaction was performed (Scheme 21).[23] Unfortunately, treatment of **28** with triphenylphosphane and diethyl azodicarboxylate (DEAD) resulted in no consumption of the starting material. It is worth mentioning that at the end of all the attempted cyclizations, the DEAD reduction product, diethyl hydrazine-1,2-dicarboxylate, was isolated, which indicated that the intermediate generated in situ by the reaction of PPh_3 with DEAD was formed.



Scheme 21. The intramolecular Mitsunobu reaction.

Synthesis of an Aza Analogue of Goniothalesdiol

As the last step in the assembly of the lactone moiety still requires further studies, we focused our attention on the synthesis of aza analogues of related styryllactones with a linear side chain connected to the THF ring instead of a lactone group. In particular, one compound that caught our attention was goniothalesdiol (Figure 4).[24] This natural product exhibits significant cytotoxicity against P388 leukemia cells, as well as pronounced insecticidal activity. In view of its important biological profile and the absence of any nitrogen-containing analogue in the literature, we decided to direct our studies to the synthesis of pyrrolidine **33**, taking advantage of the advanced intermediate **27** synthesized as described above.

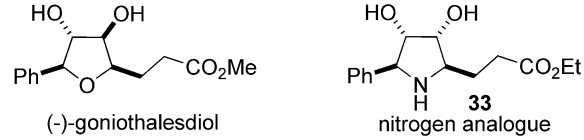
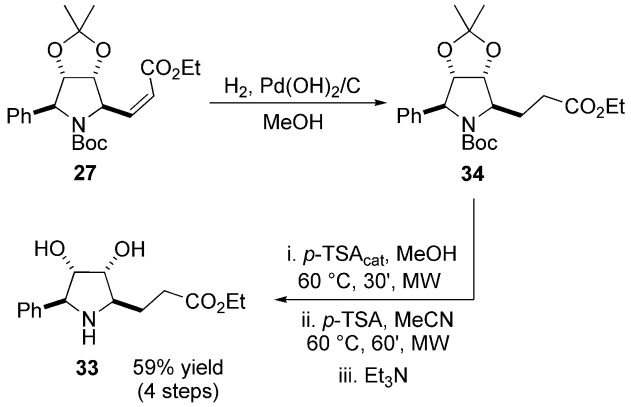


Figure 4. Goniothalesdiol and **33**.

Thus, unsaturated ester **27** was cleanly hydrogenated under a hydrogen atmosphere in the presence of $Pd(OH)_2/C$, which led to the saturated ester **34** (Scheme 22). To conclude the synthesis of pyrrolidine **33**, the acetonide and Boc protecting groups were removed in acidic media under microwave irradiation. The *epi*-aza analogue of goniothalesdiol **33** was thus obtained in 59% yield over four steps.



Scheme 22. Synthesis of **33**.

Conclusions

We have described new synthetic applications of the Heck–Matsuda arylation involving chiral, nonracemic, endocyclic enecarbamates and arenediazonium salts. This method permitted the stereoselective synthesis of (–)-azaisoaltholactone **6** and the stereoselective syntheses of two new highly substituted dihydroxypyrrolidines (–)-**28** and (+)-**33**. The latter compounds constitute optically active *epi*-aza analogues of altholactone and goniothalesdiol. The strategy relied on a divergent approach to illustrate the feasibility and synthetic potential of the stereoisomers obtained by an efficient Heck–Matsuda reaction of the chiral endocyclic enecarbamate **18** with benzenediazonium tetrafluoroborate. The lack of reactivity displayed by endocyclic enecarbamates **15** and **16** towards benzenediazonium tetrafluoroborate was intriguing, and further studies are in progress to understand the basis for these unusual results.

Experimental Section

Materials and Methods: ^{1}H NMR spectra were obtained at 250 and 500 MHz. Spectra were recorded in $CDCl_3$, CD_3CN, and CD_3OD solutions. Chemical shifts are reported in ppm and referenced to the residual solvent peak or tetramethylsilane. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. ^{13}C NMR spectra were obtained at 62.5 MHz and 125 MHz. Chemical shifts are reported in ppm and referenced to the residual solvent peak. Abbreviations to denote the multiplicity of a particular signal are s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), td (triple doublet), ddd (double double doublet) and m (multiplet). Microwave reactions were conducted with a CEM Discover® Microwave synthesizer. The machine consists of a continuous focused microwave power delivery system with selectable power output from 0–300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. Temperature measurements were conducted using an infrared temperature sensor mounted under the reaction vessel. All experiments were performed with a stirring. All experiments were carried out with simultaneous cooling by passing compressed air through the microwave cavity while heating (option PowerMAX enabled). Column chromatography was performed with silica gel (230–400 mesh) following the methods described by Still. TLC was performed with silica gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or developed with phosphomolibdic acid followed by heating. Air- and moisture-sensitive reactions were conducted in flame- or oven-dried glassware equipped with tightly fitting rubber septa under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques.

Procedure for the Heck Arylation of 18 with Benzenediazonium Tetrafluoroborate. Synthesis of 19: To a round-bottomed flask (or a test tube) were added **18** (1.13 g, 5 mmol) and acetonitrile (23 mL). To the resulting suspension were added $Pd_2(dba)_3$·dba (4 mol-%, 200 mg), sodium acetate (3 equiv., 15 mmol, 1.6 g) and the benzenediazonium salt (1.3 equiv., 6.5 mmol). The reaction was stirred at room temperature, and the reaction progress was monitored by the evolution of N_2. After the nitrogen bubbling had stopped, the crude reaction mixture was filtered through a plug of silica and concentrated under reduced pressure. The product was purified by flash chromatography (hexane/ethyl acetate as eluent) to provide **19** in 85% yield (1.28 g), as an inseparable mixture of diastereoisomers, which was used directly in the next step.

Procedure for the Reduction of Heck Adducts. Synthesis of 13a and 13b: In a flask under an argon atmosphere, a solution of **19** (0.53 g, 1.74 mmol) in THF (5 mL) and ethanol (10 mL) was prepared. Dry $CaCl_2$ (0.56 g, 5.1 mmol) was added and, after complete dissolution of $CaCl_2$, $NaBH_4$ (0.46 g, 12 mmol) was introduced. The mixture was stirred at room temperature for 3 h before a solution of 2 M K_2CO_3 (12 mL) was added. Soon after, saturated $NaHCO_3$ (12 mL) was added and the organic phase was extracted into ethyl acetate (3 × 20 mL). The organic phases were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using hexane/ethyl acetate (70:30) as eluent, providing the *trans* diastereoisomer **13a** in 37% yield (0.176 g) and the *cis* product **13b** in 45% yield (0.214 g).

***tert*-Butyl (2*S*,5*S*)-2-(Hydroxymethyl)-5-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (13a):** $[\alpha]_D^{20}$ = –203.4 (*c* = 1.14, AcOEt). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (s, 6 H), 1.26 (s, 4 H), 3.72 (dd, J^1 = 11.8, J^2 = 6.5 Hz, 1 H), 3.91 (dd, J^1 = 11.8, J^2 = 1.8 Hz, 1 H), 5.00–5.06 (m, 1 H), 5.37–5.41 (m, 1 H), 5.68 (dt, J^1 = 6.3, J^2 = 1.8 Hz, 1 H), 5.76 (dt, J^1 = 6.3, J^2 = 2.0 Hz, 1 H), 7.14–7.35 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.9, 67.2, 68.7, 69.5, 80.6, 125.5, 126.5, 127.4, 128.3, 132.2, 142.0, 155.9 ppm. IR (film): $\tilde{\nu}$ = 3349, 2975, 2930, 1656, 1411, 1135 cm^{-1}. MS (EI): *m*/*z* = 276 $[M + 1]^+$, 244, 188, 144, 115, 57.

***tert*-Butyl (2*S*,5*R*)-2-(Hydroxymethyl)-5-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (13b):** $[\alpha]_D^{20}$ = +76.1 (*c* = 1.0, AcOEt). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (s, 9 H), 3.75–3.97 (m, 2 H), 4.85 (d, *J* = 8.5 Hz, 1 H), 5.04 (d, *J* = 8.5 Hz, 1 H), 5.47 (s, 1 H), 5.69–5.76 (m, 2 H), 7.24–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 68.1, 68.5, 69.7, 81.1, 125.4, 127.0, 127.5, 128.3, 131.5, 141.1, 156.8 ppm. IR (film): $\tilde{\nu}$ = 3418, 2976, 1696, 1669, 1394, 1367, 1170 cm^{-1}. MS (EI): *m*/*z* = 275, 244, 188, 144, 57.

***tert*-Butyl (3a*S*,4*R*,6*R*,6a*R*)-4-(Hydroxymethyl)-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (20). First Step:** Olefin **13a** (0.2 g, 0.727 mmol) was dissolved in mixture of H_2O/acetone/*t*BuOH (6:3:1, 2.5 mL) and *N*-methylmorpholine *N*-oxide monohydrate (0.28 g, 2.07 mmol) was added. K_2OsO_4·$2H_2O$ (0.015 g, 0.04 mmol) was introduced and the reaction mixture was stirred at room temperature for 12 h. After this time, a saturated aqueous solution of $NaHSO_3$ was added and the mixture was stirred for 30 min. The aqueous phase was extracted into ethyl acetate and the organic phase was dried with anhydrous

Na_2SO_4, filtered, and the solvents removed under reduced pressure. Purification was performed by flash chromatography using hexane/ethyl acetate (20:80) as eluent providing the desired triol.

Second Step: In a flask under an argon atmosphere, was prepared a solution of the triol (0.218 g, 0.62 mmol), *p*-TSA (0.01 g, 0.053 mmol), and 2,2-DMP (2.5 mL) in dry acetone (5 mL). The reaction mixture was stirred for 1 h. After this time, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted into ethyl acetate. The organic phase was washed with aqueous saturated NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash chromatography eluting with a mixture of hexane/ethyl acetate afforded **20** in 87% yield for the two steps (0.189 g). $[a]_D^{20}$ = –43 (*c* = 1.0, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.30 (s, 3 H), 1.52 (s, 3 H), 3.87–4.05 (m, 2 H), 4.10–4.20 (m, 1 H), 4.55 (dd, J^1 = 6.0, J^2 = 1.0 Hz, 1 H), 4.86 (t, *J* = 6.0 Hz, 1 H), 4.99 (s, 1 H), 7.05–7.45 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.7, 26.1, 27.9, 62.9, 65.5, 68.2, 79.9, 80.9, 85.2, 111.8, 125.6, 127.5, 128.8, 140.8, 156.3 ppm. IR (film): $\tilde{\nu}$ = 1054, 1136, 1165, 1213, 1243, 1366, 1398, 1453, 1675, 2936, 2980, 3425 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{27}NO_5$ [M + H$^+$] 350.1967; found 350.1967.

***tert*-Butyl (3a*S*,4*R*,6*R*,6a*R*)-4-[(*Z*)-3-Ethoxy-3-oxoprop-1-enyl]-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (9). First Step:** In a flask under an argon atmosphere, **20** (0.027 g, 0.078 mmol) was dissolved in dry dichloromethane (1.5 mL) containing finely macerated molecular sieves (40 mg) and NMO (0.017 g, 0.126 mmol). The reaction mixture was stirred for 10 min before TPAP (5 mol-%) was added. The reaction was kept at room temperature for 20 min and then filtered through a short column of silica using ethyl acetate as eluent. The filtrate was evaporated under reduced pressure, and the aldehyde obtained was used in the next step without further purification.

Second Step: In a flask under an argon atmosphere, a suspension of sodium hydride (0.004 g, 60% dispersion in mineral oil) in dry THF (0.5 mL) was prepared at 0 °C. Then, **21** (0.035 g, 0.105 mmol) diluted in dry THF (0.5 mL) was added. The reaction mixture was stirred for 15 min before a solution of the aldehyde prepared in the first step in dry THF (0.5 mL) was added, and the reaction was stirred for 1 h. The reaction mixture was then treated with aqueous saturated ammonium chloride and extracted into ethyl ether. The solvent was removed under reduced pressure, and purification by flash chromatography eluting with a mixture of hexane/ethyl acetate (70:30) provided **9** in 70% yield for the two steps (0.023 g). $[a]_D^{20}$ = –90 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (s, 9 H), 1.26–1.33 (m, 6 H), 1.52 (s, 3 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 4.61 (d, *J* = 5.7 Hz, 1 H), 5.01 (s, 1 H), 5.14 (t, *J* = 6.0 Hz, 1 H), 5.76 (t, *J* = 6.2 Hz, 1 H), 5.96 (d, *J* = 11.5 Hz, 1 H), 6.35 (dd, J^1 = 11.5, J^2 = 7.25 Hz, 1 H), 7.10–7.40 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 25.0, 26.5, 28.2, 60.3, 61.4, 68.1, 80.3, 80.5, 86.1, 112.0, 118.8, 126.1, 127.7, 128.9, 141.4, 149.3, 155.2, 166.6 ppm. IR (film): $\tilde{\nu}$ = 1171, 1373, 1465, 1652, 1699, 1714, 2935, 2980 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{31}NO_6$ [M + H$^+$] 418.2230; found 418.2256.

(2*R*,3*R*,3a*S*,7a*R*)-3-Hydroxy-2-phenyl-1,2,3,3a-tetrahydropyrano-[3,2-*b*]pyrrol-5(7a*H*)-one Aza-isoaltholactone (6): Into a flask containing **9** (0.044 g, 0.106 mmol) was added a solution of *p*-TSA in methanol (2 mL, 0.002 g/mL of *p*-TSA). This solution was transferred to a microwave tube and reacted for 30 min at 60 °C under microwave irradiation. The solvent was evaporated under reduced pressure, and the crude reaction was dissolved in acetonitrile (4 mL). *p*-TSA (0.1 g, 0.53 mmol) was added, and the mixture was heated at 60 °C for 1 h under microwave irradiation. Triethylamine (0.5 mL) was added and the solvent was removed. Purification by flash chromatography eluting with ethyl acetate (triethylamine was used to dope the column) provided **6** in 64% yield for the three steps (0.016 g). $[a]_D^{20}$ = –31 (*c* = 0.53, MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ = 4.02 (d, *J* = 7.5 Hz, 1 H), 4.10 (t, *J* = 6.5 Hz, 1 H), 4.17 (ddd, J^1 = 6.0, J^2 = 4.5, J^3 = 1.5 Hz, 1 H), 4.93 (t, *J* = 6.0 Hz, 1 H), 6.02 (dd, J^1 = 10.0, J^2 = 1.5 Hz, 1 H), 6.83 (dd, J^1 = 10.0, J^1 = 4.0 Hz, 1 H), 7.20–7.46 (m, 5 H) ppm. ^{13}C NMR (125 MHz, CD_3CN): δ = 50.5, 66.3, 78.7, 79.6, 121.0, 127.1, 127.6, 128.7, 142.1, 146.4, 162.5 ppm. IR (KBr): $\tilde{\nu}$ = 3415, 3252, 2959, 2928, 2856, 1728, 1458, 1381, 1270, 1123, 1073 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{13}NO_3$ [M + H$^+$] 232.0974; found 232.0960.

***tert*-Butyl (1*R*,2*R*,4*S*,5*S*)-2-(Hydroxymethyl)-4-phenyl-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (12). Condition i:** To a solution of **13b** (0.055 g, 0.2 mmol) in toluene (2.5 mL) was added *m*CPBA, and the mixture was stirred at room temperature for 24 h. A saturated solution of sodium bisulfide (5 mL) was added, and the mixture was stirred for 30 min. The aqueous phase was extracted into ethyl acetate (5 mL), and the organic phases were dried with Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography using as eluent hexane/ethyl acetate (60:40) provided **12** in 53% yield (0.031 g).

Condition ii: Compound **13b** (0.041 g, 0.15 mmol) dissolved in acetone (2.5 mL) was cooled to 0 °C and an aqueous solution of $NaHCO_3$ (0.24 g in 1 mL of H_2O, 2.8 mmol) was added. A solution of Oxone® in water (0.48 g in 1.6 mL of H_2O, 1.6 mmol) was added and the reaction was kept at 0 °C for 3 h. The reaction was left at room temperature for 2 h and a saturated solution of sodium chloride (5 mL) was added. The aqueous phase was extracted into ethyl acetate (5 mL), and the combined organic phases were dried with Na_2SO_4, filtered, and the solvents removed under reduced pressure. Purification by flash chromatography using as eluent hexane/ethyl acetate (60:40) provided **12** in 60% yield (0.034 g). $[a]_D^{20}$ = +19.7 (*c* = 0.8, EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$) presence of rotamers: δ = 1.30 (s, 7 H), 1.46 (s, 2 H), 2.55 (br. s, 1 H), 3.63 (br. s, 1.6 H), 3.72–3.85 (m, 0.6 H), 3.88–3.91 (m, 1.8 H), 4.21 (t, *J* = 5.8 Hz, 0.2 H), 4.36 (t, *J* = 5.5 Hz, 0.8 H), 5.05 (s, 0.8 H), 5.20 (s, 0.2 H), 7.28–7.41 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) presence of rotamers: δ = 28.2, 28.4, 57.4, 58.1, 59.4, 60.2, 61.1, 61.3, 61.9, 62.8, 62.9, 63.9, 80.9, 81.3, 126.6, 126.8, 127.8, 127.9, 128.7, 128.8, 137.9, 138.0, 154.9, 156.7 ppm. ^{1}H NMR (500 MHz, CD_3CN) presence of rotamers: δ = 1.29 (s, 4.5 H), 1.43 (s, 4.5 H), 3.18 (t, *J* = 5.5 Hz, 0.5 H), 3.41 (t, *J* = 5.5 Hz, 0.5 H), 3.53–3.67 (m, 1.5 H), 3.75–3.86 (m, 1.5 H), 4.04 (dd, J^1 = 8.3, J^2 = 4.0 Hz, 0.5 H), 4.09 (dd, J^1 = 7.3, J^2 = 5.5 Hz, 0.5 H), 4.99 (s, 0.5 H), 5.02 (s, 0.5 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (125 MHz, CD_3CN) presence of rotamers: δ = 28.1, 28.2, 58.8, 59.5, 60.5, 61.2, 62.3, 62.4, 62.7, 62.8, 63.3, 63.9, 81.2, 81.4, 128.2, 128.3, 128.9, 129.0, 129.7, 129.8, 139.9, 140.0, 156.1, 156.7 ppm. ^{1}H NMR (250 MHz, CD_3CN, 70 °C) presence of rotamers: δ = 1.39 (s, 9 H), 3.10 (br. s, 1 H), 3.66–3.69 (m, 2 H), 3.77 (d, *J* = 2.8 Hz, 1 H), 3.82–3.89 (m, 1 H), 4.10–4.15 (m, 1 H), 5.04 (s, 1 H), 7.28–7.44 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, CD_3CN, 70 °C) presence of rotamers: δ = 28.9, 59.1, 60.9, 62.6, 63.1, 63.9, 81.4, 128.3, 128.9, 130.0, 140.2, 156.7 ppm. IR (film): $\tilde{\nu}$ = 3433, 2977, 1694, 1674, 1415, 1368, 1169 cm^{-1}. EM (EI): *m*/*z* = 292 [M + 1]$^+$, 248, 160, 142, 75, 57. HRMS (ESI): calcd. for $C_{16}H_{21}NO_4$ [M + Na]$^+$ 314.1368; found 314.1320.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate:** To a flask under an argon atmosphere were added **13b** (0.378 g, 1.37 mmol) and dry dichloromethane (5.5 mL) followed by imidazole (0.128 g, 1.91 mmol) and *tert*-butyldimethylsilyl chloride (0.24 g, 1.63 mmol), which formed

a white suspension. The mixture was stirred for 12 h at room temperature. The organic phase was washed with saturated ammonium chloride (10 mL) and the aqueous phase extracted into dichloromethane (3 × 15 mL). The organic phases were dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using as eluent hexane/ethyl acetate (95:05), which provided the protected product in 87% yield (0.463 g). $[\alpha]_D^{20}$ = +28.8 (*c* = 1.58, AcOEt). ^{1}H NMR (250 MHz, $CDCl_3$) presence of rotamers: δ = 0.09 (s, 6 H), 0.92 (s, 9 H), 1.27 (s, 6 H), 1.46 (s, 3 H), 3.58 (t, *J* = 8.8 Hz, 0.4 H), 3.79 (t, *J* = 7.5 Hz, 0.6 H), 4.05–4.18 (m, 1 H), 4.56–4.65 (m, 1 H), 5.41 (br. s, 0.6 H), 5.57 (br. s, 0.4 H), 5.70–5.80 (m, 1 H), 5.96–5.98 (m, 1 H), 7.20–7.33 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) presence of rotamers: δ = –5.3, –5.2, 18.4, 28.2, 28.5, 29.7, 65.0, 66.2, 66.7, 68.9, 69.3, 79.7, 79.9, 127.1, 127.2, 127.3, 127.9, 128.2, 128.3, 130.3, 141.5, 142.2, 154.7 ppm. IR (film): $\tilde{\nu}$ = 3008, 2967, 1741, 1372, 1222 cm^{-1}. MS (EI): *m*/*z* = 389 $[M]^+$, 276, 244, 188, 144, 73, 57.

***tert*-Butyl (1*R*,2*R*,4*S*,5*S*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-phenyl-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (22):** To a solution of **13b** (0.222 g, 0.57 mmol) in toluene (7 mL) was added *m*CPBA (0.85 g, 2.8 mmol), and the reaction mixture was stirred at room temperature for 24 h. A saturated solution of sodium bisulfite (20 mL) was added, and the mixture was stirred for 30 min. The aqueous phase was extracted into ethyl acetate (3 × 20 mL), and the organic phases were dried with Na_2SO_4, filtered, and the solvents removed under reduced pressure. Purification by flash chromatography using as eluent hexane/ethyl acetate (90:10) provided **22** in 70% yield (0.160 g). $[\alpha]_D^{20}$ = +17.2 (*c* = 1.56, AcOEt). ^{1}H NMR (250 MHz, $CDCl_3$) presence of rotamers: δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 5 H), 0.91 (s, 4 H), 1.29 (s, 5 H), 1.45 (s, 4 H), 3.56–4.22 (m, 5 H), 4.99 (s, 0.5 H), 5.15 (s, 0.5 H), 7.25–7.39 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) presence of rotamers: δ = –5.45, –5.37, 18.2, 25.8, 28.2, 28.2, 58.4, 58.5, 59.4, 60.2, 60.5, 60.7, 62.0, 62.0, 62.5, 62.9, 80.1, 80.4, 126.7, 126.8, 127.5, 127.6, 128.4, 128.6, 138.1, 138.7, 154.8 ppm. IR (film): $\tilde{\nu}$ = 3014, 2969, 2949, 1738, 1367, 1228, 1216 cm^{-1}. MS (EI): *m*/*z* = 306, 260, 248, 160, 142, 132, 73.

***tert*-Butyl (1*R*,2*R*,4*S*,5*S*)-2-(Hydroxymethyl)-4-phenyl-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (12):** To a solution of **22** (0.128 g, 0.32 mmol) in THF (2 mL) was added a 1.0 M solution of TBAF in THF (0.38 mL, 0.38 mmol) at 0 °C. After 2 h at room temperature, water (5 mL) was added, and the reaction mixture was extracted into ethyl acetate (3 × 5 mL). The organic phases were dried with $MgSO_4$, filtered, and the solvents removed under reduced pressure. Purification by flash chromatography using as eluent hexane/ethyl acetate (60:40) provided **12** in 86% yield (0.079 g).

***tert*-Butyl (2*R*,3*R*,4*S*,5*S*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-phenylpyrrolidine-1-carboxylate (25):** To **13b** (0.057 g, 0.2 mmol) dissolved in H_2O/acetone/*t*BuOH (0.42:0.18:0.07 mL) was added *N*-methylmorpholine *N*-oxide (0.07 g, 0.6 mmol) and K_2OsO_4 (0.004 g, 5 mol-%). The reaction mixture was stirred at room temperature for 48 h. A saturated solution of sodium bisulfite (3.0 mL) was added, and the mixture was stirred for 30 min. The aqueous phase was extracted into ethyl acetate (3 × 5 mL), and organic phases were dried with Na_2SO_4, filtered, and the solvents removed under reduced pressure. The crude product was purified by flash chromatography using as eluent hexane/ethyl acetate (20:80), which provided **25** in 83% yield (0.052 g). $[\alpha]_D^{20}$ = –43 (*c* = 0.7, MeOH). ^{1}H NMR (250 MHz, CD_3OD, 57 °C): δ = 1.21 (s, 9 H), 3.77–3.90 (m, 3 H), 4.03 (dd, J^1 = 6.3, J^2 = 4.0 Hz, 1 H), 4.10 (dd, J^1 = 4.1, J^2 = 2.5 Hz, 1 H), 4.55 (d, *J* = 6.3 Hz, 1 H), 7.17–7.37 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, CD_3OD, 57 °C): δ = 28.6, 63.4, 67.7, 68.5, 73.5, 79.9, 81.5, 127.5, 128.0, 129.3, 143.7, 157.7 ppm. IR (film): $\tilde{\nu}$ = 3309, 1666, 1413, 1148, 1105 cm^{-1}. EM (EI): *m*/*z* = 310 $[M + 1]^+$, 254, 210. HRMS (ESI): calcd. for $C_{16}H_{23}NO_5$ $[M + H]^+$ 310.1654; found 310.1665.

***tert*-Butyl (3a*R*,4*R*,6*S*,6a*S*)-4-(Hydroxymethyl)-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (26):** Under an argon atmosphere, was prepared a mixture of **25** (0.052 g, 0.17 mmol), anhydrous *p*-TSA (0.003 g, 0.017 mmol), and 2,2-DMP (0.73 mL) in dry acetone (1 mL) at room temperature. After stirring for 12 h, a saturated solution of sodium hydrogen carbonate (5 mL) was added, and the product extracted into ethyl acetate (3 × 5 mL). The organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using as eluent hexane/ethyl acetate (50:50), which provided **26** in 80% yield (0.047 g). $[\alpha]_D^{20}$ = –5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$, 55 °C): δ = 1.31 (s, 9 H), 1.33 (s, 3 H), 1.56 (s, 3 H), 3.72–3.85 (m, 2 H), 4.27 (td, J^1 = 5.1, J^2 = 2.0 Hz, 1 H), 4.52 (dd, J^1 = 5.6, J^2 = 2.0 Hz, 1 H), 4.62 (dd, J^1 = 5.6, J^2 = 2.0 Hz, 1 H), 5.04 (br. s, 1 H), 7.19–7.35 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$, 55 °C): δ = 25.5, 27.5, 28.1, 64.5, 66.6, 68.8, 80.8, 81.6, 86.6, 112.2, 125.7, 127.2, 128.5, 141.1, 155.9 ppm. IR (film): $\tilde{\nu}$ = 3452, 1694, 1674, 1394 cm^{-1}. EM (EI): *m*/*z* = 372 $[M + Na]^+$, 316, 272. HRMS (ESI): calcd. for $C_{19}H_{27}NO_5$ $[M + Na]^+$ 372.1787; found 372.1783.

Syntheses of 31a and 31b. First Step: To a solution of **19** (0.1 g, 0.33 mmol) in H_2O/acetone/*t*BuOH (0.69:0.3:0.12 mL) was added *N*-methylmorpholine *N*-oxide (0.116 g, 0.99 mmol) and K_2OsO_4 (0.013 g, 10 mol-%). The reaction mixture was stirred at room temperature for 48 h. A saturated solution of sodium bisulfite (3 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted into ethyl acetate (3 × 5 mL), and the organic phases were dried with Na_2SO_4, filtered, and the solvents removed under reduced pressure. The crude product was purified by flash chromatography using as eluent hexane/ethyl acetate (40:60), which provided a mixture of **32** in 64% yield (0.071 g). As it was not possible to efficiently separate the diastereoisomers by flash chromatography, the mixture was used directly in next step.

Second Step: Under an argon atmosphere was prepared a mixture of **32** (0.071 g, 0.21 mmol), dry *p*-TSA (0.0038 g, 0.022 mmol), and 2,2-DMP (0.91 mL) in dry acetone (2 mL) at room temperature. After stirring for 12 h, a saturated solution of sodium hydrogen carbonate (5 mL) was added, and the product was extracted into ethyl acetate (3 × 10 mL). The organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using as eluent hexane/ethyl acetate (80:20). The two isomers were separated, and **31b** was obtained in 0.031 g with **31a** in 0.017 g (64% yield for the formation of two acetonides).

5-*tert*-Butyl 4-Methyl (3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-4,5(4*H*)-dicarboxylate (31a): ^{1}H NMR (250 MHz, $CDCl_3$) presence of rotamers: δ = 1.13 (s, 6 H), 1.27 (s, 3 H), 1.37 (s, 3 H), 1.48 and 1.50 (2s, 3 H), 3.80 (s, 3 H), 4.57–4.62 (m, 1 H), 4.80 (d, *J* = 8.0 Hz, 0.45 H), 4.88 (d, *J* = 8.0 Hz, 0.55 H), 5.04–5.12 (m, 1 H), 5.14 (s, 0.55 H), 5.28 (s, 0.45 H), 7.10–7.16 (m, 2 H), 7.27–7.38 (m, 3 H) ppm.

5-*tert*-Butyl 4-Methyl (3a*R*,4*S*,6*S*,6a*S*)-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-4,5(4*H*)-dicarboxylate (31b): ^{1}H NMR (250 MHz, $CDCl_3$) presence of rotamers: δ = 1.22 and 1.40 (2s, 9 H), 1.32 (s, 3 H), 1.61 (s, 3 H), 3.82 (s, 3 H), 4.41–4.60 (m, 2 H), 4.80–4.83 (m, 1 H), 5.00 (br. s, 0.6 H), 5.17 (br. s, 0.4 H), 7.22–7.38 (m, 3 H), 7.52 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz,

$CDCl_3$) presence of rotamers: δ = 25.4, 27.5, 27.9, 52.5, 66.4, 67.1, 67.8, 80.7, 81.1, 81.8, 86.4, 86.9, 112.8, 126.2, 127.3, 128.4, 139.4, 140.3, 153.4, 153.9, 171.6 ppm.

(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl-4-[(*Z*)-3-ethoxy-3-oxoprop-1-enyl]-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (27). First Step: In a long tube under an argon atmosphere was prepared a solution of **31b** (0.151 g, 0.4 mmol) in dry dichloromethane (2 mL). The system was cooled to –80 °C, and DIBAL-H (0.42 mmol, 1.5 M solution in toluene) was cautiously added. It is worth pointing out that in order to avoid overreduction, the reducing agent must run down the walls of the tube to cool before reaching the reaction mixture. The reaction was maintained at that temperature for 30 min, then 5 mL of a saturated solution of Rochelle salt (K,Na tartrate) was added. The mixture was stirred for 1 h at room temperature and extracted into diethyl ether. The combined organic phases were dried with $MgSO_4$, filtered, and the solvents evaporated. The crude reaction was used in the next step without prior purification.

Second Step: To a suspension of sodium hydride (0.008 g, 0.184 mmol, 60% dispersion in mineral oil) in dry THF (1 mL) at 0 °C under an argon atmosphere was added **21** (0.064 g, 0.184 mmol) in THF (0.5 mL). After stirring for 10 min, **30** (0.016 g, 0.046 mmol) dissolved in dry THF (1 mL) was added, and the mixture was stirred for 1 h. The reaction mixture was treated with a saturated solution of ammonium chloride and extracted into ethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography using as eluent hexane/ethyl acetate (75:25), which provided **27** in 60% yield for the two steps (0.013 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.3 Hz, 3 H), 1.35 (s, 9 H), 1.59 (s, 3 H), 1.62 (s, 3 H), 4.22 (q, J = 7.3 Hz, 2 H), 4.56 (dd, J^1 = 5.5, J^2 = 1.8 Hz, 1 H), 4.71 (dd, J^1 = 5.5, J^2 = 1.8 Hz, 1 H), 5.13 (br. s, 1 H), 5.75 (d, J = 8.3 Hz, 1 H), 5.87 (dd, J^1 = 11.5, J^2 = 1.5 Hz, 1 H), 6.11–6.19 (m, 1 H), 7.20–7.40 (m, 5 H) ppm. MS (EI): m/z = 418 $[M + 1]^+$, 374, 372, 360, 328, 314. HRMS (ESI): calcd. for $C_{23}H_{31}NO_6$ $[M + Na]^+$ 440.2049; found 440.2050. HRMS (ESI): calcd. for $C_{23}H_{31}NO_6$ $[M + H]^+$ 418.2229; found 418.2228.

***tert*-Butyl (2*R*,3*R*,4*S*,5*S*)-2-[(*Z*)-3-Ethoxy-3-oxoprop-1-enyl]-3,4-dihydroxy-5-phenylpyrrolidine-1-carboxylate:** To a flask were added **27** (0.058 g, 0.135 mmol), *p*-TSA (approximately 0.003 g), and methanol (2 mL). The reaction was heated to 60 °C for 5 h. The reaction mixture was treated with a saturated solution of sodium chloride and extracted into ethyl acetate. The combined organic phases were dried with $MgSO_4$ and concentrated at reduced pressure. The product was purified by flash chromatography using as eluent hexane/ethyl acetate (50:50). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17–1.45 (m, 12 H), 3.13 (br. s, 1 H), 4.08 (br. s, 2 H), 4.22 (q, J = 7.3 Hz, 2 H), 4.90–5.40 (m, 3 H), 6.05 (d, J = 11.8 Hz, 1 H), 6.61 (br. s, 1 H), 7.20–7.40 (m, 5 H) ppm.

(*Z*)-3-[(2*R*,3*R*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-5-phenylpyrrolidin-2-yl]acrylic Acid (28): To a solution of ester described above (0.020 g, 0.053 mmol) in ethanol (0.3 mL) was added a solution of NaOH (1 M, 0.13 mL). The mixture was stirred at room temperature for 1 h and HCl (1 M, 0.053 mL) was added. The reaction mixture was evaporated to remove ethanol, and HCl (1 M, 0.071 mL) was added. The aqueous phase was extracted into ethyl acetate, and the combined organic phases were dried with $MgSO_4$ and concentrated at reduced pressure. The product was purified by flash chromatography using as eluent ethyl acetate/methanol/acetic acid (94:5:1). Compound **28** was obtained in 52% yield for two steps (0.024 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10–1.50 (m, 9 H), 4.14 (br. s, 2 H), 4.83 (br. s, 1 H), 5.34 (t, J = 6.5 Hz, 1 H), 6.07 (d, J = 11.5 Hz, 1 H), 6.46 (dd, J^1 = 11.5, J^2 = 8.0 Hz, 1 H), 7.20–7.43 (m, 5 H) ppm.

***tert*-Butyl (3a*R*,4*R*,6*S*,6a*S*)-4-(3-Ethoxy-3-oxopropyl)-2,2-dimethyl-6-phenyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (34):** To a solution of **27** (0.030 g, 0.072 mmol) in dry methanol (2 mL) under a hydrogen atmosphere was added $Pd(OH)_2$/C 10% (20% w/w). The reaction was stirred at room temperature for 24 h. The crude reaction mixture was filtered through a plug of Celite and concentrated under reduced pressure. The resulting product **34** was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.2 Hz, 3 H), 1.33 (s, 3 H), 1.38 (br. s, 9 H), 1.54 (s, 3 H), 1.68–1.83 (m, 1 H), 1.88–2.15 (m, 1 H), 2.47 (t, J = 7.7 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.15–4.19 (m, 1 H), 4.43 (dd, J^1 = 5.5, J^2 = 0.8 Hz, 1 H), 4.60–4.77 (m, 1 H), 5.12 (br. s, 1 H), 7.18–7.37 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2, 25.5, 27.4, 28.2, 29.0, 31.4, 60.5, 64.1, 68.2, 80.2, 84.1, 86.8, 112.2, 125.5, 127.1, 128.5, 140.8, 154.9, 172.8 ppm.

Ethyl 3-[(2*R*,3*R*,4*S*,5*S*)-3,4-Dihydroxy-5-phenylpyrrolidin-2-yl]propanoate (33): To crude **34** was added a solution of *p*-TSA (catalytic amount) in methanol (2 mL). The solution was transferred to a microwave tube and reacted for 30 min at 60 °C under microwave irradiation. The solvent was evaporated under reduced pressure, and the residue dissolved in acetonitrile (2 mL). *p*-TSA (0.013 g, 0.072 mmol) was added to the mixture, which was heated at 60 °C for 1 h under microwave irradiation. Triethylamine (0.5 mL) was added, and the solvent was removed. Purification by flash chromatography eluting with ethyl acetate (triethylamine was used to dope the column) provided **33** in 59% yield for the four steps (0.011 g). $[a]_D^{20}$ = +4 (c = 0.6, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3 H), 1.79–1.94 (m, 1 H), 1.96–2.10 (m, 1 H), 2.37 (br. s, 3 H), 2.50 (t, J = 7.5 Hz, 2 H), 3.13–3.20 (m, 1 H), 3.80–3.88 (m, 2 H), 4.08 (d, J = 6.0 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 7.26–7.43 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, CD_3CN): δ = 14.2, 29.7, 31.3, 60.5, 63.0, 67.1, 75.5, 78.0, 126.8, 127.5, 128.5, 141.9, 173.9 ppm. HRMS (EI): calcd. for $C_{15}H_{21}NO_4$ $[M – H_2O]^+$ 261.1365; found 261.1394.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra of selected compounds.

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