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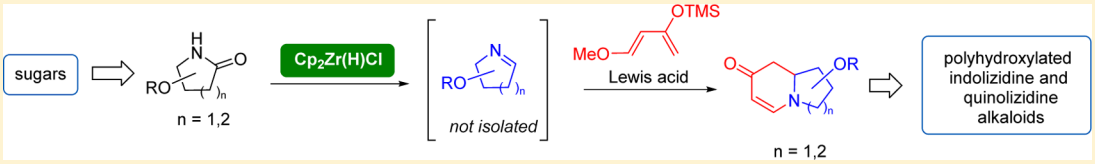
# Synthesis of Polyhydroxylated Quinolizidine and Indolizidine Scaffolds from Sugar-Derived Lactams via a One-Pot Reduction/Mannich/Michael Sequence

Piotr Szcześniak, Sebastian Stecko,* Elżbieta Maziarz, Olga Staszewska-Krajewska, and Bartłomiej Furman*

Institute of Organic Chemistry, Polish Academy of Sciences Kasprzaka 44/52, 01-224 Warsaw, Poland

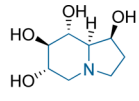
Supporting Information




**ABSTRACT:** A direct approach to the synthesis of indolizidine and quinolizidine scaffolds of iminosugars is described. The presented strategy is based on a one-pot sugar lactam reduction with Schwartz's reagent followed by a diastereoselective Mannich/Michael tandem reaction of the resulting sugar imine with Danishefsky's diene. The stereochemical course of the investigated reaction has been explained in detail. The obtained bicyclic products are attractive building blocks for the synthesis of various naturally occurring polyhydroxylated alkaloids and their derivatives.

## INTRODUCTION

The synthesis and biological properties of polyhydroxylated indolizidine alkaloids (iminosugars) such as castanospermine, swainsonine, lentiginosine, and their synthetic quinolizidine analogues (**1**−**4**) have received considerable interest in recent years.[1] Due to their structural resemblance to sugars, iminosugars are recognized by glycosidases, the enzymes responsible for formation or hydrolysis of glycosyl bonds in carbohydrates and glycoconjugates, which may result in inhibition of their activity.[1b,c] Thanks to this feature, iminosugars have demonstrated a range of biological activity (e.g., antiviral, anti-HIV, anticancer, antifeedant, immunoregulatory activity, and more) that target a wide choice of diseases.[1] The approval of Glyset and Zavesca for the treatment of complications associated with type II diabetes and for Gaucher's disease, respectively, within the past decade, is a testament to their importance as medicines for unmet medical needs.[1] Clearly, the field of iminosugars is a fertile area for research on both chemical and biological frontiers.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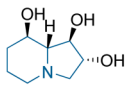
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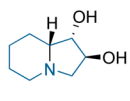
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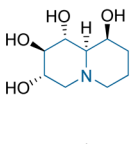
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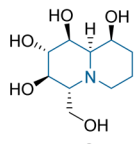
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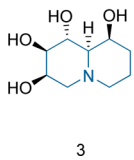
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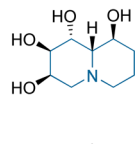
4

Several strategies for the synthesis of bicyclic iminosugar systems based on either chiral pool or enantio- and diastereoselective approaches have been developed.[2] The first group of methods employs mainly hydroxyacids and carbohydrates as starting materials.[1b,c,3,4] The last two approaches involve linear and stepwise formation of a piperidine or pyrrolidine ring followed by intramolecular cyclization leading to a bicyclic pyrrolizidine, indolizidine, or quinolizidine scaffold.[5−7] The most explored strategies rely on 1,3-dipolar cycloaddition of chiral nitrones with olefins,[8−12] developed by Tufariello[13] and extended by Brandi,[14] Vasella,[15] Vogel,[16] and our group.[17]

The asymmetric Mannich/Michael tandem reaction (formal aza-Diels−Alder reaction), which has long proven to be an invaluable aid in enabling access to highly functionalized six-membered nitrogen-containing heterocycles,[18] can be envisioned as an alternative way. In the past, we demonstrated that dihydropyridones, generated in situ via a Mannich/Michael sequence of acyclic imines with electron-rich Danishefsky-type dienes,[19] can be used as building blocks for the construction of indolizidine and quinolizidine scaffolds through either rhodium-catalyzed intramolecular conjugate addition of vinylstannanes[20] or fluoride ion induced intramolecular conjugate addition of propargylsilanes.[21]

Although the studies on the acyclic imine-involved Mannich/Michael reactions are advanced,[18b−d,22−26] the examples of analogous reactions that employ nonactivated cyclic imines are rare.[27−31] Despite the fact that the Mannich/Michael process

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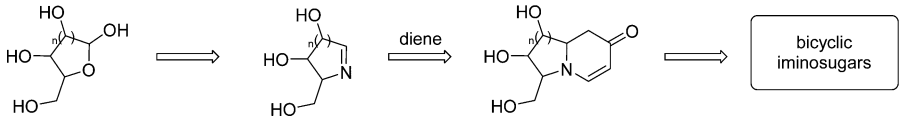
**Scheme 1**




involving cyclic imines provides a direct entry to the indolizidine or quinolizidine scaffold, its potential as a tool of synthetic organic chemistry remains unexploited. Such an approach would be even more attractive if sugar-derived imines were to be applied, since the resulting products, bicyclic enaminones, can serve as direct precursors of indolizidine or quinolizidine iminosugars (Scheme 1). Herein, we wish to report the use of optically active, sugar-derived imines as coupling partners to achieve a highly diastereoselective cyclocondensation as a route to various of bicyclic iminosugars.

## RESULTS AND DISCUSSION

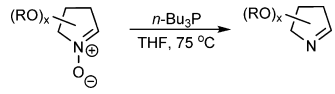
We started our investigation with the preparation of various sugar-derived imines. The standard way of preparing simple cyclic imines is *N*-chlorination of cyclic amines followed by elimination.[32] However, this approach is less viable in the case of sugar-derived imines, since it is difficult to control the regioselectivity of elimination of the corresponding *N*-chloroamines, which leads to the formation of inseparable mixtures of isomeric imines. Additionally, in many cases the synthesis of initial amines in not a straightforward task. Therefore, we considered a more facile approach to the preparation of imines.

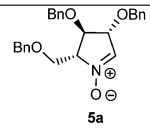
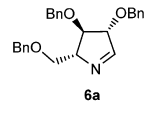
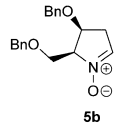
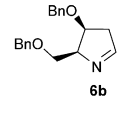
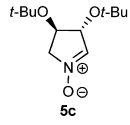
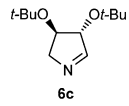
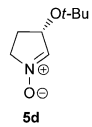
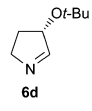
On the basis of our previous experience,[33] we focused our attention on sugar-derived nitrones as imine precursors. For this purpose the pentose-derived nitrones **5a**,**b**[34−36] were prepared according to literature protocols. The additional two nitrones **5c**[14b] and **5d**,[14d] derived from chiral hydroxyacids, were also prepared. These compounds were subjected to phosphine-mediated deoxygenation, leading to corresponding imines **6a−d** in good yields (Table 1).[37] All of the imines are rather unstable molecules; however, careful chromatography on Florisil allowed us to obtain them in pure form.

Imines **6a−d** were submitted to a $Yb(OTf)_3$-catalyzed addition/cyclization tandem reaction with Danishefsky's diene (DD) according to our previous reports.[19−21] The corresponding bicyclic enaminones **7a−d** were obtained in moderate yields and with good to high diastereoselectivity (Table 2).

Since imines have limited stability, we wondered if both steps, deoxygenation and cyclocondensation, could be performed in a one-pot manner without isolation of the intermediate imine. However, all attempts to perform the above sequence in a one-pot manner failed. No formation of the desired indolizidine product was noticed. Moreover, although the above approach worked well for five-membered imines, it was not suitable for the formation of quinolizidines from six-membered imines. The main problem was the limited availability of six-membered sugar-derived nitrones; these compounds are more difficult to prepare and are less stable than their five-membered congeners.[38] In addition, the formation of the six-membered imines was another challenging; despite many attempts, these compounds were formed in poor yields and were highly unstable. Therefore, we decided to revise our synthetic approach and find another source of cyclic imines which would provide a straightforward and general route to polyhydroxylated indolizidines and quinolizidines.

**Table 1. Synthesis of Imines via Phosphine-Mediated Deoxygenation of Nitrones**[a]




| Entry | Nitrone | Imine | Yield[b] [%] |
|---|---|---|---|
| 1 |  **5a** |  **6a** | 83 |
| 2 |  **5b** |  **6b** | 67 |
| 3 |  **5c** |  **6c** | 85 |
| 4 |  **5d** |  **6d** | 69 |

[a]Reaction conditions: $Bu_3P$ (2.0 equiv), THF, 75 °C, 24−48 h. [b]Isolated yield.

Very recently, we have demonstrated that sugar-derived imines can be easily generated by the reduction of carbohydrate-derived lactams with Schwartz's reagent.[39−41] The main advantage of the developed method relies on the fact that the generated imine can be further functionalized by direct treatment with a nucleophile in a "one-pot" manner. As we demonstrated,[39] this one-pot reduction/nucleophilic addition is an attractive way to synthesize monocyclic iminosugars, particularly in cases when other methods, for instance those based on nucleophilic addition to nitrones, cannot be applied. Encouraged by those results, we decided to apply the same approach in the current studies. Another benefit of such an approach would be the availability and stability of sugar-derived lactams. Since they are accessible from carbohydrate sources, either five- or six-membered lactams can be prepared. A typical preparation of sugar lactams is exemplified in Scheme 2.[39,42] *gluco*-Lactam **8** was chosen as a model starting material for our further studies.

Lactam **8** was treated with $Cp_2Zr(H)Cl$ (1.6 equiv) in THF to afford imine **9**, as presented in Scheme 3.[39] The progress of the reaction can be easily followed: the transition of the reaction mixture from an initially white suspension into a clear solution indicates the end of the reduction (ca. 30 min). The


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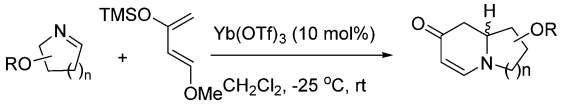
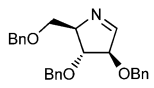
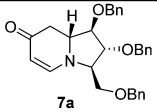
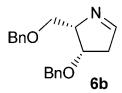
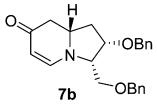
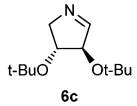
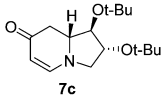
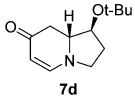
**Table 2. Synthesis of Indolizidines and Quinolizidines via Mannich/Michael Reaction of Cyclic Imines with DD[a]**



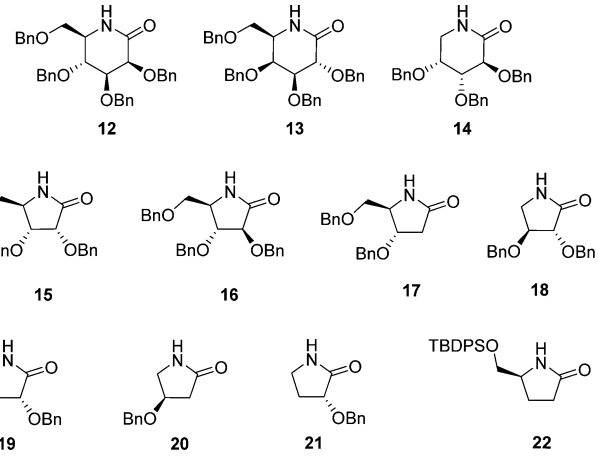

| Entry | Substrate | Product (major isomer) | Yield[b] [%] | d.r.[c] [%] |
|---|---|---|---|---|
| 1 |  **6a** |  **7a** | 68 | 95:5 |
| 2 |  **6b** |  **7b** | 55 | 86:14 |
| 3 |  **6c** |  **7c** | 69 | 86:14 |
| 4 |  **6d** |  **7d** | 64 | 92:8 |

[a]Reaction conditions: diene (2 equiv), Lewis acid (10 mol%), $CH_2Cl_2$ at −25 °C for 30 min then 3 h at room temperature. [b]Isolated yield. [c]Determined by $^1H$ NMR or HPLC of the crude reaction mixture.

resulting imine was directly subjected to the cyclocondensation reaction. Thus, the diene (2 equiv) and $Yb(OTf)_3$ (10 mol%) were added at −25 °C, and the reaction mixture was warmed to room temperature. The desired bicyclic enaminones **10** and **9a-*epi*-10** were obtained in 80% yield and with a high level of stereoselectivity (*d.e.* 94.6%) (Table 3, entry 1). The absolute configuration of the major product **10** was confirmed by X-ray analysis of its hydrogenated derivative **11** (Scheme 4).

Next, the influence of various Lewis acids on the yield and diastereoselectivity of the investigated process was evaluated. The replacement of $Yb(OTf)_3$ by scandium or lanthanum triflates resulted in a decrease of the overall yield and only had a slight influence on the reaction stereoselectivity (Table 3, entries 4 and 5 vs entry 1). The reduction of the catalyst loading resulted only in lowering of the reaction yield (Table 3, entries 2 and 3). $BF_3{\cdot}Et_2O$ displayed only moderate catalytic activity and provided the desired products **10** and **9a-*epi*-10** in 66% yield. The stereoselectivity remained very high. Among the various silyl triflates tested, TBSOTf provided the highest yield for the model reaction (Table 3, entry 8). The catalytic efficiency of TBSOTf was comparable with the results obtained for the $Yb(OTf)_3$-catalyzed process (Table 3, entry 8 vs entry 1). Thus, 10 mol% loading of the Lewis acid was optimal. To confirm that the addition step is catalyzed by an external Lewis acid and not the zirconium salts present in the reaction mixture, a blank experiment was performed. In the absence of a Lewis acid (e.g., $Yb(OTf)_3$) no formation of the desired product was observed (Table 3, entry 12).

With the optimal reaction conditions (10 mol% of $Yb(OTf)_3$ in THF) in hand, we set out to examine sugar-derived lactams **12**−**17** as well as simple enantiopure alkoxy-substituted lactams **18**−**22** to establish the reaction generality.

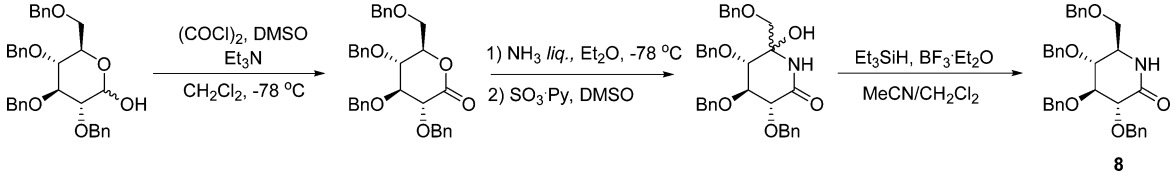



Sugar lactams **12**−**17** were prepared from commercially available carbohydrates following the general route presented in Scheme 2.[39,42,43] In the same manner, lactam **19** was prepared starting from D-erythronolactone. Its diastereomer, lactam **18**, was obtained from tartaric acid derived imide **23**,[44] via the reaction sequence depicted in Scheme 5. With L-malic acid as the starting material, regioisomeric lactams **20** and **21** were prepared (Scheme 6).[45] Finally, lactam **22** was prepared from ethyl L-pyroglutamate following a literature procedure.[45]

With various chiral cyclic lactones in hand, we subjected them to the one-pot reduction/Mannich/Michael tandem reaction. As shown in Table 4, all investigated examples of the one-pot reduction/aza-Mannich/Michael tandem reaction proceeded with good yields and good to high diastereoselectivity to provide bicyclic enaminones **10** and **32**−**41** as the major isomers. The absolute configuration at the newly formed bridgehead carbon atom was assigned on the basis of an analysis of coupling constants and NOE experiments.

Finally, we decided to ascertain if the size of the silyl group in the diene could influence the stereoselectivity of the process. As

**Scheme 2. General Route to Sugar-Derived Lactams 8 and 12−17[a]**




[a]Reagents and conditions: (a) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C; (b) (i) $NH_3$(l), $Et_2O$, −78 °C, (ii) $SO_3{\cdot}Py$, DMSO; (c) $Et_3SiH$, $BF_3{\cdot}Et_2O$, MeCN, $CH_2Cl_2$.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**Scheme 3**

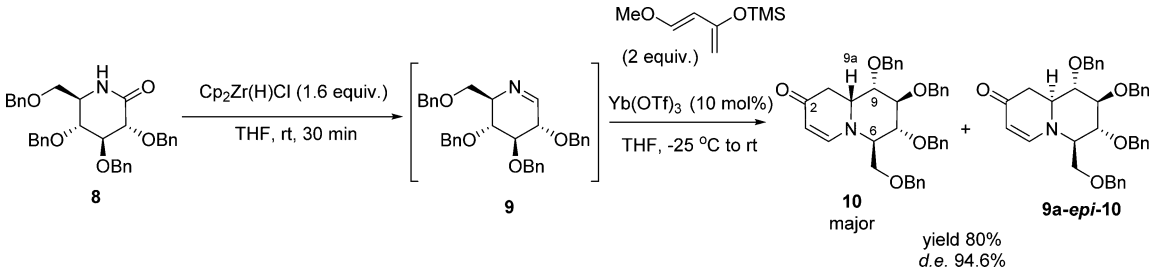
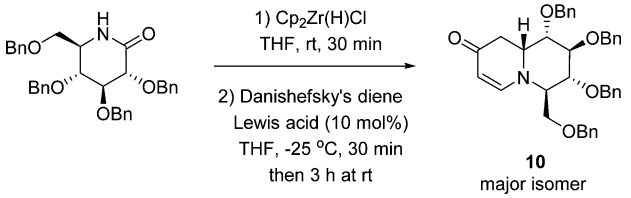



**Table 3. Lewis Acid Effect on the Formation of 10 via Lactam Reduction/Diene Addition Sequence**[a]




| entry | Lewis acid (amt (mol%)) | yield (%)[b] | d.e. (%)[c] |
|---|---|---|---|
| 1 | $Yb(OTf)_3$ (10) | 80 | 95.8 |
| 2 | $Yb(OTf)_3$ (5) | 51 | 94.4 |
| 3 | $Yb(OTf)_3$ (1) | 35 | 94.7 |
| 4 | $Sc(OTf)_3$ (10) | 55 | 96.4 |
| 5 | $La(OTf)_3$ (10) | 77 | 92.2 |
| 6 | $BF_3{\cdot}Et_2O$ (10) | 66 | 96.4 |
| 7 | TMSOTf (10) | 68 | 94.2 |
| 8 | TBSOTf (10) | 75 | 95.8 |
| 9 | TBSOTf (5) | 58 | 94.2 |
| 10 | TBSOTf (2) | 26 | 93.0 |
| 11 | TIPSOTf (10) | 53 | 96.0 |
| 12 | none | 0 | |

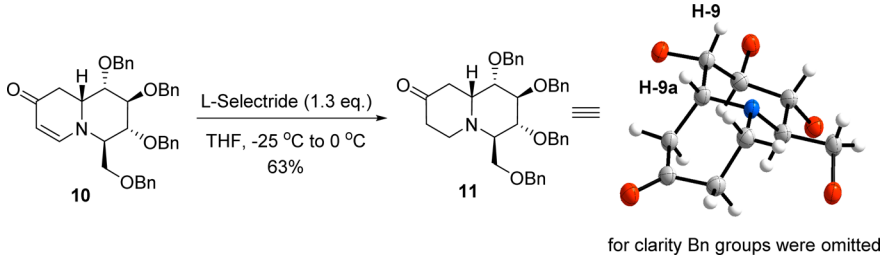
[a]Reaction conditions: (step 1) $Cp_2Zr(H)Cl$ (1.6 equiv) in THF at −25 °C for 30 min; (step 2) diene (2 equiv), Lewis acid (10 mol%) at −20 °C for 30 min and then 3 h at room temperature. [b]Isolated yield (overall after two steps). [c]Determined by HPLC of the crude reaction mixture.

shown in Table 5, replacement of Danishefsky's diene by its analogue with a TBS group let us increase the diastereoselectivity of the reaction with lactam **14** derived imine. In the case of lactam **18** the use of a diene with the bulkier silyl group resulted in a slight decrease of stereoselectivity and an increase in the overall reaction yield.

Although the method described above enables the efficient and highly stereoselective formation of polyhydroxylated indolizidinones and quinolizidinones, we encountered some problems during the isolation and purification of the desired products. Since the products, formed through the described sequential reduction/Mannich/Michael reaction, may differ only at a single bridgehead position, the separation of isomeric products was not a trivial task. In some cases the separation of products by classic column chromatography was not effective; even FCC and preparative HPLC did not give satisfying results (although the results of analytical HPLC analysis were promising). Crystallization techniques were also ineffective, since most of the obtained products were oils and all attempts to force them to crystallize failed. An alternative approach involving derivatization of the obtained products by a complete or partial exchange of O-Bn protecting groups for different groups, such as Bz, PMB, TBS, THP, etc., also did not give satisfying results in comparison to the effort expended. The increase of the selectivity of the process to minimize the formation of the minor isomer, e.g. by modifying the structure of the starting materials, could present an alternate solution to this problem. Unfortunately, the comparison of our data with those of closely related works by Shao and Yang[31] (for example, for the synthesis of **37**) indicates that the replacement of the benzyl protecting group with the bulkier *O*-TBS group gives only a slight increase in the selectivity of the process. In addition, as demonstrated in Tables 3 and 5, the use of a bulkier Lewis acid, such as TBSOTf, or a modified diene also provides only slight changes in the level of diastereoselectivity of the investigated process. So far, the isolation of products and increase of diastereoselectivity of the addition step are still an open question, and our current efforts are focused on developing a suitable solution.

**Stereochemical Proofs and Analysis of the Stereochemistry of the Investigated Reduction/Mannich/Michael Sequence.** The formation of bicyclic enaminones is a stepwise process involving a Mannich reaction followed by Michael addition. Therefore, its stereochemical outcome is governed by the course of the nucleophilic addition to the imine group. However, such analysis is not as straightforward as it seems at first glance and both steric and stereoelectronic effects must be taken into consideration to permit the correct prediction and rationalization of its stereochemical course. For this reason in our studies we employed the stereochemical

**Scheme 4**





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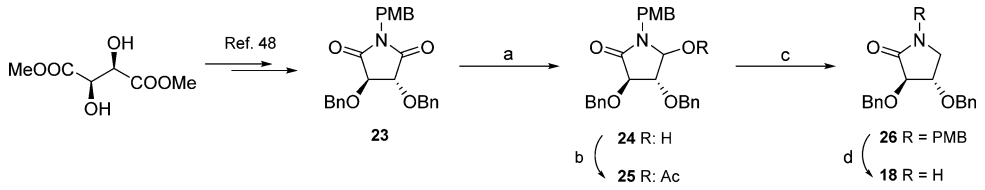
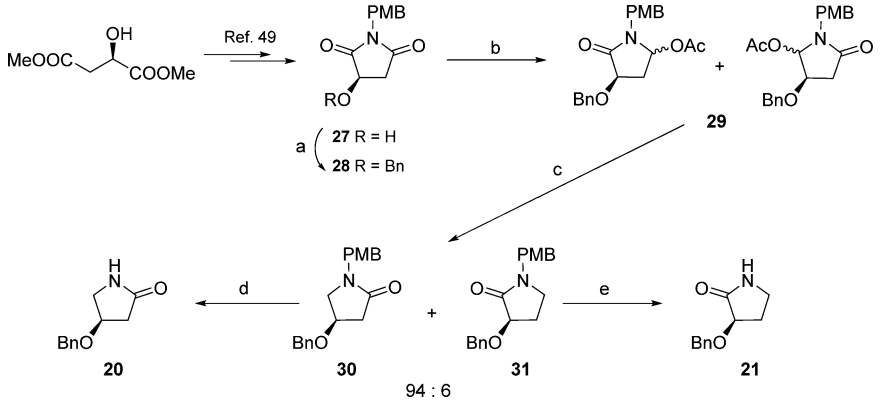
**Scheme 5. Synthesis of Lactam 18**[a]




[a]Reagents and conditions: (a) $NaBH_4$, $MeOH/CH_2Cl_2$, −78 °C to room temperature, 24 h, 89%; (b) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, 24 h, 69%; (c) $BF_3{\cdot}Et_2O$, $Et_3SiH$, $CH_2Cl_2$, −78 to 0 °C, 3 h, 95%; (d) CAN, $MeCN/H_2O$, 0 °C, 6 h, 73%.

**Scheme 6. Synthesis of Lactams 20 and 21**[a]




[a]Reagents and conditions: (a) BnBr, $Ag_2O$, $Et_2O$, room temperature, 24 h, 93%; (b) $LiEt_3BH$, $Ac_2O$, $CH_2Cl_2$, −78 °C to room temperature, 24 h, 91%; (c) $BF_3{\cdot}Et_2O$, $Et_3SiH$, $CH_2Cl_2$, −78 °C to room temperature, 24 h, 87% (**30**:**31** ratio 94:6); (d) CAN, $MeCN/H_2O$, 0 °C to room temperature, 24 h, 86%; (e) CAN, $MeCN/H_2O$, 0 °C to room temperature, 24 h, 76%.

models proposed by Woerpel and co-workers,[46] which describe the stereochemical course of *C*-allylation reactions of furanosyl and pyranosyl oxycarbenium ions. Due to several parallels between both types of reactions, we assumed that it can applied as a working model for our process.

Woerpel's rationalization is based on the conformational preferences of the intermediate oxocarbenium ions and argues that the orientation preferences of the ring substituents dictate the relative stabilities of the possible oxocarbenium ion conformers and govern the approach of allyl species to oxycarbenium ions.

*Stereochemistry of Reactions Involving Five-Membered Imines.* Woerpel's model assumes that, for furanosyl oxycarbenium ions (with an envelope conformation), alkoxy substituents at C-2 and C-3 preferentially take the equatorial and axial positions, respectively (Scheme 7).[46e] The C-4 alkyl substituent does not have a strong preference for either orientation but can play an important role in combination with the other ring substituents through mutual steric interactions. Nucleophiles would then approach the intermediate envelope oxocarbenium ions preferentially from the "inside" (the side of the envelope syn to the carbon atom which lies out of the envelope plane; Scheme 7) to avoid developing eclipsing interactions with the neighboring ring substituent.[46e]

According to the above assumptions, the addition of DD to the lactam **20** derived imine **42** should result in the formation of the 2,8a-cis isomer as the major product, as shown in Scheme 8. Indeed, NOE experiments confirmed the relative cis configuration of protons at the C-2 and C-8a positions for compound **39**. The same cis selectivity was also observed by Seebach[47] during the allylation of five-membered 3-silyloxyiminium ions.

For 4,5-disubstituted imines **6b** and **43** the observed outcome of addition also corresponded well with Woerpel's model, and compounds **7b** and **36** with a 2,8a-cis relative configuration were obtained as the major products (Scheme 9). This result also confirmed that the electronic nature of the substituent at C-4 exerts a powerful effect upon selectivity. At the same time, it confirmed a small influence of the $CH_2OBn$ substituent at the C-5 position; regardless of the configuration at the C-5 position the formation of the bridgehead stereocenter was influenced predominantly by the C-4 center of the imine.

As indicated in Table 4, the addition of DD to the 3,4-disubsituted imines *threo*-**44** and *erythro*-**45** (Schemes 9 and 10) provided compounds **37** and **38**, respectively, as the major products. In both cases the 1,8a-trans relative configuration was assigned.

As disclosed in Scheme 10, the course of the addition to imine **44** can be easily explained Woerpel's stereoelectronic model (via the $^4E$ conformer). The same course of addition of DD to imine **44** was observed by Yang and Shao.[31]

On the other hand, the formation of compound **38** as the major product is in opposition to the outcome of the allylation of the corresponding furanosyl oxycarbenium ion,[46e] which provides the cis isomer, and suggests that the addition to imine **45** is probably governed by steric effects. This effect may be associated with steric repulsion of the alkoxy substituent located at the C-3 position that should favor a syn approach of the nucleophile through the $E_4$ conformer (Scheme 11).

Another explanation is also possible. Woerpel's stereochemical model has been based on the results of addition of allyltrimethylsilane to various five- and six-membered oxycarbenium ions and does not take into consideration the


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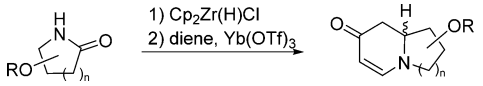
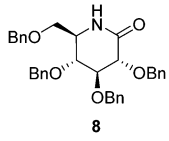
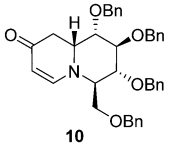
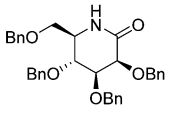
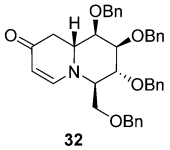
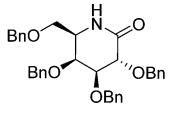
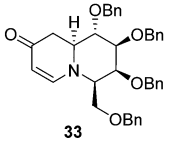
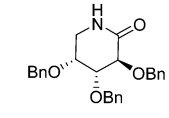
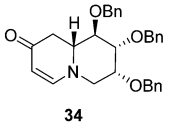
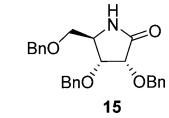
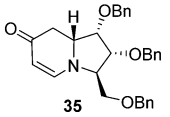
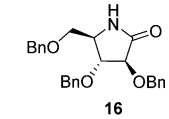
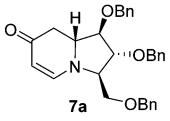
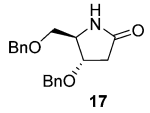
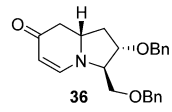
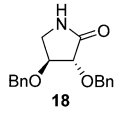
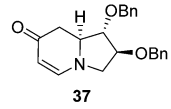
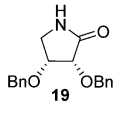
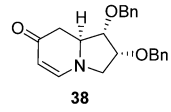
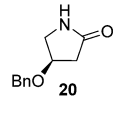
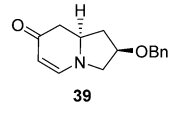
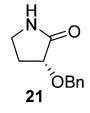
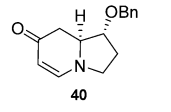
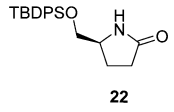
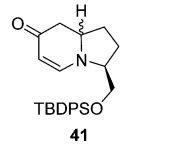
**Table 4. Synthesis of Indolizidines and Quinolizidines via One-Pot Reduction/Mannich/Michael Tandem Reaction Starting from Lactams 10 and 12−22**[a]




| Entry | Substrate | Product (major isomer) | Yield[b] [%] | d.r.[c] [%] |
|---|---|---|---|---|
| 1 |  **8** |  **10** | 80 | 98:2 |
| 2 |  **12** |  **32** | 73 | 94:6 |
| 3 |  **13** |  **33** | 81 | 90:10 |
| 4 |  **14** |  **34** | 67 | 88:12 |
| 5 |  **15** |  **35** | 62 | 96:4 |
| 6 |  **16** |  **7a** | 75 | 96:4 |
| 7 |  **17** |  **36** | 61 | 87:13 |
| 8 |  **18** |  **37** | 55 | 90:10 |
| 9 |  **19** |  **38** | 63 | 86:14 |
| 10 |  **20** |  **39** | 63 | 80:20 |
| 11 |  **21** |  **40** | 51 | 85:15 |
| 12 |  **22** |  **41** | 55 | 82:18[d] |

[a]Reaction conditions: (step 1) $Cp_2Zr(H)Cl$ (1.6 equiv) in THF for 30 min; (step 2) diene (2 equiv), Lewis acid (10 mol%) at −20 °C for 30 min and then 3 h at room temperature. [b]Isolated yield (overall after two steps). [c]Determined by $^1H$ NMR or/and HPLC of the crude reaction mixture. [d]Absolute configuration at the bridgehead position of the major product could not be unambiguously assigned.

influence of the nucleophile on the course of the addition. Surely, Danishefsky's diene is a sterically bulkier reagent than the linear allyltrimethylsilane and in certain cases may also govern the stereochemical outcome of the investigated reactions. This might be the reason for the formation of product **38**; stereoelectronically favored addition of the nucleophile to the $E_4$ conformer of **45** is plausibly affected by steric repulsion between the bulky diene and the alkoxy substituent at the C-3 position.

Addition to imine **46** (Scheme 12), obtained from lactam **21**, gave compound **40** as the major isomer (Table 4, entry 10). For both compounds, the assignment of relative configuration between H-1 and H-8a by NOE experiments was impossible; the observed enhancement of signals was small and did not enable unambiguous assignment of a configuration. However, an inspection of coupling constants of the protons at the C-8 position showed that one of them has an abnormally high value of $^3J$ to the bridgehead H-8a proton (16.3 Hz). On the basis of the Karplus equation, it was assumed that both hydrogen atoms have a plausibly antiperiplanar orientation (H-8a and H-$8_{anti}$). The same observation was made for all compounds with an indolizidine scaffold (**7a−d**, **17−22**). The presence of this effect proved useful for the structure determination of compounds **7a−d** and **17−22**. According to this, for the major product (**40**) a 1,8a-trans relation of protons was determined due to the presence of an NOE effect between H-$8_{anti}$ and H-1 protons. In the case of the minor product **8a-*epi*-40**, there was an interaction between H-1 and H-8a protons


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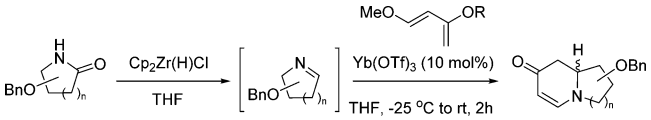
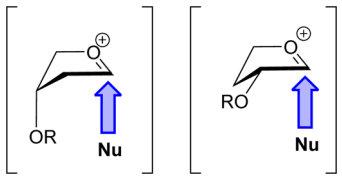
**Table 5. Effect of Diene Type on Stereoselectivity of Reduction/Mannich/Michael Tandem Reaction of Lactams 14 and 18**[a]




| entry | lactam | R (diene) | major product | yield (%)[b] | d.r. (%)[c] |
|---|---|---|---|---|---|
| 1 | **14** | TMS | **34** | 67 | 87:13 |
| 2 | **14** | TBS | **34** | 62 | 88:12 |
| 3 | **18** | TMS | **37** | 55 | 90:10 |
| 4 | **18** | TBS | **37** | 68 | 87:13 |

[a]Reaction conditions: (step 1) $Cp_2Zr(H)Cl$ (1.6 equiv) in THF for 30 min; (step 2) diene (2 equiv), Lewis acid (10 mol%) at −25 °C for 30 min and then 3 h at room temperature. [b]Isolated yield (overall after two steps). [c]Determined by HPLC of the crude reaction mixture.

**Scheme 7**




and no NOE effect between H1/H-$8_{anti}$; therefore, a 1,8a-cis relative configuration was assigned.

The formation of the 1,8a-trans product **40** is in opposition to Woerpel's model for allylation of furanosyl oxycarbenium ions,[46e] which assumes the formation of its epimer through syn addition to the $E_4$ conformer of imine **46** (Scheme 12). It seems that for 3-alkoxy-substituted imines, such as **46**, the addition is ruled again mainly by steric factors connected with steric repulsion of the bulky nucleophile and the substituent at C-3 position (Scheme 12).

Finally, for both 3,4,5-trisubstituted imines **6a** and **47**, an addition of DD provided compounds **7a** and **35**, respectively. In both cases the aforementioned compounds were formed with high stereoselectivity and, as assigned by NOE experiments, had a trans arrangement of protons at positions C-2 and C-8a (Schemes 13 and 14).

When addition to imine **6a** is considered through Woerpel's model, the low selectivity of the reaction should be expected, as is observed for allylation of arabinose-derived acetals.[46e,48] For the C-4 alkoxy group to occupy the preferred pseudoaxial orientation, all substituents must be also pseudoaxial ($E_4$ conformer of **6a**; Scheme 13). However, such an arrangement is disfavored due to unfavorable *syn*-butanol interactions.[49] As a result, the reaction course via the all equatorially substituted conformer $^4E$ should also be possible and, in consequence, lead to a poorly selective reaction. Such is not, however, the case for imine **6a**; the high stereoselectivity of the reaction, leading mainly to product **7a**, indicates that the process is stereoelectronically controlled not only by the imine (*"inside"* approach of the nucleophile via $E_4$ conformer) but also by a steric effect of the bulky nucleophilic reagent.

The addition to imine **47** proceeded syn to the C-3 alkoxy group to provide compound **35** with a 2,8a-cis arrangement of protons (Scheme 14), and such an outcome corresponds well with Woerpel's rationalization.[46e] This result is even more interesting if it is compared with the stereochemical outcome of the analogous reaction of imine **45** (Scheme 11). As already discussed, in the latter case the addition was mainly controlled by the sterics of the alkoxy group at C-3 of the imine, which resulted in the formation of 1,8a-trans-2,8a-trans product **38**. At this moment there is no reasonable explanation for this phenomenon. One can assume that observed differences may be result of the presence or absence of a $CH_2OBn$ substituent at the C-5 position. However, as proved experimentally, this substituent has a minor influence on the course of the addition process to either imines (see Scheme 9) or furanosyl oxycarbenium ions.[46e]

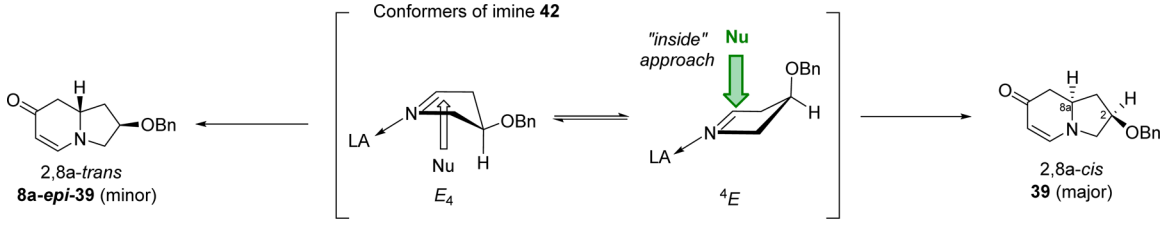
*Stereochemistry of Reactions Involving Six-Membered Imines.* As in the case of five-membered cyclic imines, Woerpel's model for addition to pyranosyl oxycarbenium ions[46b,c,f] was used as a working model for the rationalization of the stereochemical outcome of the Mannich/Michael reaction of six-membered imines.

Nucleophile additions to six-membered oxocarbenium ions occur through chairlike transition structures, not twistlike ones, through an axial trajectory (Scheme 15).[50] As indicated by Woerpel and co-workers,[46c,f,g] their stereochemical course is also governed by stereoelectronic effects. Thus, substrates bearing alkoxy groups at C-3, C-4, or C-5 give $\beta$ isomers as the major products. Again, the preference to adopt an axial orientation of substituents at C-4 and C-5 and equatorial position by groups at C-3 was crucial (for the numbering of positions see Scheme 16).

As shown in Tables 2−4, the reaction of the model *gluco*-lactam **8** with DD gave the bicyclic product **10** with a cis arrangement of H-9 and H-9a protons (Scheme 16). The assignment of absolute configuration at H-9a was not easy task since, as concluded from NMR data, the *gluco* ring in **10** has a half-boat conformation. The assignment was proven by X-ray analysis of a hydrogenated derivative of **10** (compound **11**, Scheme 4).

The formation of the 9,9a-cis product **10** plausibly results from an axial attack of the nucleophile at the all-equatorial $^4H_3$ conformer (Scheme 16). The $^3H_4$ conformer, which bears stereoelectronically more preferred axially oriented C-3 and C-4 groups, is strongly destabilized by 1,3-diaxial interactions. The observed stereochemical outcome corresponds well to our

**Scheme 8**





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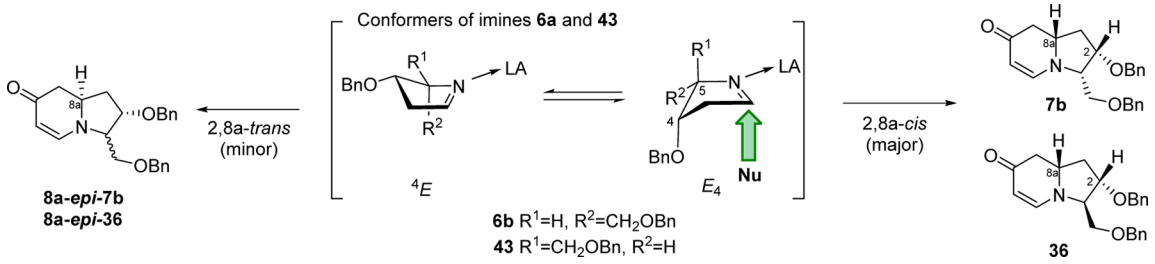
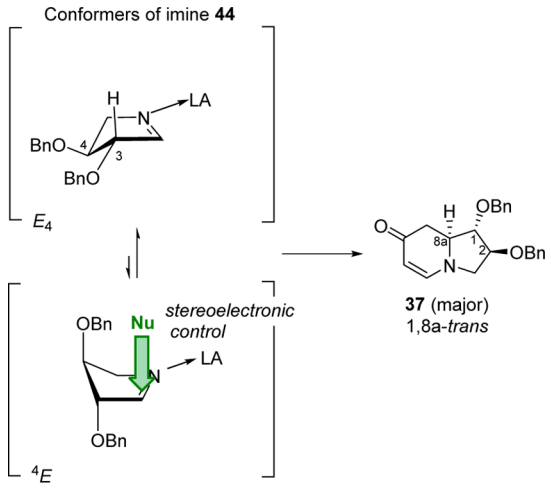
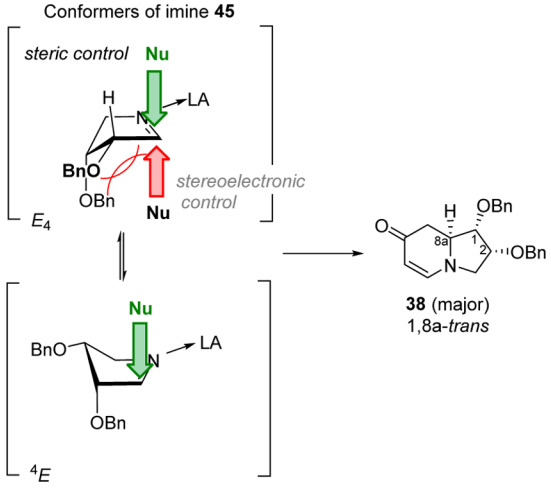
**Scheme 9**



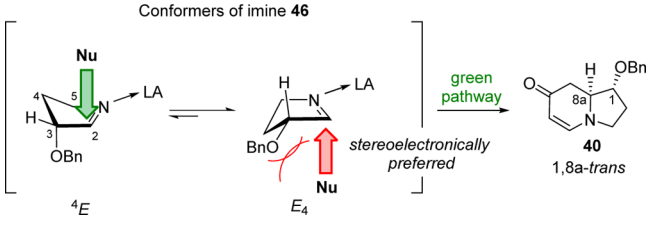

**Scheme 10**




**Scheme 11**




**Scheme 12**




previous studies of allylation of in situ generated sugar-derived imines (Scheme 17, eq 1)[39] as well as allylation of the *gluco*-oxycarbenium ion.[46b,c,f]

The stereochemistry of the addition of DD to *manno*-imine **48** (Table 4, entry 2) differed from the outcome observed during its allylation (Scheme 17, eq 2)[39] and led to compound **32**, with a 9,9a-trans relative configuration, as the major isomer.

Conformational analysis showed that the $^3H_4$ conformer of **48** is only slightly less favored than the $^4H_3$ form (by 0.3 kcal/mol), what probably arises from destabilizing 1,3-diaxial interactions between substituents at C-3 and C-5. The nucleophile's approach from the more stereoelectronically favored face of $^3H_4$ (from the top, Scheme 18) would result in the development of a *syn*-pentane[51] interaction between the nucleophile and the substituent at C-5 as well as a smaller *syn*-butanol[49] interaction with the substituent at C-3. Such destabilizing interactions, as well as the small energy difference between both conformers, plausibly result in an interconverting mixture of conformers, and the reaction proceeds through the lowest-energy transition state via conformer $^4H_3$, in accordance with the Curtin–Hammett principle, leading to compound **32** as the major product (Scheme 18). The different stereochemical preferences of the addition of Danishefsky's diene and allyltributylstannane indicate that the type of nucleophile and its size and reactivity may also influence the course of the reaction. For the more bulky diene, the addition is plausibly governed by steric factors. Thus, the approach through $^4H_3$ is preferred. In the case of the $^3H_4$ conformer of **48**, an axial approach of the nucleophile may be effected by steric repulsion between the alkoxy group at C-3 or/and C-4. In the case of the more linear allylstannane, such an interaction may be weaker and, as a result, the addition proceeds through the stereoelectronically more preferred conformer $^3H_4$.

Interestingly, in contrast to *gluco*-imine **9**, nucleophile addition to *galacto*-imine **49** followed by intramolecular Michael conjugate addition gave product **9c** as the major isomer, with a trans arrangement of H-9 and H-9a protons (Table 4, entry 3). Such an outcome also differs from the result of allylation of *galacto*-imine **49** (Scheme 17, eq 3)[39] as well as syntheses of analogous *C*-glycosides of galactose.[46f,52,53]

Computational studies showed a 1.5 kcal/mol energy difference between both conformers of imine **49** (Scheme 19). The addition of DD plausibly proceeds via the stereoelectronically more favored face of the $^3H_4$ conformer, which should result in the formation of the 9,9a-trans isomer as the predominant product.

In comparison to imines **9**, **48**, and **49**, the reaction of imine **50** with DD was slightly less selective (Table 4, entry 4). The major product was compound **34**, with a trans arrangement of H-9 and H-9a protons. Again, such a result was in opposition to the allylation of the same imine with allyltributylstannane (Scheme 17, eq 4).[39]

The calculated energy difference between the two conformers of imine **50** is low and indicates the presence of their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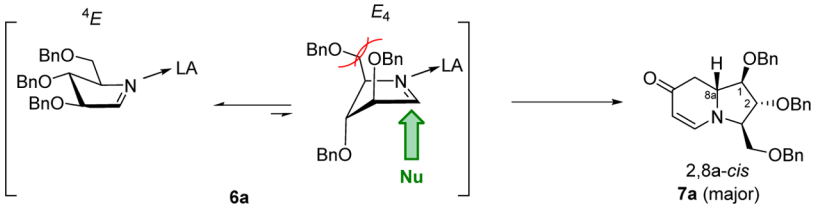
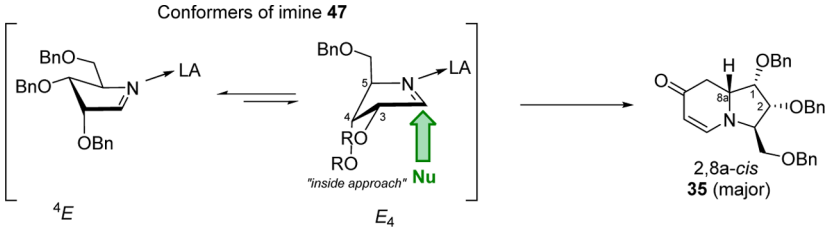
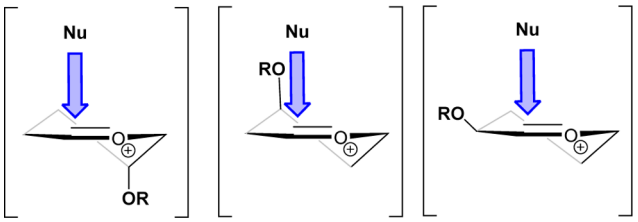
**Scheme 13**



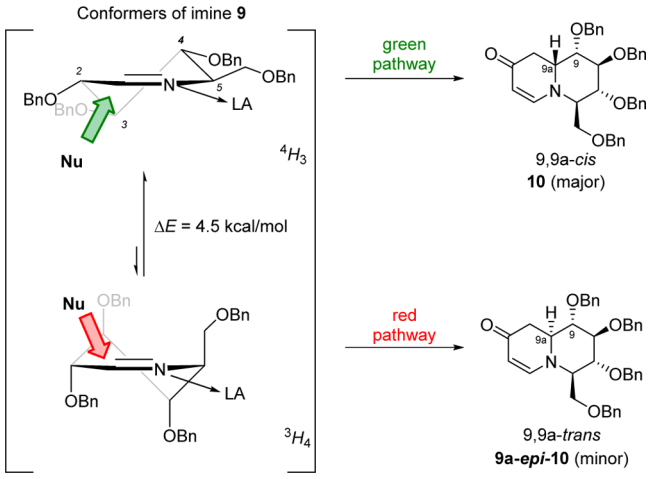

**Scheme 14**




**Scheme 15**




**Scheme 16**




interconverting mixture (Scheme 20). Woerpel's model assumes the axial approach of the nucleophile to the top face of $^3H_4$ conformer of **50** leading, as a result, to the formation of the 9,9a-cis isomer. Such an outcome was observed by us previously in the case of allylation of imine **50** (Scheme 17, eq 4).[39] However, the formation of compound **34** as the major isomer indicates that in the case of addition of DD to imine **50** the axial attack of the nucleophile through the $^4H_3$ conformer seems to be preferred. Although in this case the C-2 group occupies the disfavored axial position, such a location of the substituent minimizes any steric interaction which might occur during the axial approach of a rather bulky nucleophile (e.g., Danishefsky's diene). In case of the $^3H_4$ conformer of **50**, steric repulsion during the syn approach of the nucleophile may affect the energy of the transition state, making it less preferred. Such experimental results additionally support the statement that the course of the investigated addition reaction depends on the size of the nucleophile as well.

## CONCLUSION

In conclusion, an attractive method for the formation of indolizidine and quinolizidine scaffolds was developed. The presented strategy is based on a one-pot sugar-derived lactam reduction/Mannich/Michael tandem reaction. The availability of starting materials—sugar lactams—and the high stereoselectivity of the cyclocondensation step open a straightforward and general route to polyhydroxylated indolizidines and quinolizidines which not only provides complex 5,6- and 6,6-fused systems in a one-pot manner but also allows diverse iminosugars to be constructed in a common pathway. It is also worth emphasizing that the presence of an enaminone moiety in the resulting bicyclic products gives an opportunity for their further transformation/functionalization.

The use of sugar-derived lactams, as cyclic imine precursors, shows the crucial benefit of the disclosed synthetic method. These compounds are more easily and readily prepared, handled, and stored than the alternative precursors of cyclic imines such as nitrones, *N*-chloroamines, and azido aldehydes. As demonstrated, there is no need to isolate in situ generated imines, which can be directly used in subsequent reactions with Danishevsky's diene in the presence of a catalytic amount of a Lewis acid, such as $Yb(OTf)_3$ or TMSOTf.

As shown in the second part of the article, the stereochemical course of the investigated process, which is a stepwise aza-Mannich/Michael sequence, is determined by nucleophilic addition of DD to the in situ generated imines and is ruled not only by steric but also by stereoelectronic factors, as in the case of allylation of five- and six-membered oxycarbenium ions investigated in detail by the Woerpel group. As we pointed out, on the basis of a comparison of the current results with studies on the allylation of cyclic imines, the structure of the nucleophile is an additional factor which has an influence on the stereochemical outcome of the investigated process, giving new insights into the knowledge about addition to cyclic imines.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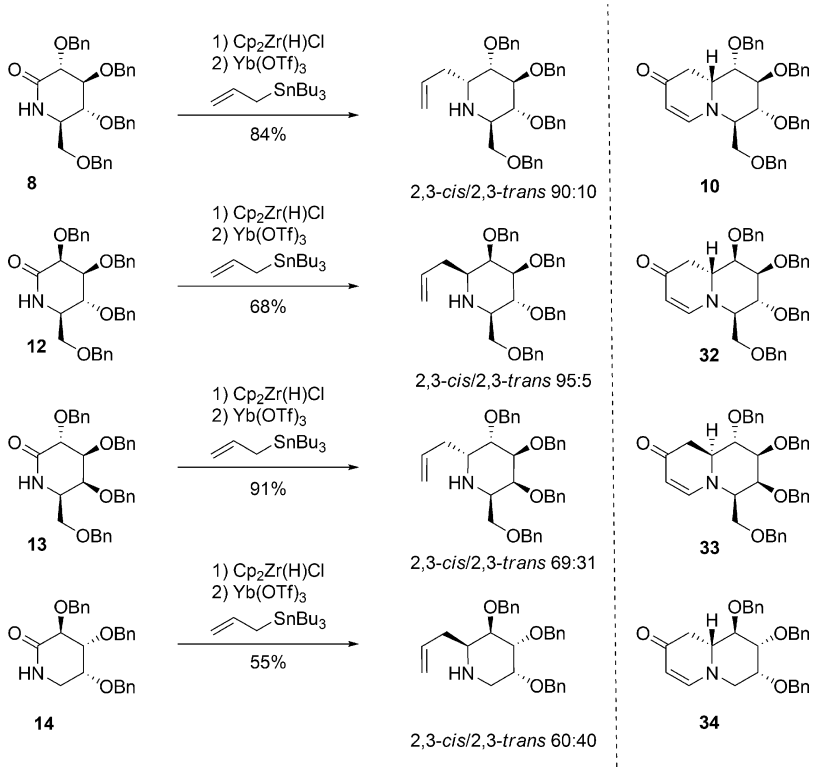
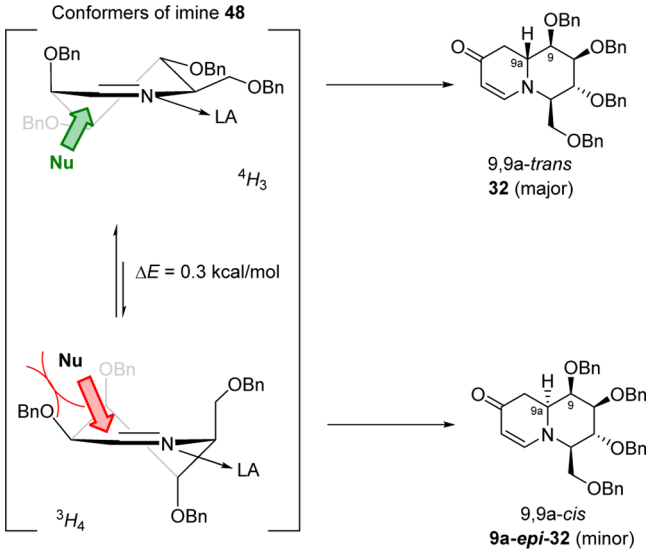
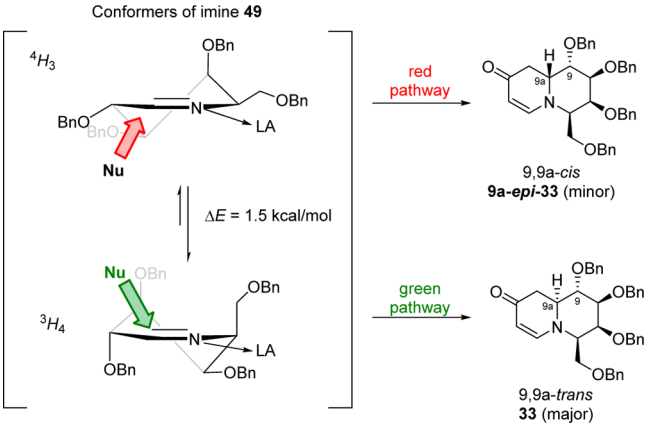
**Scheme 17**




**Scheme 18**




**Scheme 19**




## EXPERIMENTAL SECTION

**Synthesis of Nitrones 5a–d.** The known nitrones **5a**,[34] **5c**,[14b] and **5d**[14d] were prepared according to literature procedures. Compound **5b** was prepared following the synthetic procedure described by Maciejko et al.[36]

*(2S,3S)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole N-oxide (**5b**):* prepared according to literature procedure;[36] white waxy solid; $[\alpha]_D$ +22.4 (*c* 1.39, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.34–7.23 (m, 10H), 6.88 (d, *J* 1.3 Hz, 1H), 4.62–4.58 (m, 2H), 4.58–4.54 (m, 2H), 4.48 (td, *J* 6.9, 4.9 Hz, 1H), 4.14–4.08 (m, 2H), 4.05–4.01 (m, 1H), 2.82 (ddd, *J* 17.9, 6.9, 2.6 Hz, 1H), 2.77–2.70 (m, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 137.5, 137.4, 134.1, 128.5, 128.0, 127.9, 127.6, 127.5, 71.9, 71.8, 71.4, 70.4, 60.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{21}NO_3Na$ [M + $Na^+$] 334.1419, found 334.1423; IR (film) $\nu$ 3400, 3031, 2921, 2866, 1585, 1454, 1366, 1249, 1110, 738, 698 $cm^{-1}$.

**Deoxygenation of Nitrones: General Procedure.** To a stirred solution of nitrone (1.2 mmol) in THF (20 mL) under argon was added *n*-$Bu_3P$ (2.0 equiv, 600 $\mu$L, 2.4 mmol) in one portion. The reaction mixture was heated to 75 °C for 24–72 h. The progress of the reaction was followed by TLC. After removal of the solvent, the crude product was chromatographed on Florisil.

*(2R,3R,4R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole (**6a**):* colorless oil; isolated yield 400 mg (83%) starting from 500 mg (1.2 mmol) of nitrone **5a**; $[\alpha]_D$ −9.9 (*c* 0.8, $CH_2Cl_2$) (lit.[54] $[\alpha]_D$ −10.4 (*c* 0.8, $CHCl_3$)); $R_f$ = 0.35 (100% $Et_2O$); column chromatography (100% $Et_2O$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.60 (d, *J* 2.3 Hz, 1H), 7.37–7.25 (m, 15H), 4.62–4.52 (m, 7H), 4.16 (dt, *J* 7.8, 6.3 Hz, 1H), 4.11 (t, *J* 3.8 Hz, 1H), 3.76 (dd, *J* 9.8, 4.6 Hz, 1H), 3.54 (dd, *J* 9.8, 6.3 Hz, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 165.9, 138.1, 137.8, 137.5 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 90.6, 84.3, 73.3, 72.2, 71.9, 70.9; HRMS (ESI-TOF) *m*/*z*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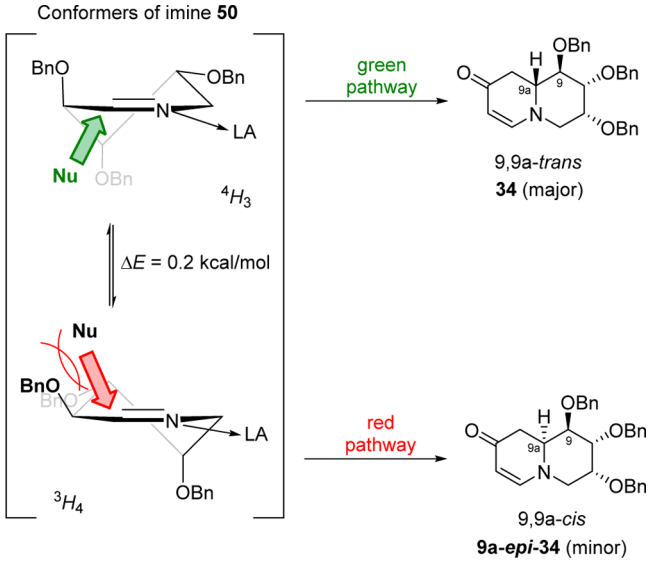
**Scheme 20**




calcd for $C_{26}H_{27}NO_3Na$ [M + $Na^+$] 424.1883, found 424.1894; IR (film) $\nu$ 2925, 2862, 1496, 1454, 1362, 1206, 1097, 1028, 736, 697 $cm^{-1}$.

*(2S,3S)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole (**6b**):* colorless oil; isolated yield 198 mg (67%) starting from 375 mg (1.2 mmol) of nitrone **5b**; $[\alpha]_D$ +14.7 (*c* 1.0, $CH_2Cl_2$); $R_f$ = 0.22 (5% MeOH in $CH_2Cl_2$); column chromatography (4/1 AcOEt/hexanes then 100% AcOEt); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (s, 1H), 7.41−7.24 (m, 11H), 4.66 (d, *J* 11.8 Hz, 1H), 4.60 (d, *J* 11.9 Hz, 1H), 4.54 (d, *J* 12.0 Hz, 1H), 4.47 (d, *J* 12.1 Hz, 1H), 4.25 (t, *J* 5.1 Hz, 1H), 4.07 (s, 1H), 4.00−3.90 (m, 2H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{21}NO_2Na$ [M + $Na^+$] 318.1456, found 318.1457; IR (film) $\nu$ 3029, 2913, 2861, 1496, 1453, 1362, 1099, 734, 696 $cm^{-1}$.

*(3R,4R)-3,4-Di-tert-butoxy-3,4-dihydro-2H-pyrrole (**6c**):* colorless oil; isolated yield 181 mg (85%) starting from 275 mg (1.2 mmol) of nitrone **5c**; $[\alpha]_D$ +68.9 (*c* 1.5, $CH_2Cl_2$); $R_f$ = 0.43 (100% AcOEt); column chromatography (7/3 AcOEt/hexanes); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.50−7.49 (m, 1H), 4.49 (d, *J* 4.0 Hz, 1H), 4.09−4.04 (m, 2H), 3.57−3.51 (m, 1H), 1.25 (s, 9H), 1.19 (s, 9H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 168.6, 84.2, 77.9, 74.5, 73.8, 66.7, 28.5, 28.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{24}NO_2$ [M + $H^+$] 214.18016, found 214.1799; IR (film) $\nu$ 2975, 1722, 1472, 1390, 1365, 1193, 1100, 888 $cm^{-1}$.

*(S)-4-tert-Butoxy-3,4-dihydro-2H-pyrrole (**6d**):* colorless oil; isolated yield 97 mg (69%) starting from 190 mg (1.2 mmol) of nitrone **5d**; $[\alpha]_D$ +20.1 (*c* 0.6, $CH_2Cl_2$); $R_f$ = 0.35 (100% acetone); column chromatography (1/1 AcOEt/hexanes then 100% AcOEt); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.49 (t, *J* 2.2 Hz, 1H), 4.65 (dd, *J* 8.1, 6.4 Hz, 1H), 4.06−4.00 (m, 1H), 3.75−3.68 (m, 1H), 2.24−2.13 (m, 1H), 1.69−1.54 (m, 2H), 1.25 (s, 6H), 1.20 (s, 3H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 168.2, 78.1, 74.1, 60.1, 31.5, 28.7, 28.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{16}NO$ [M + $H^+$] 142,1232, found 142,1248; IR (film) $\nu$ 2975, 1389, 1363, 1197, 1097, 1098, 888 $cm^{-1}$.

**Danishefsky's Diene.** To a solution of 4-methoxybut-3-en-2-one (9.5 mL, 94.0 mmol) in dry $Et_2O$ (400 mL) was added $Et_3N$ (32.9 mL, 236.0 mmol) under argon. The reaction mixture was cooled to 0 °C, and a solution of TMSOTf (19.6 mL, 108.0 mmol) in $Et_2O$ (20 mL) was added dropwise. After it was stirred overnight at 0 °C, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL, at 0 °C) followed by addition of pentane (100 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), water (2 × 100 mL), and brine (2 × 100 mL) and dried over $Na_2SO_4$. The solvent was removed, and the resulting brown oil was distilled under reduced pressure (70 °C, 15 mbar) to afford 14.4 g of the diene (89%) as a colorless liquid. The compound was stored under argon in a freezer: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.82 (d, *J* 12.4 Hz, 1H), 5.35 (d, *J* 12.4 Hz, 1H), 4.10 (s, 1H), 4.06 (s, 1H), 3.58 (s, 3H), 0.23 (s, 9H).

**TBS-Danishefsky's Diene.** To a solution of 4-methoxybut-3-en-2-one (505 $\mu$L, 5.0 mmol) in dry $Et_2O$ (20 mL) was added $Et_3N$ (1.75 mL, 12.6 mmol) under argon. The reaction mixture was cooled to 0 °C, and a solution of TBSOTf (1.3 mL, 5.74 mmol) in $Et_2O$ (1 mL) was added dropwise. After it was stirred overnight at 0 °C, the reaction mixture was quenched with addition of saturated aqueous $NaHCO_3$ (10 mL, at 0 °C) followed by addition of pentane (20 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (10 mL). The combine organic extracts were washed with aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (2 × 10 mL) and dried over $Na_2SO_4$. The solvent was removed, and the resulting brown oil was distillated under diminished pressure (71−72 °C, 3.8 Torr) to afford 808 mg of the diene (82%) as a colorless liquid. The reagent was stored under argon in the freezer: $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.11 (d, *J* 12.3 Hz, 1H), 5.58 (d, *J* 12.3 Hz, 1H), 4.30 (d, *J* 6.2 Hz, 2H), 3.81 (s, 3H), 1.19 (s, 9H), 0.42 (s, 6H).

**Mannich/Michael Reaction of Cyclic Imines with Danishefsky-Type Dienes: General Procedure.** To a solution of the imine (0.5 mmol) in dry $CH_2Cl_2$ (5 mL) was added $Yb(OTf)_3$ (10 mol%, 31 mg, 0.05 mmol) at −25 °C under argon. The mixture was stirred for 10 min at the same temperature, and then Danishefsky's diene (1.2 equiv, 117 $\mu$L, 0.6 mmol) was added dropwise. The mixture was warmed gradually to room temperature. After it was stirred for 2.5 h at room temperature (TLC monitoring), the reaction mixture was quenched with 1 M aqueous HCl (1 mL) and diluted with $CH_2Cl_2$ (3 mL). After phase separation, the organic layer was washed with water (3 mL) and brine (3 mL), dried over $Na_2SO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to give the corresponding bicyclic product(s).

*(1R,2R,3R,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**7a** and **8a-epi-7a**):* inseparable mixture of diasteromers; colorless oil; for yield and *d.r.* see Tables 2 and 4; column chromatography (7/3 AcOEt/hexanes); major isomer **7a** (pure sample obtained by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/1) $[\alpha]_D$ −191.7 (*c* 0.15, $CH_2Cl_2$); $R_f$ = 0.32 (7/3 AcOEt/hexanes); $^1H$ NMR (600 MHz, $C_6D_6$) $\delta$ 6.94−6.80 (m, 15H, 3 × Ph), 6.48 (d, *J* 7.3 Hz, 1H, C*H*=CHC=O), 4.82 (d, *J* 7.3 Hz, 1H, CH=C*H*C=O), 4.09 (d, *J* 11.9 Hz, 1H, PhCH*H*O), 4.04 (d, *J* 11.9 Hz, 1H, PhC*H*HO), 4.02 (d, *J* 11.7 Hz, 1H, PhCH*H*O), 3.97 (d, *J* 11.7 Hz, 1H, PhC*H*HO), 3.85 (m, 2H, PhC$H_2$O), 3.53 (ps t, *J* 4.3, 4.0, 1H, H-2), 3.43 (dd, *J* 6.9, 4.3 Hz, 1H, H-1), 3.38 (dt, *J* 16.1, 6.7, 5.1 Hz, 1H, H-8a), 3.17−3.13 (m, *J* 6.5, 4.8, 4.0 Hz, 1H, H-3), 2.82 (dd, *J* 10.0, 4.8 Hz, 1H, C*H*HOBn), 2.79 (dd, *J* 10.0, 6.5 Hz, 1H, CH*H*OBn), 2.24 (dd, *J* 15.9, 5.1 Hz, 1H, H-$8_{syn}$), 2.03 (ps t, *J* 16.1, 15.9 Hz, 1H, H-$8_{anti}$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 191.2, 149.8, 137.3, 137.2, 128.6, 128.5, 128.12, 128.07, 128.0, 127.8, 127.7, 98.1, 87.9, 84.2, 73.4, 72.6, 72.3, 69.3, 64.6, 61.4, 40.6; minor isomer **8a-*epi*-7a** selected signals $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 6.61 (d, *J* 7.3 Hz, 1H, C*H*=CHC=O), 4.88 (d, *J* 7.3 Hz, 1H, CH=C*H*C=O), 3.26 (m, 1H, H-8a), 2.95 (dd, *J* 7.4, 2.7 Hz, 1H, C*H*HOBn) 2.53 (t, *J* 16.3, 16.0 Hz, 1H, H-$8_{anti}$), 1.97 (dd, *J* 16.0, 4.6 Hz, 1H, H-$8_{syn}$); HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{31}NO_4Na$ [M + $Na^+$] 492.2145, found 492.2167; IR (film) $\nu$ 2864, 1638, 1577, 1454, 1115, 1096, 740, 698 $cm^{-1}$; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 0.5 mL/min, UV 313 nm, $R_t$ 23.1 min (**7a** major isomer), 35.8 min (**8a-*epi*-7a** minor isomer).

*(2S,3S,8aS)-2-(Benzyloxy)-3-(benzyloxymethyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**7b** and **8a-epi-7b**):* inseparable mixture of diasteromers; colorless oil; isolated yield 99 mg (55%, both isomers) starting from 150 mg (0.5 mmol) of imine **6b**; *d.r.* 86:14 (determined by $^1$HNMR of crude reaction mixture); column chromatography (100% AcOEt); major isomer **7b** (pure sample after preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/9) $[\alpha]_D$ −190.7 (*c* 2.87, $CH_2Cl_2$); $R_f$ = 0.22 (100% AcOEt); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.39−7.19 (m, 11H, 2 × Ph, C*H*=CHC=O), 4.99 (d, *J* 7.2 Hz, 1H, CH=C*H*C=O), 4.58−4.56 (m,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2H, OC$H_2$Ph), 4.53−4.49 (m, 2H, OC$H_2$Ph), 4.26−4.20 (m, 1H, H-8a), 3.86 (td, *J* 8.5, 7.1, 3.3 Hz, 1H, H-3), 3.77 (dd, *J* 10.0, 3.3 Hz, 1H, CH*H*OBn), 3.75−3.71 (m, 1H, H-2), 3.52 (dd, *J* 10.0, 8.5 Hz, 1H, C*H*HOBn), 2.41 (dt, *J* 12.3, 6.2 Hz, 1H, H-1), 2.38−2.34 (m, 2H, H-8′, H-8″), 1.85−1.75 (m, 1H, H-1′); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 192.3, 150.7, 137.7, 137.4, 128.53, 128.45, 128.0, 127.8, 127.7, 127.5, 98.5, 73.6, 72.3, 70.4, 60.8, 55.7, 42.1, 36.3; minor isomer **8a-*epi*-7b** selected signals $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.95 (d, *J* 7.3 Hz, 1H), 4.15−4.10 (m, 1H, H-3); minor isomer **8a-*epi*-7b** selected signals $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.5, 149.8, 137.6, 137.5, 97.6, 78.0, 73.6, 71.5, 69.7, 63.5, 55.9, 41.4, 36.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{25}NO_3Na$ [M + $Na^+$] 386.1745, found 386.1745; IR (film) $\nu$ 2922, 2866, 1634, 1571, 1453, 1335, 1096, 738, 698 $cm^{-1}$.

*(1R,2R,8aR)-1,2-Di-tert-butoxy-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**7c** and **8a-epi-7c**):* inseparable mixture of diasteromers; isolated yield 96 mg (69%, both isomers) sterting from 135 mg (0.5 mmol) of imine **6c**; *d.r.* 86:14 (determined by HPLC of crude reaction mixture); $R_f$ = 0.22 (100% AcOEt); column chromatography (4/1 AcOEt/hexanes); major isomer **7c** (pure sample prepared by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/1); colorless oil; $[\alpha]_D$ +280.6 (*c* 0.9, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.05 (d, *J* 7.1 Hz, 1H), 4.95 (d, *J* 7.1 Hz, 1H), 3.98 (dd, *J* 12.3, 5.9 Hz, 1H), 3.88−3.84 (m, 1H), 3.73−3.68 (m, 1H), 3.57 (dt, *J* 15.5, 6.3 Hz, 1H), 3.26 (dd, *J* 10.7, 5.8 Hz, 1H), 2.55−2.44 (m, 2H), 1.20 and 1.18 (2 × s, 18H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.9, 150.4, 97.7, 75.5, 74.6, 74.2, 61.0, 54.9, 39.5, 29.0, 28.4; minor isomer **8a-*epi*-7c** selected signals: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.15 (d, *J* 7.0 Hz, 1H); HRMS (EI) *m*/*z* calcd for $C_{16}H_{27}O_3N$ [$M^+$] 281.1990, found 281.1985; IR (film) $\nu$ 2975, 1637, 1579, 1364, 1191, 1092 $cm^{-1}$; HPLC Chiralpak OD-H, 20% *i*-PrOH in hexanes, flow 1.0 mL/min, UV 335 nm, $R_t$ 4.9 min (minor isomer **8a-*epi*-7c**), 8.1 min (major isomer **7c**).

*(1S,8aR)-1-tert-Butoxy-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**7d** and **8a-epi-7d**):* mixture of diasteroisomers; isolated yield 67 mg (64%, both isomers) starting from 70 mg (0.5 mmol) of imine **6d**; *d.r.* 92:8 (determined by HPLC of crude reaction mixture); column chromatography (100% AcOEt); major isomer **7d**; colorless oil; $[\alpha]_D$ −25.6 (c 0.9, $CH_2Cl_2$); (Lit.[55] $[\alpha]_D$ −28.3 (c 0.5, $CH_2Cl_2$)); $R_f$ = 0.20 (100% AcOEt); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.08 (t, *J* 9.4 Hz, 1H), 4.94 (d, *J* 7.1 Hz, 1H), 3.98 (dd, *J* 15.2, 7.8 Hz, 1H), 3.60 (td, *J* 10.2, 3.6 Hz, 1H), 3.57−3.52 (m, 1H), 3.47 (dd, *J* 18.3, 9.2 Hz, 1H), 2.56 (dd, *J* 15.9, 5.0 Hz, 1H), 2.33 (t, *J* 16.2 Hz, 1H), 2.27 (dtd, *J* 12.4, 7.4, 3.5 Hz, 1H), 1.90 (ddd, *J* 17.7, 12.7, 9.2 Hz, 1H), 1.20 (s, 9H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.8, 150.3, 97.6, 76.4, 74.0, 62.1, 47.3, 39.5, 33.3, 28.4; minor isomer **8a-*epi*-7d** selected signals $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.19 (d, *J* 7.2 Hz, 1H), 4.92 (d, *J* 7.0 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{19}NO_2Na$ [M + $Na^+$] 232.1308, found 232.1305; IR (film) $\nu$ 2974, 1634, 1578, 1097 $cm^{-1}$; HPLC Chiralpak OD-H, 20% *i*-PrOH in hexanes, flow 1.0 mL/min, UV 329 nm, $R_t$ 9.3 min (major isomer **7d**), 15.5 min (minor isomer **8a-*epi*-7d**).

*(3R,4R)-3,4-Bis(benzyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**23**):* prepared according to the literature procedure.[44]

*(3R,4R,5S)-3,4-Bis(benzyloxy)-5-hydroxy-1-(4-methoxybenzyl)-pyrrolidin-2-one (**24** and **5-epi-24**).* To a solution of **23** (1.764 g, 4.09 mmol) in dry MeOH (14 mL) and $CH_2Cl_2$ (25 mL) was added $NaBH_4$ (1.2 equiv, 186 mg, 4.91 mmol) in small portions at −78 °C. The reaction mixture was warmed quickly to room temperature and stirred for 12 h. When the reaction was complete (TLC 2/5 AcOEt/hexanes; $R_f$ = 0.45), it was quenched by slow addition of $H_2O$ (10 mL) at 0 °C. After phase separation, the aqueous phase was washed with $CH_2Cl_2$ (3 × 10 mL). The combined organic solutions were washed with $H_2O$ (10 mL) and dried over $Na_2SO_4$. The crude mixture of products was used directly in the next step: inseparable mixture of diasteroisomers; colorless oil; isolated yield 89% (both isomers); *d.r.* 86:14 (determined by $^1$H NMR of crude reaction mixture); major isomer **24** $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.40−7.24 (m, 8H), 7.20 (dd, *J* 7.2, 4.8 Hz, 4H), 6.84−6.81 (m, 2H), 4.98 (d, *J* 11.7 Hz, 1H), 4.84 (d, *J* 14.6 Hz, 1H), 4.76 (d, *J* 11.6 Hz, 2H), 4.55 (d, *J* 11.7 Hz, 1H), 4.49 (d, *J* 11.7 Hz, 1H), 4.11 (d, *J* 14.6 Hz, 1H), 4.08 (d, *J* 4.6 Hz, 1H), 3.90 (dd, *J* 4.5, 2.9 Hz, 1H), 3.76 (s, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 169.9, 159.2, 137.2, 137.1, 129.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.7, 114.1, 84.7, 83.9, 79.6, 72.9, 72.1, 55.3, 42.4; **5-*epi*-24** selected signals $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 5.05 (d, *J* 11.7 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{27}NO_5Na$ [M + $Na^+$] 456.1787, found 456.1789; IR (film) $\nu$ 3348, 2925, 1683, 1513, 1454, 1247, 1105, 738, 697 $cm^{-1}$.

*(2S,3R,4R)-3,4-Bis(benzyloxy)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl acetate (**25** and **2-epi-25**).* To a solution of **24**/**5-*epi*-24** (1.57g, 3.62 mmol) in dry $CH_2Cl_2$ (35 mL) were added $Et_3N$ (9.0 equiv, 3.24 mL, 21.73 mmol) and $Ac_2O$ (6.0 equiv, 2.0 mL, 21.73 mmol). The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was followed by TLC (1/3 AcOEt/hexanes, $R_f$ = 0.35). Afterward, the solvent was removed under diminished pressure and the residue was chromatographed on silica gel (1/5 AcOEt/hexanes) to afford 1.19 g of the product (69% diastereoisomeric mixture, *d.r.* 89.2:10.8 based on $^1$H NMR spectra of crude mixture) as a colorless oil: major isomer **25** $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.40−7.34 (m, 5H), 7.32−7.27 (m, 4H), 7.21−7.17 (m, 2H), 7.17−7.14 (m, 2H), 6.84−6.81 (m, 2H), 4.97 (d, *J* 11.9 Hz, 1H), 4.77 (d, *J* 11.9 Hz, 1H), 4.62 (d, *J* 12.9 Hz, 1H), 4.54 (d, *J* 7.3 Hz, 1H), 4.48−4.46 (m, 1H), 4.20 (d, *J* 14.9 Hz, 1H), 4.07 (d, *J* 2.8 Hz, 1H), 3.91 (dd, *J* 2.8, 1.5 Hz, 1H), 3.77 (s, 3H), 1.90 (s, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 171.2, 170.1, 159.2, 137.2, 136.9, 129.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 114.0, 84.7, 81.6, 79.4, 72.7, 71.9, 55.2, 43.9, 20.8; minor isomer **2-*epi*-25** selected signals $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.94 (d, *J* 11.8 Hz, 1H), 4.82 (d, *J* 11.7 Hz, 1H), 4.66 (d, *J* 14.7 Hz, 1H), 3.93 (dd, *J* 2.7, 1.4 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{28}H_{29}NO_6Na$ [M + $Na^+$] 498.1893, found 498.1894; IR (film) $\nu$ 3032, 2934, 1716, 1514, 1248, 1226, 1177, 1108, 1019, 738, 698 $cm^{-1}$.

*(3R,4R)-5-Acetoxy-3,4-bis(benzyloxy)-N-(4-methoxybenzyl)-pyrrolidin-2-one (**26**).* To a **25**/**2-*epi*-25** mixture (709 mg 1.49 mmol) in dry $CH_2Cl_2$ (20 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (2.0 equiv, 374 $\mu$L, 2.98 mmol). The mixture was stirred for 30 min, and then $Et_3SiH$ (5.0 equiv, 1.2 mL, 7.45 mmol) was added. The mixture was warmed to room temperature and quenched by saturated aqueous $Na_2CO_3$ (5 mL). After phase separation, the aqueous phase was washed with $CH_2Cl_2$ (10 mL). The combined organic phases were dried over $Na_2SO_4$. The crude product (590 mg, 95%, colorless oil) was used directly in the next step. A pure sample was obtained by filtration through a short pad of silica gel ($CH_2Cl_2$): $[\alpha]_D$ +73.8 (*c* 6.1, $CHCl_3$); (lit.[56] $[\alpha]_D$ +77.5 (*c* 7.0, $CHCl_3$)); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.44−7.41 (m, 2H), 7.37−7.22 (m, 7H), 7.16−7.13 (m, 2H), 6.85−6.83 (m, 2H), 5.12 (d, *J* 11.6 Hz, 1H), 4.84 (d, *J* 11.6 Hz, 1H), 4.53 (d, *J* 11.6 Hz, 1H), 4.47 (d, *J* 11.6 Hz, 1H), 4.38 (s, 2H), 4.23 (d, *J* 5.7 Hz, 1H), 4.14 (dt, *J* 7.5, 5.8 Hz, 1H), 3.78 (s, 3H), 3.40 (dd, *J* 10.0, 7.6 Hz, 1H), 3.06 (dd, *J* 10.1, 5.8 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 170.6, 159.2, 137.7, 137.4, 129.6, 128.4, 128.4, 128.3, 127.9, 127.9, 127.7, 127.6, 114.1, 80.8, 77.5, 72.5, 71.8, 55.3, 48.5, 45.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{27}NO_4Na$ [M + $Na^+$] 440.1838, found 440.1838; IR (film) $\nu$ 2869, 1701, 1513, 1248, 1109, 1029, 738, 698 $cm^{-1}$.

*(3R,4S)-3,4-Bis(benzyloxy)pyrrolidin-2-one (**18**).* To a solution of **26** (408 mg, 0.89 mmol) in dry acetonitrile (9 mL) at 0 °C was added a solution of cerium ammonium nitrate (5.0 equiv, 2.44 g, 4.46 mmol) in $H_2O$ (1 mL). After it was stirred for 6 h at 0 °C (TLC 1/2 AcOEt/hexanes), the reaction mixture was warmed to room temperature, and the organic layer was separated. The aqueous phase was washed with AcOEt (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and dried over $Na_2SO_4$. The crude product was purified by column chromatography on silica gel (1/2 AcOEt/hexanes) to give 177 mg of **18** (73%) as a yellow waxy solid: $R_f$ = 0.15; $[\alpha]_D$ +81.7 (*c* 1.23, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.42−7.39 (m, 2H), 7.36−7.32 (m, 3H), 7.31−7.27 (m, 5H), 6.39 (s, 1H), 5.07 (t, *J* 9.7 Hz, 1H), 4.80 (d, *J* 11.7 Hz, 1H), 4.59 (d, *J* 11.7 Hz, 1H), 4.52 (d, *J* 11.7 Hz, 1H), 4.27 (dd, *J* 13.8, 6.3 Hz, 1H), 4.17 (d, *J* 6.3 Hz, 1H), 3.57−3.52 (m, 2H), 3.17 (dd, *J* 9.8, 6.3 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 173.9, 137.5, 137.4, 128.5, 128.4, 128.2, 127.90, 127.86, 127.80, 79.8, 79.6, 72.5, 71.9, 44.5;

HRMS (ESI-TOF) $m/z$ calcd for $C_{18}H_{19}NO_3Na$ [M + $Na^+$] 320.1263, found 320.1266; IR (film) $\nu$ 3245, 2874, 1714, 1111, 737, 697 $cm^{-1}$.

*(3R,4R)-3,4-Bis(benzyloxy)pyrrolidin-2-one (**19**).* prepared according to the literature procedure;[39] white waxy solid, $[\alpha]_D$ +57.6 ($c$ 0.61, $CHCl_3$); $R_f$ = 0.47 (100% AcOEt); column chromatography (1/1 then 4/1 AcOEt/hexanes); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.42−7.26 (m, 10H), 6.57 (s, 1H), 5.05 (d, $J$ 11.7 Hz, 1H), 4.80 (d, $J$ 11.7 Hz, 1H), 4.58 (d, $J$ 11.7 Hz, 1H), 4.52 (d, $J$ 11.7 Hz, 1H), 4.26 (dd, $J$ 13.7, 6.4 Hz, 1H), 4.17 (d, $J$ 6.4 Hz, 1H), 3.54 (ddd, $J$ 9.3, 7.6, 1.4 Hz, 1H), 3.15 (dd, $J$ 9.8, 6.4 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 173.9, 137.6, 137.4, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 79.9, 79.6, 72.5, 71.9, 44.5; HRMS (ESI-TOF) $m/z$ calcd for $C_{18}H_{19}NO_3Na$ [M + $Na^+$] 320.1263, found 320.1263; IR (film) $\nu$ 3243, 2873, 1712, 1110, 738, 697 $cm^{-1}$.

*(R)-3-Hydroxy-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**27**).* prepared according to the literature procedure;[57] $[\alpha]_D$ −66.0 ($c$ 0.84, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.29 (m, 2H), 6.95−6.70 (m, 2H), 4.69−4.52 (m, 3H), 3.78 (s, 3H), 3.29 (s, 1H), 3.04 (dd, $J$ 18.2, 8.4 Hz, 1H), 2.66 (dd, $J$ 18.2, 4.8 Hz, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 177.9, 173.7, 159.4, 130.4, 127.5, 114.0, 67.0, 55.3, 42.0, 37.1; HRMS (ESI-TOF) $m/z$ calcd for $C_{18}H_{19}NO_3Na$ [M + $Na^+$] 320.1263, found 320.1263; IR (film) $\nu$ 3435, 2943, 1698, 1514, 1248, 1107 $cm^{-1}$.

*(R)-3-(Benzyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**28**).* To a solution of **27** (2.74 g, 11.65 mmol) in dry $Et_2O$ (100 mL) were added BnBr (3.0 equiv, 4.15 mL, 34.89 mmol) and $Ag_2O$ (3.6 equiv, 9.80 g, 42.29 mmol). After it was stirred overnight in the dark, the mixture was filtered through a pad of Celite. The collected solid was washed with AcOEt (50 mL), and the solvent was evaporated. The residue was chromatographed on silica gel (1/4 than 1/3 AcOEt/hexanes) to give 3.524 g of product **28** as a colorless oil: isolated yield 93%; $[\alpha]_D$ −73.3 ($c$ 0.81, $CHCl_3$); $R_f$ = 0.57 (4/6 AcOEt/hexanes); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.37−7.29 (m, 7H), 6.84−6.79 (m, 2H), 4.97 (d, $J$ 11.7 Hz, 1H), 4.77 (d, $J$ 11.7 Hz, 1H), 4.63−4.54 (m, 2H), 4.33 (dd, $J$ 8.2, 4.2 Hz, 1H), 3.77 (s, 3H), 2.91 (dd, $J$ 18.2, 8.2 Hz, 1H), 2.63 (dd, $J$ 18.2, 4.2 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 175.6, 173.8, 159.3, 136.7, 130.4, 128.6, 128.23, 128.18, 127.7, 114,0, 73.0, 72.1, 55.2, 41.7, 36.3; HRMS (ESI-TOF) $m/z$ calcd for $C_{19}H_{19}NO_4Na$ [M + $Na^+$] 348.1212, found 348.1210; IR (film) $\nu$ 2937, 1709, 1514, 1249, 699 $cm^{-1}$.

*(3R)-3-(Benzyloxy)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl Acetate (**29**).* To a solution of **28** (3.12 g, 9.59 mmol) in dry $CH_2Cl_2$ (41 mL) was added a 1 M solution of $LiEt_3BH$ in THF (11.3 mL, 95 mmol) dropwise at −78 °C. After the mixture was stirred for 15 min at −78 °C, $Ac_2O$ (1.26 mL, 13.3 mmol) was added dropwise. Then the reaction mixture was warmed to ambient temperature and stirred overnight. The reaction progress was monitored by TLC (2/3 AcOEt/hexanes). At the end of the reaction activated carbon was added and the mixture was stirred for 15 min and then filtered through a pad of Celite. The collected solid was washed with AcOEt (30 mL), and the solvent was evaporated. The residue was chromatographed on silica gel (3/7 AcOEt/hexanes) to give 3.224 g of acetate **29** as a colorless oil: isolated yield 91%; $R_f$ = 0.34; $[\alpha]_D$ −50.6 ($c$ 0.90, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.34−7.29 (m, 2H), 7.29−7.23 (m, 3H), 7.19−7.14 (m, 2H), 6.86−6.80 (m, 2H), 6.23 (d, $J$ 5.0 Hz, 1H), 4.67 (d, $J$ 14.6 Hz, 1H), 4.52 (d, $J$ 11.7 Hz, 1H), 4.44 (d, $J$ 11.7 Hz, 1H), 4.13−4.05 (m, 2H), 3.78 (s, 3H), 2.61 (d, $J$ 8.6 Hz, 2H), 1.97 (s, 3H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 172.3, 170.7, 159.2, 137.1, 129.8, 128.5, 128.1, 128.0, 127.6, 114.1, 81.5, 72.17, 72.16, 55.3, 44.0, 35.0, 20.8; HRMS (ESI-TOF) $m/z$ calcd for $C_{21}H_{23}NO_5Na$ [M + $Na^+$] 392.1474, found 392.1472; IR (film) $\nu$ 2934, 1742, 1715, 1514, 1248, 1230, 1179, 1029, 966 $cm^{-1}$.

*(R)-4-(Benzyloxy)-1-(4-methoxybenzyl)pyrrolidin-2-one (**30**) and (R)-3-(Benzyloxy)-1-(4-methoxybenzyl)pyrrolidin-2-one (**31**).* To a solution of **29** (3.26 g, 8.83 mmol) in dry $CH_2Cl_2$ (117 mL) was added $BF_3{\cdot}Et_2O$ (2.0 equiv, 2.2 mL, 17.5 mmol) dropwise at −78 °C. After the mixture was stirred for 30 min, $Et_3SiH$ (5 equiv, 7.0 mL, 31.3 mmol) was added dropwise. After this mixture was stirred for an additional 30 min, the cooling bath was removed and the reaction mixture was left overnight at room temperature. The reaction progress was monitored by TLC (2/3 AcOEt/hexanes). The reaction was quenched with saturated aqueous $Na_2CO_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (50 mL). The combined organic extracts were dried over $Na_2SO_4$. After removal of solvent the residue was chromatographed on silica gel (2/3 AcOEt/hexanes) to give 2.248 g of **30** (yield 82%) and 143 mg of **31** (yield 5%) Compound **30**: $R_f$ = 0.1 (2/3 AcOEt/hexanes); $[\alpha]_D$ +8.4 ($c$ 0.36, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.35−7.30 (m, 2H), 7.29−7.21 (m, 3H), 7.18−7.12 (m, 2H), 6.87−6.81 (m, 2H), 4.48 (d, $J$ 11.7 Hz, 1H), 4.42 (d, $J$ 11.7 Hz, 1H), 4.40 (s, 2H), 4.18 (m, 1H), 3.78 (s, 3H), 3.43 (dd, $J$ 10.8, 6.2 Hz, 1H), 3.28 (dd, $J$ 10.8, 2.9 Hz, 1H), 2.67 (dd, $J$ 17.3, 7.0 Hz, 1H), 2.57 (dd, $J$ 17.3, 3.4 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 172.2, 159.1, 137.4, 129.4, 128.5, 128.2, 127.9, 127.6, 114.1, 70.9, 70.8, 55.3, 52.6, 45.6, 38.2; HRMS (ESI-TOF) $m/z$ calcd for $C_{19}H_{21}NO_3Na$ [M + $Na^+$] 334.1419, found 334.1422; IR (film) $\nu$ 2932, 1687, 1513, 1247, 1031 $cm^{-1}$. Compound **31**: $R_f$ = 0.31 (2/3 AcOEt/hexanes); $[\alpha]_D$ −73.1 ($c$ 1.02, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.42−7.37 (m, 2H), 7.36−7.31 (m, 2H), 7.29−7.24 (m, 1H), 7.18−7.13 (m, 2H), 6.87−6.81 (m, 2H), 5.00 (d, $J$ 11.9 Hz, 1H), 4.77 (d, $J$ 11.9 Hz, 1H), 4.40 (d, $J$ 14.5 Hz, 1H), 4.37 (d, $J$ 14.5 Hz, 1H), 4.13 (dd, $J$ 7.7, 6.9 Hz, 1H), 3.77 (s, 3H), 3.24 (ddd, $J$ 9.7, 8.8, 3.9 Hz, 1H), 3.11−3.01 (m, 1H), 2.27−2.17 (m, 1H), 1.98−1.90 (m, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 172.4, 159.1, 137.9, 129.5, 128.4, 128.1, 128.0, 127.7, 114.1, 75.9, 72.0, 55.3, 46.1, 43.1, 26.4; HRMS (ESI-TOF) $m/z$ calcd for $C_{19}H_{21}NO_3Na$ [M + $Na^+$] 334.1419, found 334.1414; IR (film) $\nu$ 2935, 1693, 1513, 1247, 1030 $cm^{-1}$.

*(R)-4-(Benzyloxy)pyrrolidin-2-one (**20**).* To a solution of **30** (2.248 g, 7.22 mmol) in MeCN (70 mL) was added a mixture of CAN (5 equiv, 19.8 g, 36.1 mmol) and water (8.4 mL) portionwise at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The progress of the reaction was monitored by TLC (100% AcOEt). The reaction mixture was diluted with $H_2O$ (20 mL) and extracted with AcOEt (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and dried over $Na_2SO_4$, and the solvent was removed under diminished pressure. The crude product was purified by column chromatography (1/1 AcOEt/hexanes, 100% AcOEt, and then 5/95 MeOH/$CH_2Cl_2$) to give 1.187 g of product **20**: yield 86%; $[\alpha]_D$ +2.4 ($c$ 0.88, $CHCl_3$); $R_f$ = 0.4 (100% AcOEt); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.35−7.26 (m, 5H), 6.86 (s, 1H), 4.48 (q, $J$ 11.7 Hz, 2H), 4.27 (dq, $J$ 9.5, 3.2 Hz, 1H), 3.56 (dd, $J$ 10.6, 6.2 Hz, 1H), 3.40 (dd, $J$ 10.6, 2.6 Hz, 1H), 2.55 (dd, $J$ 17.3, 6.9 Hz, 1H), 2.43 (dd, $J$ 17.3, 3.6 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 176.6, 137.5, 128.5, 127.9, 127.7, 73.8, 71.0, 48.8, 37.3; HRMS (ESI-TOF) $m/z$ calcd for $C_{11}H_{13}NO_2Na$ [M + $Na^+$] 214.0844, found 214.0842; IR (film) $\nu$ 3236, 2916, 1693, 1667, 1354, 1095, 728 $cm^{-1}$.

*(R)-3-(Benzyloxy)pyrrolidin-2-one (**21**):* prepared following the procedure for the synthesis of **20**: isolated yield 76%; $[\alpha]_D$ −125.2 ($c$ 0.29, $CHCl_3$); $R_f$ = 0.19 (100% AcOEt); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.41−7.24 (m, 5H), 6.64 (s, 1H), 4.94 (d, $J$ 11.9 Hz, 1H), 4.74 (d, $J$ 11.9 Hz, 1H), 4.10−4.03 (m, 1H), 3.43 (td, $J$ 9.0, 3.8 Hz, 1H), 3.27 (dt, $J$ 9.7, 7.2 Hz, 1H), 2.36 (dtd, $J$ 13.0, 7.6, 3.8 Hz, 1H), 2.11 (ddt, $J$ 13.5, 8.4, 7.0 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 176.3, 137.8, 128.4, 128.0, 127.8, 74.8, 72.1, 39.0, 28.8; HRMS (ESI-TOF) $m/z$ calcd for $C_{11}H_{13}NO_2Na$ [M + $Na^+$] 214.0844, found 214.0843; IR (film) $\nu$ 3244, 2894, 1708, 1454, 1297, 1125, 741, 699 $cm^{-1}$.

*(4S,5R)-4-Benzyloxy-5-benzyloxymethylpyrrolidin-2-one (**17**):* prepared according to the literature procedure.[39,58]

**(*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (**22**):** prepared according to the literature procedure.[59−62]

**Dicyclopentadienylzirconium Hydrochloride (Schwartz's Reagent).**[63] A solution of $Cp_2ZrCl_2$ (10.0 g, 34.2 mmol) in dry THF (65 mL) was stirred under argon in a Schlenk tube (covered with aluminum foil) until all solids dissolved. Then a 2 M solution of $LiAlH_4$ in THF (4.6 mL, 9.23 mmol) was added dropwise. The mixture was stirred for 90 min at room temperature. The white precipitate was filtered off under argon and, under argon, washed with dry THF (4 × 20 mL), dry $CH_2Cl_2$ (2 × 20 mL), and dry $Et_2O$ (4 × 20 mL), sequentially. The resulting white solid was dried under


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vacuum and stored under argon in a flask covered with aluminum foil at −10 °C.

**One-Pot Lactam Reduction/Mannich/Michael Reaction: General Procedure.** To a solution of $Cp_2Zr(H)Cl$ (Schwartz's reagent; 1.6 equiv, 206 mg, 0.8 mmol) in THF (5 mL) was added a solution of the sugar lactam (0.5 mmol) in THF (5 mL). The initially formed white suspension disappeared during the reaction progress; formation of a clear solution indicated the end of the reaction (ca. 1.5 h, TLC monitoring). Then the solution was cooled to −25 °C and $Yb(OTf)_3$ was added (10 mol%, 31 mg, 0.05 mmol). After 10 min neat diene (2.0 equiv 194 μL, 1.0 mmol) was added dropwise. The mixture was warmed gradually to room temperature and stirred for 2.5 h (TLC monitoring). The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and diluted with $Et_2O$ (5 mL). The organic layer was separated, and the aqueous layer was washed with $Et_2O$ (3 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was removed. The residue was purified by chromatography on silica gel to give the corresponding enaminone.

*(6R,7R,8R,9S,9aR)-7,8,9-Tris(benzyloxy)-6-(benzyloxymethyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (**10** and **9a-epi-10**):* for yield and de see Table 3; column chromatography (50% AcOEt in hexanes); major isomer **10** (pure sample obtained by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 2/1); colorless oil; $[\alpha]_D$ −49.3 (*c* 0.3, $CH_2Cl_2$); $R_f$ = 0.24 (50% AcOEt in hexanes); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.36−7.21 (m, 18H), 7.11−7.05 (m, *J* 6.6, 2.8 Hz, 2H), 7.01 (d, *J* 7.7 Hz, 1H, C*H*═CHCO), 4.98 (d, *J* 7.7 Hz, 1H, CH═CHCO), 4.60 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.58−4.51 (m, 2H, OC*H*$_2$Ph), 4.45 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.41−4.38 (m, 2H, OC*H*$_2$Ph), 4.31 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.26 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 3.80 (ddd, *J* 13.4, 6.2, 2.5 Hz, 1H, H-9a), 3.78−3.74 (m, *J* 8.0, 5.3, 1.6 Hz, 1H, H-6), 3.73−3.70 (m, *J* 3.0, 2.8 Hz, 1H, H-8), 3.70−3.67 (dd, *J* 10.0, 8.0 Hz, 1H, CH*H*OBn), 3.65−3.62 (m, *J* 3.0, 2.1 Hz, 1H, H-7), 3.52 (dd, *J* 10.0, 5.3 Hz, 1H, C*H*HOBn), 3.34−3.30 (m, *J* 2.8, 2.5 Hz, 1H, H-9), 3.02 (dd, *J* 16.4, 13.5 Hz, 1H, H-1′), 2.19 (dd, *J* 16.4, 6.2 Hz, 1H, H-1″); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 192.6, 155.3, 137.6, 137.5, 137.2, 137.1, 128.6, 128.5, 128.4, 128.1, 128.1, 123.0, 127.9, 127.8, 127.7, 98.7, 75.0, 73.3, 72.9, 72.7, 72.2, 72.0, 71.9, 67.5, 63.0, 51.3, 37.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{38}H_{39}NO_5Na$ [M + Na$^+$] 612.2721, found 612.2700; IR (film) ν 3433, 2923, 2863, 1637, 1586, 1454, 1092, 738, 698 cm$^{-1}$; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 0.5 mL/min, UV 315 nm, $R_t$ 19.8 min (**10** major isomer), 24.5 min (**9a-*epi*-10** minor isomer).

*(6R,7R,8R,9R,9aR)-7,8,9-Tris(benzyloxy)-6-(benzyloxymethyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (**32** and **9a-epi-32**):* mixture of diasteroisomers; isolated yield 107 mg (73%, both isomers) starting from 135 mg (0.25 mmol) of lactam **12**; *d.r.* 94:6 (determined by HPLC of crude reaction mixture); $R_f$ = 0.34 (3/2 AcOEt/hexanes); column chromatography (1/1 AcOEt/hexane); major isomer **32** (pure sample obtained by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 2/1): colorless oil; $[\alpha]_D$ −67.6 (*c* 1.3, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.36−7.22 (m, 16H), 7.19−7.14 (m, 4H), 6.93 (d, *J* 7.7 Hz, 1H, C*H*═CHCO), 4.98 (d, *J* 7.7 Hz, 1H, CH═C*H*CO), 4.57 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.48−4.37 (m, 6H, 3 × OC*H*$_2$Ph) 4.35 (d, *J* 12.2 Hz, 1H, OC*H*HPh), 3.91−3.87 (m, *J* 10.2, 8.2, 6.7 Hz, 1H, H-9a), 3.83−3.75 (m, 3H, H-6, H-8, H-9), 3.66 (d, *J* 3.7 Hz, 1H, H-7), 3.60−3.55 (m, 2H, C*H*$_2$OBn), 2.77 (dd, *J* 16.7, 6.7 Hz, 1H, H-1′), 2.60 (dd, *J* 16.7, 8.2 Hz, 1H, H-1″); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 155.4, 137.7, 137.5, 137.4, 128.6, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127.5, 98.7, 74.5, 74.3, 73.29, 73.25, 73.1, 72.5, 71.7, 67.9, 64.8, 51.5, 37.2; minor isomer **9a-*epi*-32** selected signals $^1$H NMR (600 MHz, $CDCl_3$) δ 6.85 (d, *J* 7.9 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{38}H_{39}NO_5Na$ [M + Na$^+$] 612.2721, found 612.2734; IR (film) ν 2924, 2866, 1640, 1588, 1453, 1100, 737, 698 cm$^{-1}$; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 0.5 mL/min, UV 313 nm, $R_t$ 14.4 min (**9a-*epi*-32** minor isomer), 15.8 min (**32** major isomer).

*(6R,7S,8R,9S,9aS)-7,8,9-Tris(benzyloxy)-6-(benzyloxymethyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (**33** and **9a-epi-33**):* inseparable mixture of diasteroisomers; colorless oil; isolated yield 120 mg (81%, both isomers) starting from 135 mg (0.25 mmol) of lactam **13**; *d.r.* 90:10 (determined by $^1$H NMR of crude reaction mixture); $R_f$ = 0.26 (50% AcOEt in hexanes); column chromatography (50% AcOEt in hexanes); major isomer **33** $^1$H NMR (600 MHz, $CDCl_3$) δ 7.40−7.23 (m, 18H), 7.26−7.21 (m, 2H), 6.89 (d, *J* 7.8 Hz, 1H, C*H*═CHCO), 5.02 (d, *J* 7.7 Hz, 1H, CH═C*H*CO), 4.91 (d, *J* 10.5 Hz, 1H, OCH*H*Ph), 4.76 (d, *J* 12.3 Hz, 1H, OCH*H*Ph), 4.66 (d, *J* 12.3 Hz, 1H, OCH*H*Ph), 4.62 (d, *J* 10.5 Hz, 1H, OCH*H*Ph), 4.60−4.58 (m, 2H, OC*H*$_2$Ph), 4.44 (s, 2H, OC*H*$_2$Ph), 3.97 (t, *J* 9.3 Hz, 1H, H-9), 3.89 (t, *J* 2.8 Hz, 1H, H-7), 3.68 (dt, *J* 6.2, 5.8, 2.8 Hz, 1H, H-6), 3.63 (dd, *J* 8.8, 2.7 Hz, 1H, H-8), 3.53−3.46 (m, 2H, C*H*HOBn, H-9a), 3.38 (dd, *J* 9.9, 5.8 Hz, 1H, CH*H*OBn), 2.82 (dd, *J* 16.5, 6.2 Hz, 1H, H-1′), 2.62 (dd, *J* 16.5, 9.9 Hz, 1H, H-1″); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 191.2, 155.2, 137.9, 137.8, 137.2, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.87, 127.8, 127.7, 99.3, 79.7, 77.6, 75.8, 73.6, 73.4, 72.4, 72.3, 67.5, 64.1, 56.2, 38.4; minor isomer **9a-*epi*-33** selected signals $^1$H NMR (600 MHz, $CDCl_3$) δ 7.13 (d, *J* 7.7 Hz, 1H), 5.00 (d, *J* 7.8 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{38}H_{39}NO_5Na$ [M + Na$^+$] 612.2721, found 612.2739; IR (film) ν 3443, 2923, 2867, 1638, 1587, 1453, 1095, 738, 698 cm$^{-1}$.

*(7R,8R,9R,9aR)-7,8,9-Tris(benzyloxy)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (**34** and **9a-epi-34**):* mixture of diasteroisomers; yield 78 mg (67%) starting from 100 mg (0.25 mmol) of lactam **14**; *d.r.* 88:12; $R_f$ = 0.36 (100% AcOEt); column chromatography (100% AcOEt); major isomer **34** (pure sample obtained by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/9): colorless oil; $[\alpha]_D$ −162.7 (*c* 0.16, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.36−7.26 (m, 15H), 6.80 (d, *J* 7.6 Hz, 1H, C*H*═CHCO), 5.05 (d, *J* 7.6 Hz, 1H, CH═C*H*CO), 4.96 (d, *J* 10.5 Hz, 1H, OCH*H*Ph), 4.77 (d, *J* 12.4 Hz, 1H OCH*H*Ph), 4.68−4.62 (m, 4H, 2 × OC*H*$_2$Ph), 3.97 (ps t, *J* 9.9, 9.3 Hz, 1H, H-9), 3.86−3.83 (m, 1H, H-7), 3.49 (dd, *J* 9.3, 2.9 Hz, 1H, H-8), 3.40 (dd, *J* 13.9, 2.8 Hz, 1H, H-6′), 3.28 (dt, *J* 9.9, 7.2, 6.8 Hz, 1H, H-9a), 3.03 (d, *J* 13.9 Hz, 1H, H-6″), 2.83 (dd, *J* 16.8, 6.8 Hz, 1H, H-1′), 2.70 (dd, *J* 16.8, 7.2 Hz, 1H, H-1″); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 155.1, 137.9, 137.8, 137.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.65, 127.64, 99.1, 83.3, 76.2, 75.9, 72.6, 72.2, 72.1, 60.0, 54.7, 36.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{31}NO_4Na$ [M + Na$^+$] 492.2145, found 492.2122; IR (film) ν 2900, 1623, 1574, 1455, 1383, 1200, 1173, 1125, 1105, 739, 718, 697 cm−1; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 0.5 mL/min, UV 304 nm, $R_t$ 18.4 min (**9a-*epi*-34** minor isomer), 22.9 min (**34** major isomer).

*(1S,2R,3R,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**35**):* isolated yield 72 mg (62%, both isomers) starting from 100 mg (0.25 mmol) of lactam **15**; *d.r.* 96:4 (determined by HPLC of crude reaction mixture); column chromatography (100% AcOEt); pure sample of **35** obtained by preparative TLC (Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/9); colorless oil; $[\alpha]_D$ −181.4 (*c* 1.1, $CH_2Cl_2$); $R_f$ = 0.28 (100% AcOEt); $^1$H NMR (600 MHz, 5% $CDCl_3$ in PhMe-$d_7$) δ 7.19−6.95 (m, 15H, 3 × Ph), 6.76 (d, *J* 7.3 Hz, 1H, C*H*═CHCO), 4.98 (d, *J* 7.3 Hz, 1H, CH═C*H*CO), 4.48 (d, *J* 11.7 Hz, 1H, OC*H*HPh), 4.34 (d, *J* 11.7 Hz, 1H, OCH*H*Ph), 4.30 (d, *J* 11.9 Hz, 1H, OC*H*HPh), 4.10−4.06 (m, 3H, 3× OCH*H*Ph), 3.59−3.55 (m, 2H, H-2, H-3), 3.40−3.36 (m, 1H, H-1), 3.33 (dt, *J* 16.4, 3.9 Hz, 1H, H-8a), 3.24 (dd, *J* 10.5, 1.6 Hz, 1H, CH*H*OBn), 3.15 (dd, *J* 10.5, 3.5 Hz, 1H, C*H*HOBn), 2.86 (t, *J* 16.4, 15.7 Hz, 1H, H-8$_{anti}$), 2.06 (dd, *J* 15.7, 4.7 Hz, 1H, H-8$_{syn}$); $^{13}$C NMR (151 MHz, toluene-$d_7$) δ 189.8, 146.2, 137.1, 128.6, 128.5, 128.3, 128.2, 127.7, 127.5, 127.4, 124.9, 124.7, 124.6, 97.6, 79.6, 75.2, 67.2, 60.7, 60.0, 36.1, 20.4, 20.3, 20.1, 20.0, 19.9, 19.8, 19.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{31}NO_4Na$ [M + Na$^+$] 492.2145, found 492.2126; IR (film) ν 2920, 2864, 1574, 1454, 1260, 1172, 1030, 738, 698, 638 cm$^{-1}$; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 0.5 mL/min, UV 329 nm, $R_t$ 22.3 min (**35** major isomer), 28.4 min (**8a-*epi*-35** minor isomer).

*(1S,2S,8aS)-1,2-Bis(benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**37** and **8a-epi-37**):* inseparable mixture of diasteroisomers; colorless oil; yield 48 mg (55%) starting from 75 mg (0.25 mmol) of lactam **18**; *d.r.* 90:10; $R_f$ = 0.22 (100% AcOEt); column chromatography (100% AcOEt); major isomer **37** $^1$H NMR


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(600 MHz, $CDCl_3$) $\delta$ 7.40−7.22 (m, 10H), 7.03 (d, *J* 7.2 Hz, 1H, C*H*=CHCO), 4.96 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 4.64−4.55 (m, 6H, OC$H_2$Ph), 4.14 (dt, *J* 5.9, 4.0 Hz, 1H, H-2), 3.95 (dd, *J* 5.8, 4.1 Hz, 1H, H-1), 3.81−3.75 (m, 1H, H-8a), 3.68 (dd, *J* 11.3, 6.1 Hz, 1H, H-3′), 3.45 (dd, *J* 11.3, 3.9 Hz, 1H, H-3″), 2.53−2.50 (m, 2H, H-8, H-8″); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.4, 150.1, 137.3, 137.2, 128.59, 128.57, 128.11, 128.09, 127.74, 127.72, 98.3, 87.0, 82.0, 72.4, 72.1, 61.7, 53.4, 40.0; minor isomer **8a-*epi*-37** $^1$H NMR (600 MHz, $CDCl_3$, selected signals) $\delta$ 4.06 (m, 1H, H-8a), 2.88 (ps t, *J* 16.7, 16.2, Hz, H-8$_{anti}$), 2.22 (dd, *J* 16.2, 4.8 Hz, 1H, H-8$_{syn}$); HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{24}NO_3$ [M + H$^+$] 350.1756, found 350.1716; IR (film) $\nu$ 3031, 2923, 2868, 1634, 1580, 1454, 1359, 1353, 1250, 1096, 738, 698 cm$^{-1}$; HPLC LiChrosphere Si60, 40% *i*-PrOH in hexanes, flow 1.0 mL/min, UV 329 nm, $R_t$ 9.8 min (**8a-*epi*-37** minor isomer); 12.1 min (**37** major isomer).

*(1S,2R,8aS)-1,2-Bis(benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**38** and **8a-epi-38**):* inseparable mixture of diastereoisomers; colorless oil; isolated yield 55 mg (63%, both isomers) starting from 75 mg (0.25 mmol) of lactam **19**; *d.r.* 86:14 (determined by HPLC of crude reaction mixture); $R_f$ = 0.27 (100% AcOEt); column chromatography (100% AcOEt); major isomer **38** $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.17−7.09 (m, 7H), 7.09−7.03 (m, 3H), 6.19 (d, *J* 7.3 Hz, 1H, C*H*=CHCO), 5.08 (d, *J* 7.3 Hz, 1H, CH=C*H*CO), 4.26−4.23 (m, 2H, OC$H_2$Ph), 4.16 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.11 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 3.62 (dt, *J* 6.3, 4.5 Hz, 1H, H-2), 3.58 (dd, *J* 6.4, 4.5 Hz, 1H, H-1), 3.43−3.37 (ps dt, *J* 16.2, 6.4, 4.8 Hz, 1H, H-8a), 2.78 (dd, *J* 11.0, 6.3 Hz, 1H, H-3′), 2.70 (dd, *J* 11.0, 4.4 Hz, 1H, H-3″), 2.50 (dd, *J* 15.6, 4.8 Hz, 1H, H-8′), 2.28 (ps t, *J* 16.2, 15.6 Hz, 1H, H-8″); $^{13}$C NMR (151 MHz, $C_6D_6$) $\delta$ 189.4, 148.5, 137.91, 137.90, 128.32, 128.25, 127.7, 127.5, 127.4, 98.7, 87.0, 81.8, 71.8, 71.4, 61.2, 52.4, 40.5; minor isomer **8a-*epi*-38** selected signals $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 6.38 (d, *J* 7.2 Hz, 1H, C*H*=CHCO), 5.12 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 3.73 (dt, *J* 16.9, 4.7, 3.2 Hz, H-8a), 3.46 (d, *J* 3.2 Hz, H-1), 3.07 (dd, *J* 11.6, 4.8 Hz, H-3′), 2.87 (ps t, *J* 16.9, 15.6 Hz, H-8′), 2.23 (dd, *J* 15.6, 4.7 Hz, H-8″); $^{13}$C NMR (151 MHz, $C_6D_6$) $\delta$ 190.3, 148.1, 97.7, 80.6, 79.4, 71.9, 70.8, 59.2, 52.7, 35.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{24}NO_3$ [M + H$^+$] 350.1756, found 350.1750; IR (film) $\nu$ 3030, 2868, 1634, 1578, 1455, 1356, 1335, 1250, 1095, 739, 698 cm$^{-1}$; HPLC Chiralpak AD-H, 40% *i*-PrOH in hexanes, flow 1.0 mL/min, UV 340 nm, $R_t$ 10.2 min (**8a-*epi*-38** minor isomer), 12.8 min (**38** major isomer).

*(2R,8aR)-2-(Benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**39** and **8a-epi-39**):* inseparable mixture of diasteroisomers; colorless oil; isolated yield 79 mg (63%, both isomers) starting from 100 mg (0.52 mmol) of lactam **20**; *d.r.* 80:20 (determined by $^1$H NMR of crude reaction mixture); $R_f$ = 0.33 (3/2 acetone/hexanes); column chromatography (100% AcOEt); major isomer **39** $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.15−7.07 (m, 5H), 6.22 (d, *J* 7.3 Hz, 1H, C*H*=CHCO), 5.10 (d, *J* 7.3 Hz, 1H, CH=C*H*CO), 4.08 (d, *J* 12.1 Hz, 1H, OCH*H*Ph), 3.99 (d, *J* 12.1 Hz, 1H, OCH*H*Ph), 3.40 (dt, *J* 13.2, 6.6 Hz, 1H, H-2), 3.03 (m, 1H, H-8a), 2.73 (dd, *J* 10.6, 5.7 Hz, 1H, H-3′), 2.61 (dd, *J* 10.6, 6.9 Hz, 1H, H-3″), 2.24 (dd, *J* 15.6, 4.6 Hz, 1H, H-8′), 2.13 (t, *J* 15.7 Hz, H-8″), 1.62 (dt, *J* 12.3, 6.3 Hz, 1H, H-1′), 1.20 (ddd, *J* 12.3, 10.1, 7.6 Hz, 1H, H-1″); $^{13}$C NMR (151 MHz, $C_6D_6$) $\delta$ 190.0, 148.1, 138.1, 128.3−127.3 (Ar), 98.5, 76.3, 71.1, 56.1, 53.7, 41.9, 38.0; minor isomer **8a-*epi*-39** selected signals $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 6.31 (d, *J* 7.3 Hz, 1H, C*H*=CHCO), 5.14 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 2.66 (dd, *J* 11.6, 5.0 Hz, 1H, H-3′), 2.31 (dd, *J* 15.6, 4.6 Hz, H-8′); 1.98 (ps t, *J* 16.2, 15.5 Hz, 1H, H-8″); HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{18}NO_2$ [M + H$^+$] 244.1338, found 244.1339; IR (film) $\nu$ 3253, 2926, 2870, 1699, 1632, 1577, 1455, 1330, 1251, 1096, 742, 699 cm$^{-1}$.

*(1R,8aS)-1-(Benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**40**):* colorless oil; isolated yield 54 mg (43%) starting from 100 mg (0.52 mmol) of lactam **21**; $[\alpha]_D$ −241.5 (*c* 3.3, $CHCl_3$); $R_f$ = 0.43 (100% acetone); column chromatography (35% acetone in hexanes); $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.14−7.04 (m, 5H), 6.21 (d, *J* 7.2 Hz, 1H, C*H*=CHCO), 5.07 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 4.08−4.07 (m, 2H, OC$H_2$Ph), 3.38 (dt, *J* 16.3, 6.3, 4.8 Hz, 1H, H-8a), 3.24 (m, H-1), 2.64−2.59 (m, 1H, H-3′), 2.54 (dd, *J* 15.6, 4.8 Hz, 1H, H-8′), 2.42 (dt, *J* 10.0, 7.6 Hz, 1H, H-3″), 2.07 (ps t, *J* 16.2, 15.6 Hz, 1H, H-8″), 1.51−1.48 (m, 1H, H-2′), 1.33−1.27 (m, 1H, H-2″); $^{13}$C NMR (151 MHz, $C_6D_6$) $\delta$ 189.5, 148.4, 138.1, 128.2, 127.5, 127.3, 98.0, 82.6, 71.2, 62.0, 46.6, 40.5, 30.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{18}NO_2$ [M + H$^+$] 244.1338, found 244.1337; IR (film) $\nu$ 3437, 2877, 1633, 1576, 1456, 1361, 1248, 1110, 742, 699 cm$^{-1}$.

*(1R,8aR)-1-(Benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**8a-epi-40**):* colorless oil; isolated yield 10 mg (8%) starting from 100 mg (0.52 mmol) of lactam **21**; $[\alpha]_D$ +276.7 (*c* 0.5, $CHCl_3$); $R_f$ = 0.38 (100% acetone); column chromatography (35% acetone in hexanes); $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 7.13−7.01 (m, 5H), 6.33 (d, *J* 7.2 Hz, 1H, C*H*=CHCO), 5.14 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 4.05 (d, *J* 12.1 Hz, 1H, OCH*H*Ph), 3.95 (d, *J* 12.1 Hz, 1H, OCH*H*Ph), 3.20 (ps t, *J* 3.9, 3.7 Hz, 1H, H-1), 3.11 (dt, *J* 16.0, 4.6, 3.9 Hz, 1H, H-8a), 2.88 (ps t, *J* 16.0, 15.6 Hz, 1H, H-8′), 2.85−2.80 (m, 1H, H-3′), 2.41 (t, *J* 9.4 Hz, 1H, H-3″), 2.23 (dd, *J* 15.6, 4.6 Hz, 1H, H-8″), 1.41 (dd, *J* 13.5, 7.0 Hz, 1H, H-2′), 1.31−1.25 (m, 1H); $^{13}$C NMR (151 MHz, $C_6D_6$) $\delta$ 190.5, 147.9, 138.1, 128.2, 127.9−127.4 (Ar), 127.2, 97.4, 78.0, 70.9, 61.2, 46.3, 36.2, 29.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{18}NO_2$ [M + H$^+$] 244.1338, found 244.1339; IR (film) $\nu$ 3434, 2921, 1625, 1573, 1455, 1356, 1256, 1172, 1115, 1064, 1030, 742, 699 cm$^{-1}$.

*(2S,3R,8aS)-2-(Benzyloxy)-3-(benzyloxymethyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**36** and **8a-epi-36**):* mixture of diastereoisomers; isolated yield 70 mg (61%, both isomers) starting from 100 (0.32 mmol) of lactam **17**; *d.r.* 87:13 (determined by $^1$H NMR of crude reaction mixture); $R_f$ = 0.26 (100% AcOEt); column chromatography (100% AcOEt); major isomer **36** (pure sample obtained by preparative TLC, Merck preparative TLC plates Si60 F254, 20 × 20 cm, hexanes/AcOEt 1/8); yellow oil; $[\alpha]_D$ −141.3 (*c* 0.6, $CHCl_3$); $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 7.15−7.04 (m, 10H), 6.72 (d, *J* 7.1 Hz, 1H, C*H*=CHCO), 5.18 (d, *J* 7.0 Hz, 1H, CH=C*H*CO), 4.15 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 4.09−4.06 (m, 2H, OC$H_2$Ph), 4.04 (d, *J* 12.0 Hz, 1H, OCH*H*Ph), 3.58−3.53 (m, 1H, H-2), 3.37−3.28 (m, 2H, H-3, H-8a), 3.01 (dd, *J* 10.3, 3.8 Hz, 1H, H-3′), 2.96 (dd, *J* 10.3, 5.5 Hz, 1H, H-3″), 2.27 (dd, *J* 15.6, 4.8 Hz, 1H, H-8′), 2.19 (t, *J* 15.6 Hz, 1H, H-8″), 1.68 (dt, *J* 12.3, 6.3 Hz, 1H, H-1′), 1.24−1.15 (m, 1H, H-1″); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ 189.7, 147.1, 138.1, 137.7, 128.3, 128.2, 127.9, 127.7, 127.5, 127.3, 98.4, 78.9, 72.9, 71.1, 69.3, 64.7, 56.5, 42.2, 37.3; minor isomer **8a-*epi*-36** selected signals $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 6.61 (d, *J* 7.4 Hz, 1H, C*H*=CHCO), 5.20 (d, *J* 7.4 Hz, 1H, CH=C*H*CO); HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{26}NO_3$ [M + H$^+$] 364.1913, found 364.1910; IR (film) $\nu$ 3475, 2924, 2862, 1632, 1572, 1455, 1285, 1096, 1031, 740, 699, 638 cm$^{-1}$.

*(3S)-3-((tert-Butyldiphenylsilyloxy)methyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (**41** and **8a-epi-41**):* inseparable mixture of diasteroisomers; colorless oil; isolated yield 57 mg (55%, both isomers) starting from 90 mg (0.25 mmol) of lactam **22**; *d.r.* 82:18 (determined by HPLC of crude reaction mixture); $R_f$ = 0.44 (100% AcOEt); column chromatography (100% $Et_2O$ then 100% AcOEt); major isomer **41** $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.68−7.57 (m, 5H), 7.47−7.36 (m, 5H), 7.34 (d, *J* 7.2 Hz, 1H, C*H*=CHCO), 4.93 (d, *J* 7.2 Hz, 1H, CH=C*H*CO), 3.86 (ddd, *J* 15.6, 10.7, 5.6 Hz, 1H, H-8a), 3.82−3.78 (m, 1H, H-3), 3.69 (dd, *J* 11.0, 3.5 Hz, 1H, CH*H*OSi), 3.61 (dd, *J* 11.0, 5.8 Hz, 1H, CH*H*OSi), 2.43 (dd, *J* 15.9, 6.1 Hz, 1H, H-8′), 2.36 (t, *J* 15.9 Hz, 1H, H-8″), 2.23−2.19 (m, 1H, H-1′), 2.15−2.09 (m, 1H, H-2′), 1.79−1.72 (m, 1H, H-2″), 1.67−1.62 (m, 1H, H-1″), 1.04 (s, 9H, *t*-Bu); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.8, 149.5, 135.6, 135.5, 132.7, 132.6, 130.0, 129.89, 127.85, 127.84, 127.81, 96.9, 65.1, 61.5, 58.5, 41.8, 31.7, 27.0, 26.8, 19.1; minor isomer **8a-*epi*-41** selected signals $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.99 (d, *J* 7.1 Hz, 1H), 3.48 (dd, *J* 10.4, 7.4 Hz, 1H), 2.01−1.95 (m, 2H), 1.82 (dd, *J* 13.1, 7.1 Hz, 1H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{25}H_{31}NO_2NaSi$ [M + Na$^+$] 428.20347, found 428.2035; IR (film) $\nu$ 2958, 2931, 2857, 1635, 1574, 1427, 1252, 1112, 703, 504 cm$^{-1}$; HPLC Chiralpak AD-H, 20% *i*-PrOH in hexanes, flow 1.0 mL/min, UV 327 nm, $R_t$ 8.9 min (minor isomer **8a-*epi*-41**), 10.4 min (major isomer **41**).

*(6R,7R,8R,9S,9aR)-7,8,9-Tris(benzyloxy)-6-(benzyloxymethyl)-hexahydro-1H-quinolizin-2(6H)-one (**11**).* To a solution of **10** (58 mg, 0.1 mmol) in dry THF (5 mL) was added a 1 M solution of L-


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Selectride in THF (1.3 equiv, 0.13 mmol) dropwise at −25 °C. The mixture was stirred for 25 min at −25 °C. The reaction progress was monitored by TLC (1/1 AcOEt/hexanes). Then the mixture was warmed gradually to 0 °C and was quenched with saturated aqueous $NH_4Cl$ (5 mL). The organic layer was separated, and the aqueous layer was washed with $Et_2O$ (3 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was removed. The residue was chromatographed on silica gel (1/4 AcOEt/hexanes) to give 36 mg of **11** as a white solid: isolated yield 63%; mp 107−108 °C; $[\alpha]_D$ +19.0 (*c* 1.0, $CHCl_3$); $R_f$ = 0.54 (1/1 AcOEt/hexanes); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.35−7.23 (m, 18H), 7.12 (d, *J* 7.5 Hz, 2H), 4.89 (dd, *J* 10.7, 3.6 Hz, 2H), 4.77 (d, *J* 10.8 Hz, 1H), 4.64−4.60 (m, 2H), 4.54−4.44 (m, 3H), 4.40 (d, *J* 10.8 Hz, 1H), 3.83 (dd, *J* 9.3, 5.6 Hz, 1H), 3.75−3.67 (m, 2H), 3.64 (d, *J* 10.1 Hz, 1H), 3.62−3.54 (m, 2H), 3.51 (dd, *J* 13.5, 7.6 Hz, 1H), 3.02 (d, *J* 9.1 Hz, 1H), 2.96 (t, *J* 12.9 Hz, 1H), 2.51 (d, *J* 8.0 Hz, 2H), 2.14 (d, *J* 14.6 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 208.3, 138.5, 138.1, 137.9, 137.5, 128.5, 128.40, 128.36, 128.2, 128.0, 127.92, 127.85, 127.8, 127.7, 127.6, 82.4, 78.6, 78.4, 75.5, 75.3, 73.6, 72.7, 66.3, 60.1, 56.1, 48.8, 37.5, 37.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{11}H_{13}NO_2Na$ [M + $Na^+$] 214.0844, found 214.0842; IR (film) $\nu$ 3236, 2916, 1693, 1667, 1354, 1095, 728 $cm^{-1}$. Absolute configuration was confirmed by X-ray analysis.[64]

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures, tables, and a CIF file giving $^1$H and $^{13}$C NMR spectra, stereochemical proofs, HPLC data for selected compounds, and X-ray crystallographic data for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail for S.S.: sebastian.stecko@icho.edu.pl.
*E-mail for B.F.: bartlomiej.furman@icho.edu.pl.

### Notes

The authors declare no competing financial interest.

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