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SmI_2-Mediated Radical Cross-Couplings of α-Hydroxylated Aza-hemiacetals and *N,S*-Acetals with α,β-Unsaturated Compounds: Asymmetric Synthesis of (+)-Hyacinthacine A_2, (−)-Uniflorine A, and (+)-7-*epi*-Casuarine

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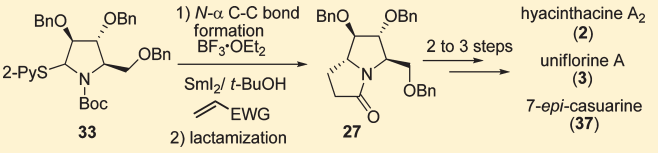
Supporting Information

ABSTRACT: The SmI_2-mediated radical coupling reactions of β-hydroxylated pyrrolidine/piperidine aza-hemiacetals **8** and **9** and *N,S*-acetals **6** and **33** with α,β-unsaturated compounds are described. This method allows a rapid access to β-hydroxylated pyrrolidines, piperidines, pyrrolizidinones, and indolizidinones. Starting from *N,S*-acetal **33** and via a common intermediate **27**, the alkaloids hyacinthacine A_2 (**2**), uniflorine A (**3**, 6-*epi*-casuarine), and the unnatural epimer 7-*epi*-casuarine (**37**) have been synthesized in four and five steps with overall yields of 34%, 16%, and 13%, respectively. The radical mechanism of the coupling reactions has been confirmed by controlled experiments, which also allowed deducing the anionic mechanism in the coupling between *N,S*-acetal **6** and carbonyl compounds. This demonstrates that the mechanisms of these SmI_2-mediated reactions are switchable from Barbier-type anionic to radical by cooperative action of $BF_3 \cdot OEt_2$ and *t*-BuOH.



INTRODUCTION

The saturated β-hydroxylated *N*-containing heterocycles constitute an important subclass of pharmaceutically relevant molecules and bioactive natural products.[1,2] Polyhydroxylated alkaloids (e.g., **1**−**5** in Figure 1), also known as azasugars and iminosugars,[2] exhibit potent inhibitory activity toward carbohydrate-processing enzymes and are particularly promising for the development of drugs against metabolite-disorder-associated diseases.[2]

The key reaction for the synthesis of this kind of molecule is the carbon−carbon bond formation at the *N*-α-carbon, which has attracted considerable attention of many organic synthetic chemists.[3−6] The radical-based coupling methods[5] are unique and complementary to those based on the carbocations (iminium ions) (route 1 in Scheme 1),[3] umpoled *N*-acyl-carbanions (route 2 in Scheme 1),[4] and organometallic intermediates.[6] The classical radical reactions generally required the use of highly toxic tin reagents and carcinogenic benzene as the solvent. Thanks to the pioneering work of Kagan on the chemistry of samarium diiodide,[7] the use of SmI_2 as a versatile single electron reducing agent has opened a new avenue for radical chemistry[8] and is a basis for the development of new carbon−carbon bond formation methods at the *N*-α-carbon.[9]

Previously, we have developed a SmI_2-mediated Barbier-type reductive coupling of *N,S*-acetal **6** with carbonyl compounds (Scheme 2), which was assumed to proceed through an organosamarium(III) intermediate, namely, via the anionic route 2 shown in Scheme 1.[10]

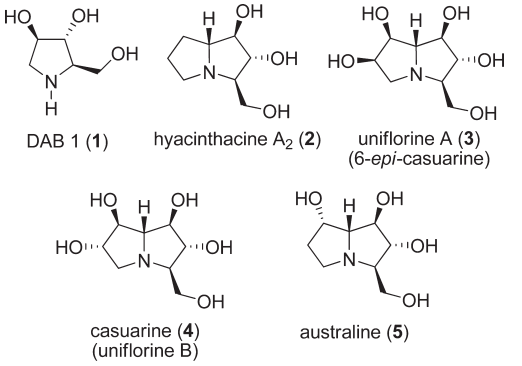


Figure 1. Some polyhydroxylated alkaloids.

With the dual aims to, on one hand, develop a complementary radical-based method and, on the other hand, explore the possibility to use aza-hemiacetals/ *N,S*-acetals as precursors of α-aminoalkyl radicals, we decided to develop the chemistry outlined by route 3 in Scheme 1, and the preliminary results have been reported in a recent communication.[11] In order to widen the scope of this method, we decided to investigate the coupling reactions of β-hydroxylated pyrrolidine/piperidine aza-hemiacetals **8**/**9** with α,β-unsaturated compounds (Figure 2). The use of aza-hemiacetals as the synthetic equivalents of radical

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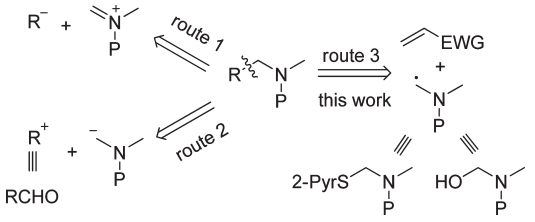
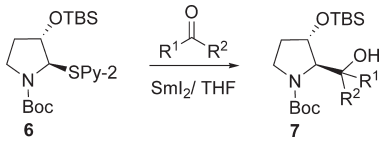
Scheme 1. Three Types of Carbon−Carbon Bond Formation Methods at the *N*-α-Carbon



Scheme 2



synthons **A** would provide an alternative to overcome the difficulties encountered in the generation and reaction of carbanion synthons **B**,[12] which is challenging yet quite attractive for the synthesis of azasugars.[10,12] In this paper, we report the full details of this study, which also include the confirmation of the radical mechanism, and the application of the newly developed method to the asymmetric synthesis of the alkaloids hyacinthacine A_2 (**2**), uniflorine A (**3**), and the unnatural epimer (+)-7-*epi*-casuarine (**37**).

RESULTS AND DISCUSSION

SmI_2-Mediated Coupling Reaction of α-Silyloxy *N,S*-Acetal 6 with Ethyl Acrylate. As a model study, the coupling of the known *N,S*-acetal **6**[10a] with ethyl acrylate was first investigated under the conditions previously defined for the reductive coupling of **6** with carbonyl compounds.[10a] Treatment of *N,S*-acetal **6** and ethyl acrylate with SmI_2 led only to the reduced product **11** in 35% yield (Table 1, entry 1). When 4.0 equiv of *tert*-butanol was used as an additive, the desired product **10a** was obtained in 24% yield (Table 1, entry 2), while use of $BF_3 \cdot OEt_2$ (2.0 equiv) as an additive afforded only the reduced product **11** in 65% yield (Table 1, entry 3). To our delight, in the presence of both $BF_3 \cdot OEt_2$ (2.0 equiv) and *tert*-butanol (4.0 equiv), the desired product **10a** was obtained in 60% yield as a diastereomeric mixture (dr = 87: 13), along with the reduced product **11** in 15% yield (Table 1, entry 4).

Mechanism for the SmI_2-Mediated Coupling Reactions between *N,S*-Acetal 6 and Ethyl Acrylate. To probe the mechanism of the coupling reaction, *N,S*-acetal **6** and cyclohexanone were subjected to the coupling conditions indicated in Table 1, entry 4; however, only the reduced product **11** was obtained in 61% yield (Scheme 3, a). The reaction of *N,S*-acetal **6** with a mixture of cyclohexanone and ethyl acrylate led to the formation of compound **10a** and the reduced product **11** in 62% and 15% yields, respectively (Scheme 3, b). The coupling product (**12**) of *N,S*-acetal **6** with cyclohexanone was obtained in 63% yield only in the absence of both Lewis acid and proton source, namely, under the conditions we previously established for the Barbier-type reactions (Scheme 2 and Scheme 3, c).[10a] Based on these results, it could be concluded that in the presence

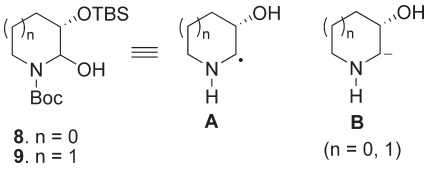
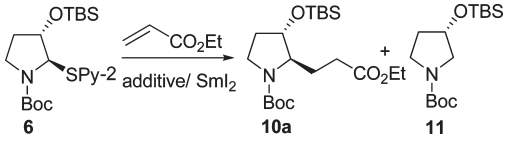


Figure 2. Plausible synthetic equivalents of β-hydroxylated pyrrolidine/piperidine *N*-α-radical synthons as alternatives to the corresponding *N*-α-carbanion synthons.

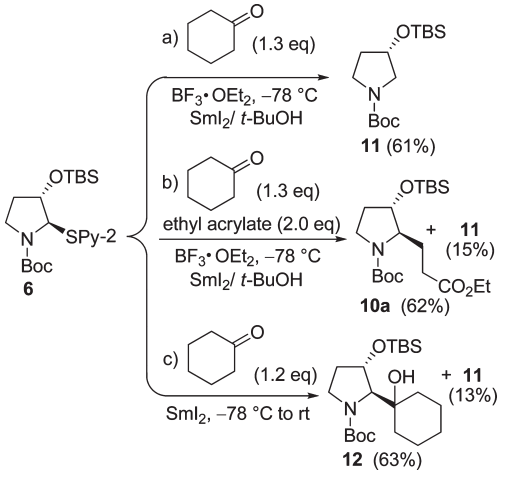
Table 1. Results on the SmI_2-Mediated Radical Coupling Reaction of α-Silyloxy *N,S*-Acetal 6 with Ethyl Acrylate



	additive	T (°C)	% yield[a] of **10a** (dr)[b]	% yield[a] of **11**
1	none	rt	none	35
2	*t*-BuOH (4.0 equiv)	0	24 (87:13)	59
3	$BF_3 \cdot OEt_2$ (2.0 equiv)	−78	trace	65
4	$BF_3 \cdot OEt_2$ (2.0 equiv)/ *t*-BuOH (4.0 equiv)	−78	60 (87:13)	15

[a] Isolated yield. [b] Determined by HPLC analysis.

Scheme 3. Mechanistic Study on the SmI_2-Mediated Coupling Reactions between *N,S*-Acetal 6 and Ethyl Acrylate/ Cyclohexanone



of both a Lewis acid ($BF_3 \cdot OEt_2$)[13] and a proton source (*t*-BuOH)[14] the coupling reaction between *N,S*-acetal **6** and an α,β-unsaturated compound proceeds through a radical mechanism (cf. Scheme 4). These results also allowed deducing the anionic mechanism in the coupling between *N,S*-acetal **6** and carbonyl compounds.[10a] Thus, the complementary mechanisms of these SmI_2-mediated reactions are switchable from Barbier-type anionic to radical by use of both $BF_3 \cdot OEt_2$ and *t*-BuOH as additives.

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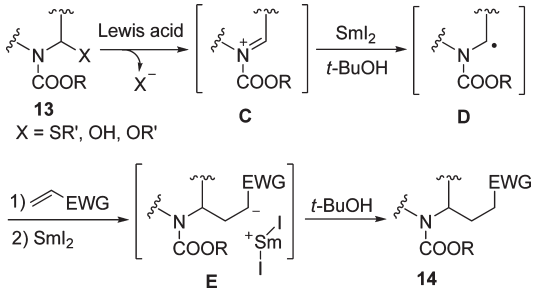
Scheme 4. Plausible Main Mechanism for the SmI_2-Mediated Coupling Reactions of *N,S(O)*-Acetals/Aza-hemiacetals 13 with α,β-Unsaturated Compounds



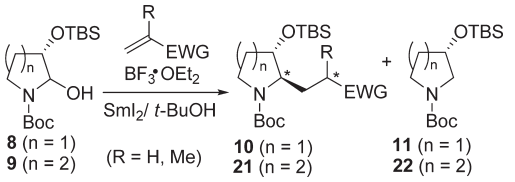
With the radical nature of the reaction confirmed, a generalized mechanism for the SmI_2-mediated coupling reactions between *N,S(O)*-acetals/aza-hemiacetals **13** and α,β-unsaturated compounds was proposed in Scheme 4. In the presence of a Lewis acid (such as $BF_3 \cdot OEt_2$), the *N*-acyliminium ion **C** is generated from *N,S(O)*-acetals/aza-hemiacetals **13**, which is reduced by SmI_2 to give the α-acylaminoalkyl radical intermediate **D**.[9a,h,15] The radical **D** is trapped by an α,β-unsaturated compound, and the resultant radical receives a second electron from SmI_2 to produce the samarium(III) salt **E** that is quenched by *t*-BuOH to give the cross-coupling product **14**.[14] It is worthy to mention that on account of the result displayed in Table 2, entry 2, a partial generation of α-acylaminoalkyl radical intermediate **D** by SmI_2-mediated direct homocleavage of the C−S bond[16] could not be excluded.

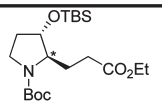
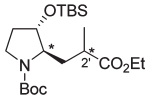
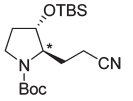
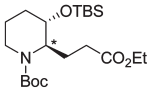
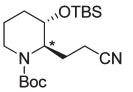
The formation of the α-acylaminoalkyl radical intermediate **D** via *N*-acyliminium ion (**C**) was proven by the coupling reactions of aza-hemiacetals/ *N,O*-acetals **15** with α,β-unsaturated compounds to give **16** (Scheme 5, a).[11] The radical mechanism was also confirmed by the isolation of dimeric product **19** from the homocoupling of aza-hemiacetal **18** in the absence of an α,β-unsaturated compound (Scheme 5, b).[11] Considering the ready availability of both aza-hemiacetals and *N,O*-acetals by numerous methods,[3,17] it is of great synthetic value that they can be used as general precursors of *N*-α carbon radicals.

SmI_2-Mediated Coupling Reactions of α-Hydroxylated Aza-hemiacetals with α,β-Unsaturated Compounds. We next investigated the coupling of α-hydroxylated aza-hemiacetals with α,β-unsaturated compounds. The synthesis of the β-hydroxylated pyrrolidine aza-hemiacetal (*S*)-**8** (cf. Figure 2) has been reported previously.[10a] The aza-hemiacetal **9** was synthesized as a separable 1:1 diastereomeric mixture by a regioselective reduction (DIBAL-H, CH_2Cl_2, −78 °C) of the known activated lactam (*S*)-**20**[12d,e] (Scheme 6).

The cross-coupling reaction of the chiral aza-hemiacetal **8** with α,β-unsaturated compounds was first investigated. Treatment of aza-hemiacetal **8** and ethyl acrylate with $BF_3 \cdot OEt_2$ and a freshly prepared *t*-BuOH-containing SmI_2 solution in THF at −40 °C for 10 min produced the desired coupling product **10a** as a *trans*/*cis* diastereomeric mixture in 89:11 ratio (combined yield 72%), along with the reduced product **11** in 9% yield (Table 2, entry 1). The cross-coupling reaction with ethyl α-methylacrylate gave **10b** as a mixture of three diastereomers in a ratio of 50:39:11 (Table 2, entry 2), which implicated that *trans*/*cis* diastereoselectivity was 89:11, and the diastereomeric ratio at C-2′ was 56:44. The coupling with more active acrylonitrile gave

Table 2. SmI_2-Mediated Cross-Coupling Reactions of the Aza-hemiacetals 8/9 with α,β-Unsaturated Compounds



Entry	Starting material	Coupling product[a] (% yield)[b] (dr)	Reduced product (% yield)[b]
1	**8**/ CO_2Et	 **10a** (72) (89: 11)[c]	**11** (9)
2	**8**/ CO_2Et	 **10b** (72) (50: 39: 11)[c]	**11** (9)
3	**8**/ CN	 **10c** (64) (74: 26)[d]	**11** (5)
4	**9**/ CO_2Et	 **21a** (71) (75: 25)[d]	–
5	**9**/ CN	 **10c** (64) (52: 48)[d]	–

[a] Only the major diastereomer shown. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by chromatographic separation.

two diastereomers (**10c**) in 76:24 ratio with 64% combined yield (Table 2, entry 3). Compared with the pyrrolidine aza-hemiacetal **8**, the couplings of the piperidine aza-hemiacetal **9** with ethyl acrylate and acrylonitrile produced the corresponding products **21a** and **21b** in similar yields but with lower diastereoselectivities (Table 2, entries 4 and 5). The stereochemistry of major diastereomers was assumed to be *trans* in light of the literature precedents,[18] which was confirmed by converting products **10a** and **21a** into the known compounds, respectively (vide infra).

Synthesis of 1-Hydroxypyrrolizidine (1*S*,7a*R*)-25 and 8-Hydroxyindolizidinone (8*S*,8a*R*)-26. With dual aims to confirm the stereochemistry of the coupling products and to demonstrate the applicability of the method, the coupling products **10a** and **21a** were converted into 1-hydroxypyrrolizidine (1*S*,7a*R*)-**25** and 8-hydroxyindolizidinone (8*S*,8a*R*)-**26**, respectively. Successive treatment of the diastereomeric mixture **10a** and 2-*epi*-**10a** with a solution of 2 N HCl in EtOAc and K_2CO_3 in $EtOH/H_2O$ yielded the pyrrolizidinone **23a**/**23b**

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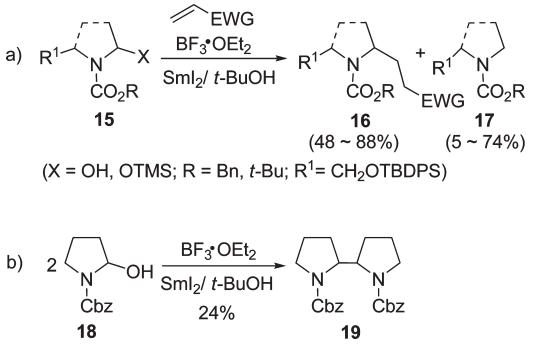
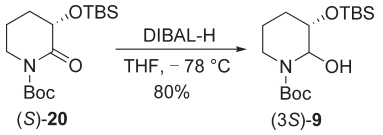
Scheme 5



Scheme 6. Preparation of Aza-hemiacetal 9

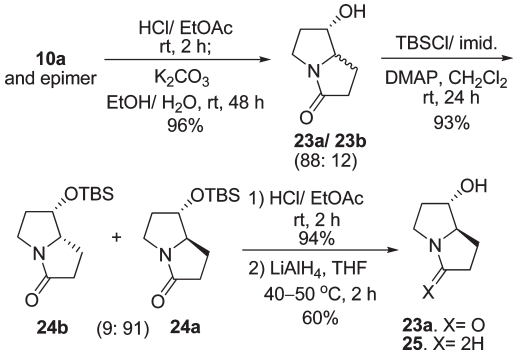


(dr = 88:12) as an inseparable diastereomeric mixture (Scheme 7). After silylation, the two diastereomers **24a** and **24b** (dr = 91:9) were separated. The minor diastereomer (7*S*,7a*S*)-**24b** is identical to a known compound, which has served as a key intermediate for the asymmetric synthesis of the necine base (−)-supinidine.[19] The major diastereomer **24a** was deprotected by treatment with a solution of 2 N HCl in EtOAc, and pure pyrrolizidinone **23a** was reduced with $LiAlH_4$ to afford (1*S*,7a*R*)-1-hydroxypyrrolizidine **25** in 56% yield over two steps {$[\alpha]^{20}_D$ +23.5 (*c* 0.6, $CHCl_3$); lit.[20a] $[\alpha]^{20}_D$ −26 (*c* 2.3, $CHC1_3$) for the antipode}.

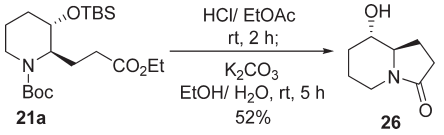
Successive treatment of the major diastereomer **21a** with 2 N HCl and K_2CO_3 led to the formation of the 8-hydroxyindolizidinone (8*S*,8a*R*)-**26** in 52% yield (Scheme 8).[21] The spectral data of the synthetic products **25** and **26** were in agreement with those reported.[20,21] Thus the cross-coupling reaction is confirmed to be 2,3-*trans*-diastereoselective. It is worth mentioning that the *O*-TBS-protected derivative of **26** and its enantiomer have been used as the key intermediates for the asymmetric syntheses of (−)-swainsonine[22b] and its analogues.[22a]

Attempted Asymmetric Synthesis of (+)-Hyacinthacine A_2 (2) and (−)-Uniflorine A (3). To further demonstrate the scope and synthetic value of the method, the syntheses of the polyhydroxylated pyrrolizidine alkaloids hyacinthacine A_2 (**2**) and uniflorine A (**3**) were envisioned. Hyacinthacine A_2,[23,24] isolated along with hyacinthacines A_1, A_3, and B_2 from the bulbs of *Muscari armeniacum* (Hyacinthaceae), exhibited selective inhibitory activity against amyloglucosidase (*Aspergillus niger*) with an IC_{50} of 8.6 μM.[23] (−)-Uniflorines A and B,[25−27] were isolated from the leaves of the Paraguayan tree *Eugenia uniflora L*, which has been used as a traditional antidiabetic agent in Paraguay for a long time. As an inhibitor of the α-glucosidases, uniflorine A showed inhibitory activities against rat intestinal maltase and sucrase with IC_{50}'s of 12 and 3.1 μM, respectively.[25] The originally assigned structure for (−)-uniflorine A has been revised to that shown in Figure 1,[26] while uniflorine B turned out to share the same structure as casuarine,[28,29] another azasugar isolated from the bark of *Casuarina equisetfolia* L. (Casuarinaceae).[28]

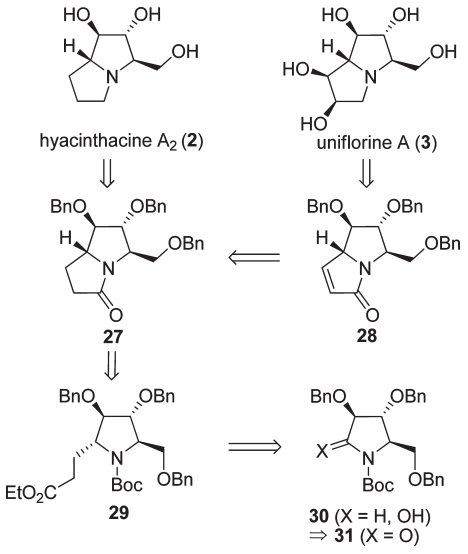
Scheme 7. Synthesis of 1-Hydroxypyrrolizidine (1*S*,7a*R*)-25



Scheme 8. Synthesis of 8-Hydroxyindolizidinone (8*S*,8a*R*)-26



Scheme 9. Retrosynthetic Analysis of Hyacinthacine A_2 and Uniflorine A



Due to their significant bioactivities and intriguing structural features, the syntheses of both hyacinthacine A_2[24] and (−)-uniflorine A[26,27] have attracted much attention. Our retrosynthetic analyses of hyacinthacine A_2 (**2**) and uniflorine A (**3**) are shown in Scheme 9, which features, first, the use of the hydroxylated pyrrolizidinone derivative **27** as a common intermediate and, second, the formation of tetrasubstituted pyrrolidine **29** via the key SmI_2-mediated radical cross-coupling reaction of the aza-hemiacetal **30** with ethyl acrylate.

The synthesis started with the known activated amide **31**, which was obtained by reductive benzyloxymethylation of a protected (*R*,*R*)-tartarimide.[30] Treatment of compound **31** with

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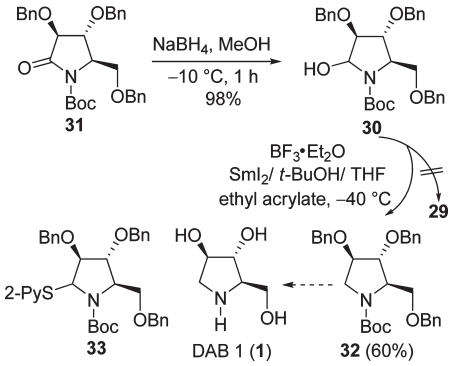
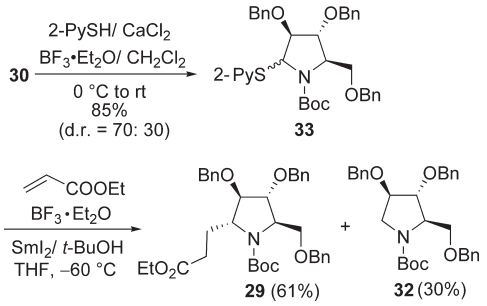
Scheme 10



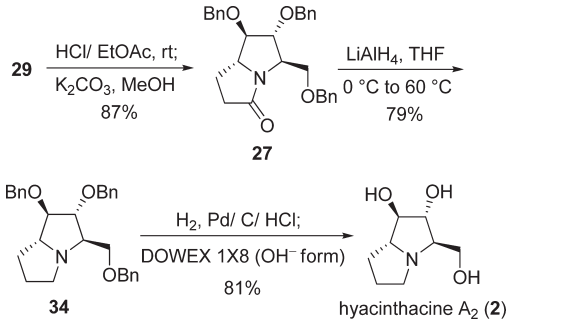
Scheme 11



$NaBH_4$ at −10 °C produced a diastereomeric mixture of aza-hemiacetal **30** in 98% yield. Unfortunately, the SmI_2-mediated cross-coupling of aza-hemiacetal **30** with ethyl acrylate was unsuccessful; only the reduced product **32** was obtained in 60% yield (Scheme 10). The different reactivity between aza-hemiacetal **30** and **8** may be due to the effects of the substituent on the pyrrolidine ring. The α-acylaminoalkyl radical intermediates generated from more substituted pyrrolidine aza-hemiacetal are less reactive toward α,β-unsaturated compounds (e.g., ethyl acrylate), which were further reduced by SmI_2 to yield the reduced product. This is evident from the yields of cross-coupling products/reduced product that change from 76%/0 for unsubstituted pyrrolidine aza-hemiacetal **18**,[11] to 72%/9% for monosubstituted pyrrolidine aza-hemiacetal **8** (Table 2, entry 1), and 0/60% for trisubstituted pyrrolidine aza-hemiacetal **30**. Compound **32** is a fully protected form of 1,4-dideoxy-1,4-imino-D-arabinitol (**1**, known as DAB 1), which was isolated from two types of leguminose plants, *Arachniodes standishii*[31a,b] and *Angylocalyx boutiqueanus*.[31c]

Asymmetric Synthesis of (+)-Hyacinthacine A_2 (2). The failure in the radical coupling of aza-hemiacetal **30** with ethyl acrylate led us to envision the use of *N*,*S*-acetal **33** as a more reactive substrate. The requisite *N*,*S*-acetal **33** was prepared by reaction of the aza-hemiacetal **30** with 2-mercaptopyridine ($CaCl_2$, $BF_3 \cdot Et_2O$, CH_2Cl_2) as a separable diastereomeric mixture in 70:30 ratio with 85% yield (Scheme 11). The SmI_2-mediated radical coupling of the diastereomeric mixture of *N*,*S*-acetal **33** with ethyl acrylate at −60 °C went smoothly to produce the desired product **29** as a single diastereomer in 61% yield, along with the fully reduced product **32** in 30% yield. The stereochemistry of the coupling product **29** was assumed to be 4,5-*trans*, which was confirmed by conversion into the natural products hyacinthacine A_2 and uniflorine A (vide infra).

Scheme 12. Asymmetric Synthesis of (+)-Hyacinthacine A_2



According to the experiments, *N*,*S*-acetal **33** can generate the α-acylaminoalkyl radical intermediate at a lower temperature (−60 °C) than aza-hemiacetal **30** (−40 °C). The different reactivity between *N*,*S*-acetal **33** and aza-hemiacetal **30** may be due to the stability of the same radical intermediate under different temperature. At −60 °C, the radical intermediate is stable enough to be captured by ethyl acrylate, but at −40 °C, the radical intermediate is able to be further reduced by SmI_2 to generate a carbanion, followed by protonation to provide the reduced product **32**.

Cleavage of the *N*-Boc group in urethane pyrrolidine **29** with a solution of 2 N HCl in EtOAc, followed by K_2CO_3-promoted cyclization gave the pyrrolizidinone **27**[24d] in 87% yield over two steps (Scheme 12). Reduction of compound **27** with $LiAlH_4$ in THF gave the known pyrrolizidine derivative **34**[24b,d,h] in 79% yield. The stereochemistry of **34** was established by analysis of NOESY spectrum (cf. Supporting Information) to be 1*R*,2*R*,3*R*,7a*R*.

Finally, tris-*O*-debenzylation of pyrrolizidine **34** by catalytic hydrogenolysis in acidic medium (H_2, 10% Pd/C, 6 N HCl, rt) followed by neutralization (DOWEX OH^- form) provided hyacinthacine A_2 (**2**) in 81% yield {$[\alpha]^{20}_D$ +10.6 (*c* 1.2, H_2O); lit.[24c] $[\alpha]^{20}_D$ +10.5 (*c* 0.6, H_2O)} (Scheme 12). The spectral data of the synthetic hyacinthacine A_2 (**1**) matched those reported.[23,24]

Asymmetric Synthesis of (−)-Uniflorine A (3) and (+)-7-*epi*-Casuarine (37). For the synthesis of uniflorine A (**3**), compound **27** was successively treated with LDA (2.4 equiv) and PhSeBr (1.1 equiv) to yield the phenylselenylated product, which without separation was subjected to the oxidative elimination (H_2O_2, CH_2Cl_2, rt)[32] to produce the α,β-unsaturated indolizidinone **28** in 71% overall yield, along with 10% of the recovered starting material **27** (Scheme 13).

For the diastereoselective dihydroxylation of α,β-unsaturated lactam **28**, several conditions have been tried (cf. Supporting Information). It was found that treatment of compound **28** with OsO_4/NMO in a mixed solvent system of *t*-BuOH/H_2O (v/v 1:1) and in the presence of citric acid[33] produced polyhydroxylated pyrrolizidinones **35** and its diastereomer **36** (dr = 60:40) as a separable diastereomeric mixture in a combined yield of 93%, whereas treatment of compound **28** with $KMnO_4$/18-crown-6[34] at −10 °C produced diastereomers **35** and **36** in a reversed 14:86 ratio with a combined yield of 64% (Scheme 13).

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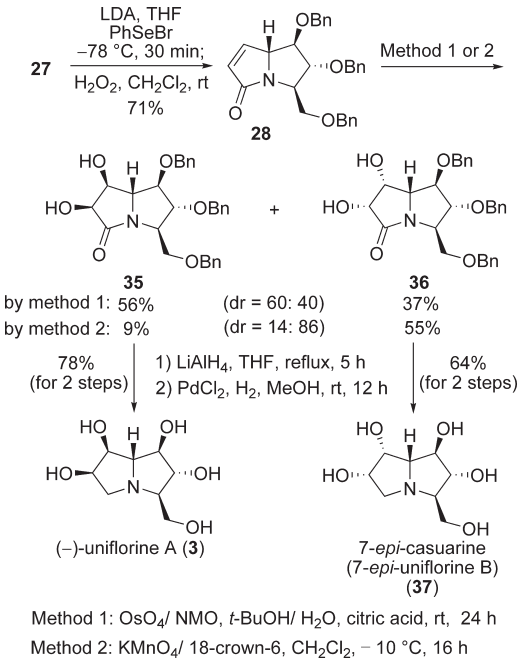
Scheme 13. Asymmetric Synthesis of (−)-Uniflorine A (3) and (+)-7-*epi*-Casuarine (37)



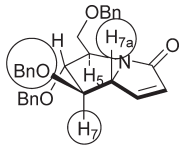


Figure 3. Conformation of α,β-unsaturated pyrrolizidinone **28**.

The stereochemistry of diastereomer **35** was established via NOESY spectrum of its bisacetyl derivative **38** (cf. Supporting Information).

The different face-selectivity observed in the dihydroxylation of α,β-unsaturated lactam **28** with different oxidation methods can be understood on the basis of the conformation shown in Figure 3. The concave face is somewhat sterically more congested, and thus the osmylation occurred more preferentially from the convex face (dr = 60:40, combined yield 93%). With sterically more hindered dihydroxylation reagent system $KMnO_4$/18-crown-6, severe interaction with H-7a and the benzyloxy group became a predominating fact that prevented an attack on the convex face. A concave face attack thus occurred to give indolizidinone **36** as the major diastereomer but in a much lower yield (dr = 14:86, combined yield 64%).

To complete the synthesis of (−)-uniflorine A (**3**), diastereomer **35** was reduced with $LiAlH_4$, and the resulting product was tris-*O*-debenzylated (H_2, $PdCl_2$, rt) to give the desired polyhydroxylated pyrrolizidine (−)-uniflorine A (**3**) in 78% yield over two steps (Scheme 13). The optical rotation $\{[\alpha]^{20}_D$ −6.7 (*c* 0.42, H_2O); lit.[27b] $[\alpha]_D^{21}$ −6.9 (*c* 0.415, H_2O)$\}$ and spectral data of the synthetic uniflorine A (**3**) matched those reported.[27a] Following the same procedure, diastereomer **36** was converted into 7-*epi*-casuarine (**37**)[35] $\{[\alpha]^{20}_D$ +6.1 (*c* 0.62, H_2O); lit.[35] $[\alpha]_D^{22}$ +6.2 (*c* 0.65, H_2O)$\}$ in 64% yield over two steps.

CONCLUSIONS

In conclusion, we have demonstrated that under appropriate conditions (SmI_2, $BF_3\cdot OEt_2$, *t*-BuOH), aza-hemiacetals/*N*,*O*-acetals **15**, aza-hemiacetals **8**, **9**, and *N*,*S*-acetals **6**, **33** can serve as valuable synthetic equivalents of the corresponding α-aminoalkyl radical synthons, in particular β-hydroxylated pyrrolidine/piperidine α-radical synthons **A**. The one-pot radical coupling reactions of **8**, **9**, **6**, and **33** with α,β-unsaturated compounds overcome the challenges associated with the validation of the corresponding β-hydroxylated pyrrolidine/piperidine *N*-α carbanions (**B**). The coupling reactions have been shown to be 2,3-*trans*-diastereoselective. The method provides a ready access to β-hydroxylated pyrrolidines, piperidines, pyrrolizidinone, and indolizidinone systems. From *N*,*S*-acetal **33**, the polyhydroxylated pyrrolizidine alkaloids hyacinthacine A_2 (**2**), uniflorine A (**3**, 6-*epi*-casuarine), and the unnatural epimer 7-*epi*-casuarine (**37**) have been synthesized in four and five steps with overall yields of 34%, 16%, and 13%, respectively. The formation of the fully protected form of DAB 1 (**32**) implies that the SmI_2-mediated reaction may be used as an alternative method for the reductive dehydroxylation of aza-hemiacetals.[12c,36] This methodology is also applicable to the synthesis of other pyrrolizidine alkaloids and their diastereomers.

EXPERIMENTAL SECTION

General Procedure for the Cross-Coupling of Aza-hemiacetals 8/9 with α,β-Unsaturated Compounds. To a slurry of Sm powder (flame-dried under Ar, 826 mg, 5.5 mmol) in anhydrous THF (50 mL) was added I_2 (1.27 g, 5.0 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 h at 45 °C to yield a SmI_2 (0.1 N in THF) reagent. To the resulting mixture was added *t*-BuOH (0.43 mL, 5.0 mmol), and the mixture was stirred for 10 min to yield a *t*-BuOH-containing SmI_2 (both 0.1 N in THF).

To a solution of an aza-hemiacetal (**8** or **9**) (0.50 mmol), an α,β-unsaturated compound (1.0 mmol), and $BF_3\cdot Et_2O$ (1.0 mmol) in anhydrous THF (10 mL) was added dropwise a freshly prepared *t*-BuOH-containing SmI_2 (both 0.1 N in THF, 20 mL, 2.0 mmol) at −40 °C under an argon atmosphere. The reaction mixture was stirred for 10 min and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired cross-coupling product. In some cases, the reduced product was isolated as a byproduct.

(2*R*/*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butyloxycarbonyl-2-[(2-ethyloxycarbonyl)ethyl]pyrrolidine (10a and 2-*epi*-10a). *Cross-Coupling of N,S-Acetal* ***6*** *with Ethyl Acrylate.* To a solution of *N*,*S*-acetal **6** (205 mg, 0.50 mmol), ethyl acrylate (0.11 mL, 1.0 mmol), and $BF_3\cdot Et_2O$ (0.12 mL, 1.0 mmol) in anhydrous THF (10 mL) was added dropwise a freshly prepared *t*-BuOH-containing SmI_2 (both 0.1 N in THF, 20 mL, 2.0 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 30 min and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford **10a** and 2-*epi*-**10a** as an inseparable mixture (dr = 87:13, determined by HPLC) in a combined yield of 60% and the reduced product **11** in 15% yield.

Cross-Coupling of Aza-hemiacetal ***8*** *with Ethyl Acrylate.* Following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal

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8 with ethyl acrylate afforded **10a** and 2-*epi*-**10a** as an inseparable mixture [dr = 89:11, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 70:30, 1.0 mL/min, λ = 254 nm, t_1 = 8.8 min (88.8%), t_2 = 14.7 min (11.2%)] in a combined yield of 72%, and the reduced product **11** in 9% yield. Mixture of **10a** and 2-*epi*-**10a**: colorless oil; IR (film) ν_{max} 2956, 2930, 2858, 1736, 1697, 1391 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.83 and 0.87 (2s br, 9H), 1.18−1.28 (m, 3H), 1.43 (s, 9H), 1.56−2.06 (m, 4H), 2.24−2.50 (m, 2H), 3.24−3.35 (m, 1H), 3.36−3.76 (m, 2H), 3.98−4.05 (m, 1H), 4.05−4.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 14.2, 17.9, 18.0, 25.6, 25.7, 28.4, 31.1, 31.4, 31.9, 32.6, 44.0, 44.5, 60.4, 65.8, 74.8, 75.6, 78.9, 79.3, 155.3, 173.1, 173.3. MS (ESI, *m*/*z*): 424 ($M + Na^+$). HRESIMS calcd for $[C_{20}H_{39}NO_5SiNa]^+$ ($M + Na^+$): 424.2489; found: 424.2485.

(2*R*/*S*,3*S*,2′*R*/*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butyloxycarbonyl-2-(2-ethyloxycarbonyl)propylpyrrolidine (10b). Following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal **8** with ethyl α-methacrylate afforded compound **10b** as an inseparable diastereomeric mixture [dr = 50:39:11, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75:25, 1.0 mL/min, λ = 254 nm, t_1 = 24.4 min (50%), t_2 = 25.6 min (39%), t_3 = 30.6 min (11%)] in a combined yield of 72% as a colorless oil and reduced product **11** in 9% yield. **10b**: IR (film) ν_{max} 2956, 2932, 2858, 1734, 1698, 1392, 1254 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (diastereomeric mixture) δ 0.01−0.07 (m, 6H), 0.80−0.89 (m, 9H), 1.15−1.26 (m, 6H), 1.40−1.46 (m, 9H), 1.46−2.01 (m, 4H), 2.38−2.70 (m, 1H), 3.14−3.84 (m, 3H), 3.93−4.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (diastereomeric mixture) δ −5.1, −4.8, 14.1, 14.2, 17.5, 17.7, 17.8, 18.0, 25.6, 25.7 (3C), 28.5 (3C), 31.8, 32.6, 36.5, 36.9, 37.3, 43.8, 44.4, 60.2, 64.4, 64.8, 75.6, 75.8, 78.8, 79.3, 155.1, 155.4, 176.2. MS (ESI, *m*/*z*): 438 ($M + Na^+$, 100). Anal. Calcd for $C_{21}H_{41}NO_5Si$: C, 60.68; H, 9.94; N, 3.37. Found: C, 60.70; H, 9.86; N, 3.63.

(2*R*/*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butyloxycarbonyl-2-(2-cyanoethyl)pyrrolidine (10c and 2-*epi*-10c). Following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal **8** with acrylonitrile afforded compound **10c** (yield 47%), its diastereomer 2-*epi*-**10c** (yield 17%) (dr = 74:26), and reduced product **11** in 5% yield. **10c** (major diastereomer): colorless oil; $[\alpha]^{20}_D$ −0.3 (*c* 1.3, $CHCl_3$). IR (film) ν_{max} 2956, 2931, 2858, 2244, 1694, 1392, 1366 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 and 0.04 (2s br, 6H), 0.83 (s, 9H), 1.43 (s, 9H), 1.61−1.83 (m, 3H), 1.84−1.97 (m, 1H), 2.29−2.51 (m, 2H), 3.23−3.37 (m, 1H), 3.38−3.72 (2 m, 2H), 3.88−4.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, 14.4, 17.8, 25.5 (3C), 28.4 (3C), 29.4, 31.9, and 32.6 (rotamers), 44.1 and 44.6, 65.2 and 65.3, 74.9 and 75.4, 79.4 and 80.0, 119.2 and 119.6, 155.1, and 155.6. MS (ESI, *m*/*z*): 377 ($M + Na^+$, 100). Anal. Calcd for $C_{18}H_{34}N_2O_3Si$: C, 60.97; H, 9.67; N, 7.90. Found: C, 60.88; H, 9.95; N, 8.12.

2-*epi*-**10c** (minor diastereomer): colorless oil; $[\alpha]^{20}_D$ +10.6 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} 2956, 2931, 2853, 2245, 1697, 1392 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 1.45 and 1.45 (2s br, 9H), 1.70−1.88 (m, 2H), 1.94−2.15 (m, 2H), 2.36−2.54 (m, 2H), 3.23−3.45 (m, 2H), 3.73−3.88 (m, 1H), 4.23−4.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, −5.0, 14.5, 18.0, 25.7 (3C), 28.5 (3C), 29.7, 31.9 and 32.1, 42.8 and 43.2, 58.4, 71.7 and 72.4, 79.7 and 80.3, 119.9 and 120.2, 154.6, and 155.1. MS (ESI, *m*/*z*): 377 ($M + Na^+$, 100).

(2*R*/*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butyloxycarbonyl-2-[(2-ethyloxycarbonyl)ethyl]piperidine (21a and 2-*epi*-21a). Following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal **9** with ethyl acrylate afforded **21a** in 53% yield and 2-*epi*-**21a** in 18% yield (dr = 75:25). **21a** (major diastereomer): colorless oil; $[\alpha]^{20}_D$ −9.1 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 2954, 2930, 2857, 1736, 1693, 1419, 1365, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 1.50−1.74 (m, 4H), 1.82−1.97 (m, 2H), 2.25−2.32 (m, 2H), 2.52−2.84 (m, 1H), 3.64−3.72 (m, 1H), 3.84−4.20 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.03, −5.01, 14.2, 18.0, 19.2, 24.0, 25.7 (3C), 27.2, 28.4 (3C), 30.9, 37.9, 57.1, 60.4, 68.2, 79.1, 155.6, 173.2. MS (ESI, *m*/*z*): 438 ($M + Na^+$, 100), 454 ($M + K^+$, 68), 416 ($M + H^+$, 56). Anal. Calcd for $C_{21}H_{41}NO_5Si$: C, 60.68; H, 9.94; N, 3.37. Found: C, 60.69; H, 9.98; N, 3.45.

2-*epi*-**21a** (minor diastereomer): colorless oil; $[\alpha]^{20}_D$ +19.9 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} 2951, 2932, 2857, 1736, 1696, 1417, 1364, 1252 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 and 0.07 (2s br, 6H), 0.89 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 1.47−1.70 (m, 4H), 1.78−1.91 (m, 1H), 1.94−2.06 (m, 1H), 2.15−2.40 (m, 2H), 2.53−2.75 (m, 1H), 3.61−3.73 (m, 1H), 3.74−4.00 (m, 1H), 4.05−4.35 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, 14.2, 18.1 and 18.5, 24.2, 25.8 (3C), 28.4 (3C), 30.9 and 31.0, 36.6, 38.1, 54.7 and 56.1, 60.3, 69.5 and 70.0, 79.6, 155.0, 173.4. MS (ESI, *m*/*z*): 438 ($M + Na^+$, 100).

(2*R*/*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butyloxycarbonyl-2-(2-cyanoethyl)piperidine (21b and 2-*epi*-21b). Following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal **9** with acrylonitrile afforded compound **21b** (yield 32%) and its diastereomer 2-*epi*-**21b** (yield 30%) (dr = 52:48). **21b** (more polar diastereomer): colorless oil; $[\alpha]^{20}_D$ −1.5 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 2954, 2930, 2857, 2244, 1690, 1419, 1366, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 and 0.06 (2s br, 6H), 0.87 (s, 9H), 1.26−1.36 (m, 1H), 1.45 (s, 9H), 1.56−1.71 (m, 3H), 1.83−2.03 (m, 2H), 2.21−2.39 (m, 2H), 2.56−2.78 (m, 1H), 3.65−3.71 (m, 1H), 3.96−4.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.05, −4.98, 14.2, 17.9, 19.0, 25.1, 25.7 (3C), 27.3, 28.1, and 28.3 (3C), 38.2, 56.7, 67.9, 79.8, 119.4, 155.5. MS (ESI, *m*/*z*): 391 ($M + Na^+$, 100). Anal. Calcd for $C_{19}H_{36}N_2O_3Si$: C, 61.91; H, 9.84; N, 7.60. Found: C, 61.91; H, 10.07; N, 7.87.

2-*epi*-**21b** (less polar diastereomer): colorless oil; $[\alpha]^{20}_D$ +7.8 (*c* 0.9, $CHCl_3$). IR (film) ν_{max} 2954, 2932, 2859, 2244, 1695, 1413, 1366, 1253 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.02−0.12 (m, 6H), 0.81−0.92 (m, 9H), 1.38−1.54 (m, 11H), 1.55−1.71 (m, 2H), 1.78−1.92 (m, 1H), 1.98−2.14 (m, 1H), 2.16−2.42 (m, 2H), 2.44−2.72 (m, 1H), 3.64−3.74 (m, 1H), 3.80−4.10 (m, 1H), 4.17−4.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, 14.1 and 14.2, 18.0, 19.9 and 20.3, 24.0 and 24.2, 25.7 (3C), 28.3 and 28.5 (3C), 28.7, 36.7 and 38.3, 54.6 and 55.4, 69.4 and 69.5, 80.0 and 80.3, 119.4 and 120.0, 154.8. MS (ESI, *m*/*z*): 391 ($M + Na^+$, 100). Anal. Calcd for $C_{19}H_{36}N_2O_3Si$: C, 61.91; H, 9.84; N, 7.60. Found: C, 61.72; H, 10.12; N, 7.92.

(7*S*,7a*R*/*S*)-7-(*tert*-Butyldimethylsilyloxy)pyrrolizidin-3-one (24a/b). To a solution of the diastereomeric mixture of **10a** and 2-*epi*-**10a** (203 mg, 0.51 mmol) in EtOAc (1.5 mL) was added a 2 N aqueous solution of HCl (1.0 mL, 2.0 mmol). The reaction mixture was stirred at rt for 2 h and concentrated under reduced pressure. The residue was dissolved in $EtOH/H_2O$ (4.0 mL/2.0 mL), and K_2CO_3 (141 mg, 1.0 mmol) was added. The reaction mixture was stirred for 48 h, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: $MeOH/CH_2Cl_2$ 1:10) to afford (7*S*,7a*S*/*R*)-7-hydroxy-pyrrolizidin-3-ones **23a**/**23b** as an inseparable diastereomeric mixture (dr = 88:12, determined by integral of ^1H NMR) in a combined yield of 96%: white solid. IR (film) ν_{max} 3279, 2981, 2894, 1659, 1441, 1369 cm^{-1}. MS (ESI, *m*/*z*): 164 ($M + Na^+$, 100%). (7*S*,7a*R*)-**23a**: A pure sample of **23a** was obtained via silylated derivative and the data are given in the subsequent section.

(7*S*,7a*S*)-**23b** (data read from spectrum of the diastereomeric mixture): ^1H NMR (400 MHz, $CDCl_3$) δ 1.88−2.02 (m, 1H), 2.05−2.46 (m, 4H), 2.56−2.68 (m, 1H), 3.00−3.09 (m, 1H), 3.50−4.07 (m, 4H including OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 34.5, 36.0, 39.4, 66.6, 69.0, 176.7.

To a diastereomeric mixture of **23a/b** (580 mg, 4.1 mmol), DMAP (cat.), TBSCl (930 mg, 6.2 mmol), and imidazole (560 mg, 8.2 mmol) was added anhydrous CH_2Cl_2 (25 mL). The reaction mixture was stirred for 24 h, quenched with water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford compound (7*S*,7a*R*)-**24a** (890 mg, yield 85%) and its diastereomer (7*S*,7a*S*)-**24b** (82 mg, yield 8%) (dr = 91:9). (7*S*,7a*R*)-**24a** (major diastereomer): colorless oil; $[\alpha]^{20}_D$ +38.1 (*c* 0.9, $CHCl_3$). IR (film) ν_{max} 2955, 2930, 2857, 1704, 1408, 1257 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.81 (s, 9H), 1.61−1.75 (m, 1H), 1.78−1.92 (m, 1H), 2.07−2.18 (m, 1H), 2.19−2.38 (m, 2H), 2.58 (ddd, *J* = 8.3, 10.0, 16.6 Hz, 1H), 3.05−3.17 (m, 1H), 3.48−3.57 (m, 1H), 3.62 (ddd app. q, *J* = 6.8 Hz, 1H), 3.75 (ddd app. q, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (CH_3), −4.8 (CH_3), 17.8 (C), 24.9 (CH_2), 25.5 (3C, CH_3), 34.1 (CH_2), 35.5 (CH_2), 39.7 (CH_2), 67.3 (CH), 76.5 (CH), 174.9 (CO). MS (ESI, *m*/*z*): 256 (M + H^+, 100). HRESIMS calcd for $[C_{13}H_{26}NO_2Si]^+$ (M + H^+): 256.1727; found: 256.1722.

(7*S*,7a*S*)-**24b** (minor diastereomer): colorless oil; $[\alpha]^{20}_D$ +31.1 (*c* 1.0, $CHCl_3$) {lit.[19] $[\alpha]^{20}_D$ +32.81 (*c* 1.045, $CHCl_3$)}. IR (film) ν_{max} 2955, 2930, 2857, 1698, 1404, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.83 (s, 9H), 1.86−2.14 (m, 4H), 2.32 (ddd, *J* = 4.2, 10.3, 16.8 Hz, 1H), 2.53 (ddd, *J* = 8.4, 8.4, 16.8 Hz, 1H), 3.00−3.10 (m, 1H), 3.50−3.63 (m, 1H), 3.74 (ddd, *J* = 2.7, 5.5, 8.1 Hz, 1H), 3.97−4.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1 (CH_3), −4.8 (CH_3), 17.7 (C), 18.0 (CH_2), 25.5 (3C, CH_3), 34.0 (CH_2), 36.1 (CH_2), 39.7 (CH_2), 66.5 (CH), 70.5 (CH), 177.0 (CO). MS (ESI, *m*/*z*): 256 (M + H^+, 100).

(7*S*,7a*R*)-7-Hydroxypyrrolizidin-3-one (23a). To a solution of pyrrolizidinone (7*S*,7a*R*)-**24a** (257 mg, 1.0 mmol) in EtOAc (3.0 mL) was added a 2 N HCl aqueous solution (2.0 mL, 4.0 mmol). The reaction mixture was stirred at rt for 2 h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1:10) to afford compound **23a** (132 mg, yield 94%) as a white solid: mp 113−114 °C (MeOH/CH_2Cl_2 1:10); $[\alpha]^{20}_D$ +19.4 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 3279, 2981, 2894, 1659, 1441, 1369 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.71−1.85 (m, 1H), 1.89−2.01 (m, 1H), 2.18−2.29 (m, 1H), 2.29−2.41 (m, 2H), 2.64 (ddd, *J* = 10.0, 10.0, 17.0 Hz, 1H), 3.12−3.23 (m, 1H), 3.58 (ddd, *J* = 7.6, 7.6, 11.8 Hz, 1H), 3.69 (s br, 1H, OH), 3.73 (ddd app. q, *J* = 7.0 Hz, 1H), 3.83−3.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (CH_2), 34.3 (CH_2), 35.3 (CH_2), 40.1 (CH_2), 67.5 (CH), 75.6 (CH), 175.6 (CO). MS (ESI, *m*/*z*): 164 (M + Na^+, 100). HRESIMS calcd for $[C_7H_{11}NO_2Na]^+$ (M + Na^+): 164.0682; found: 164.0677.

(1*S*,7a*R*)-1-Hydroxypyrrolizidine (25). To a suspension of LAH (114 mg, 3.0 mmol) in anhydrous THF (10 mL) was added a solution of pyrrolizidinone **23a** (141 mg, 1.0 mmol) in THF (3.0 mL) at 0 °C. The reaction was warmed to 40−50 °C and stirred overnight. The reaction was quenched by successive and careful addition of H_2O (0.12 mL), 15% NaOH (0.24 mL), and H_2O (0.12 mL) at −10 °C. The resulting mixture was filtered through Celite, washed with EtOAc (5.0 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2/ NH_3 aq. 4:6:1) to afford pyrrolizidine **25** (77 mg, 60% yield) as a pale yellow oil: $[\alpha]^{20}_D$ +22.5 (*c* 0.6, $CHCl_3$) {for the antipode, lit. $[\alpha]^{20}_D$ −26 (*c* 2.3, $CHC1_3$);[20a] $[\alpha]^{20}_D$ −31.6 (*c* 0.5, $CHC1_3$)[20b]}. IR (film) ν_{max} 3345, 2924, 2965, 1445, 1327, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.37−1.50 (m, 1H), 1.73−1.95 (m, 3H), 1.95−2.17 (m, 2H), 2.60 (ddd, *J* = 6.7, 8.0, 11.3 Hz, 1H), 2.74 (ddd, *J* = 4.7, 7.1, 11.3 Hz, 1H), 3.28 (ddd, *J* = 5.6, 5.6, 11.2 Hz, 1H), 3.44 (ddd, *J* = 6.6, 8.8, 11.2 Hz, 1H), 3.62 (ddd, *J* = 2.0, 7.8, 7.8 Hz, 1H), 4.05−4.12 (m, 1H), 4.98 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (CH_2), 30.2 (CH_2), 33.7 (CH_2), 52.6 (CH_2), 55.2 (CH_2), 72.7 (CH), 76.96 (CH). MS (ESI, *m*/*z*): 128 (M + H^+, 100). HRESIMS calcd for $[C_{14}H_{27}N_2O_2]^+$ (2 M + H^+): 255.2067; found: 255.2063

(8*S*,8a*R*)-8-Hydroxyindolizidin-3-one (26). To a solution of **21a** (65 mg, 0.16 mmol) in EtOAc (1.0 mL) was added a 2 N aqueous solution of HCl (0.35 mL, 0.70 mmol). The reaction mixture was stirred at rt for 2 h and concentrated under reduced pressure. The residue was dissolved in EtOH/H_2O (2.0 mL/1.0 mL) and treated with K_2CO_3 (44 mg, 0.32 mmol). The reaction mixture was stirred for 5 h, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1:20) to afford the known indolizidinone **26**[21] (13 mg, yield 52%) as a white wax: $[\alpha]^{20}_D$ +33.4 (*c* 0.4, $CHCl_3$) (no rotation data given in ref 21). IR (film) ν_{max} 3297, 2916, 2854, 1648, 1445, 1282 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.35−1.52 (m, 2H), 1.72−1.92 (m, 2H), 2.05−2.15 (m, 1H), 2.26−2.42 (m, 3H), 2.44−2.61 (m, 2H), 3.14−3.30 (m, 2H), 4.00−4.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.3, 30.2, 33.4, 39.3, 62.8, 73.2, 173.8. MS (ESI, *m*/*z*): 156 (M + H^+, 100).

(2*R*,3*R*,4*R*)-1-*tert*-Butyloxycarbonyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (32). To a solution of (3*S*,4*R*,5*R*)-5-benzyloxymethyl-1-(*tert*-butoxycarbonyl)-3,4-dibenzyloxy -pyrrolidin-2-one (**31**)[30] (1.00 g, 1.93 mmol) in MeOH (50 mL) was added $NaBH_4$ with vigorous stirring in two portions (220 mg, 5.79 mmol and 150 mg, 3.95 mmol) over 30 min at −13 °C. The reaction mixture was stirred for 30 min before addition of $NaHCO_3$ (10 mL) and brine (10 mL). The mixture was extracted with CH_2C1_2 (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **30** (980 mg, yield 98%) was obtained as a colorless oil. Without further purification and following the general procedure, the SmI_2-mediated coupling reaction of aza-hemiacetal **30** with ethyl acrylate afforded only the reduced product **32** in 60% yield as a colorless oil: $[\alpha]^{20}_D$ −32.0 (*c* 1.4, $CHCl_3$). IR (film) ν_{max} 3030, 2927, 1694, 1453, 1392, 1365, 1258, 1171, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.35−1.55 (2 m, 9H, $3CH_3$), 3.40−3.52 (m, 1H), 3.52−3.64 (m, 1H), 3.65−4.20 (m, 4H), 4.22 (m, 1H), 4.74−4.34 (m, 6H, 3 × $PhCH_2$), 7.40−7.22 (m, 15H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (3C), 50.4 and 51.3, 61.6 and 61.9, 68.6 and 69.0, 71.3, 73.1, 79.8, 80.5, 81.6, 83.1, 127.57, 127.62, 127.8, 127.9, 128.35, 128.43, 128.45, 137.7, 138.0, 138.6, 154.4, and 154.7. HRESIMS calcd for $[C_{31}H_{37}NO_5Na]^+$ (M + Na^+): 526.2564; found: 526.2560.

(2*R/S*,3*S*,4*R*,5*R*)-1-*tert*-Butyloxycarbonyl- 3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2-(pyridin-2-ylthio)pyrrolidine (33H/L). To a mixture of the aza-hemiacetal **30** (980 mg, 1.89 mmol), $CaCl_2$ (425 mg, 3.86 mmol), and 2-thiol-pyridine (322 mg, 2.90 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise $BF_3 \cdot Et_2O$ (0.24 mL, 1.93 mmol) under nitrogen atmosphere at 0 °C. The mixture was stirred for 1 h and allowed to warm to room temperature. After stirring at rt for another 3 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:8) to afford **33H** (295 mg, yield 25.5%) and its diastereomer **33L** (688 mg, yield 59.5%) (dr = 30:70). **33H** (minor and less polar diastereomer): colorless oil; $[\alpha]^{20}_D$ +53.1 (*c* 1.13, $CHCl_3$). IR (film) ν_{max} 3030, 2975, 2927, 2864, 1698, 1578, 1453, 1415, 1383, 1365, 1120, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04−1.40 (2 m, 9H), 3.42−3.55 (m, 1H), 3.68−3.95 (m, 1H), 4.00−4.25 (m, 2H), 4.33 (s, 1H), 4.34−4.85 (m, 6H), 6.24−6.42 (2 m, 1H), 6.85−6.92 (m, 1H), 7.05−7.15 (m, 1H), 7.15−7.32 (m, 15H), 7.35−7.45 (m, 1H), 8.35−8.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9 and 28.4 (3C), 63.2 and 63.6, 65.7 and 66.0, 68.2, 70.8, 71.5, 73.0, 80.5 and 80.6, 81.6, 83.2, 85.9, 87.5, 119.4, 122.4 and 122.9,

127.4, 127.5, 127.57, 127.62, 127.7, 128.3, 128.4, 135.9, 137.8, 137.9, 138.3, 138.6, 149.2, 153.9, 159.5. MS (ESI, *m*/*z*): 613 ($M + H^+$, 100).

33L (major and more polar diastereomer): colorless oil; $[\alpha]^{20}_D$ −160 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} 3030, 2924, 2863, 1705, 1578, 1454, 1415, 1210, 1124, 1186, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05−1.42 (m, 9H), 3.52−3.88 (m, 3H), 4.20−4.30 (m, 2H), 4.32−4.71 (m, 6H), 6.75−6.80 (m, 1H), 6.88−6.92 (m, 1H), 7.05−7.32 (m, 15H), 7.32−7.42 (m, 1H), 8.35−8.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (3C), 60.5, 72.7, 73.3, 80.6, 82.7, 119.9, 123.8, 127.4, 127.55, 127.63, 127.7, 127.8, 128.0, 128.3, 136.0, 137.7, 138.4, 149.3, 153.2. MS (ESI, *m*/*z*): 613 ($M + H^+$, 100). HRESIMS calcd for $[C_{36}H_{41}N_2O_5S]^+$ ($M + H^+$): 613.2731; found: 613.2723.

(2*R*,3*R*,4*R*,5*R*)-1-*tert*-Butyloxycarbonyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-[(2-ethyloxycarbonyl)ethyl]pyrrolidine (29). To a solution of the diastereomeric mixture **33H**/**L** (200 mg, 0.33 mmol), ethyl acrylate (0.08 mL, 0.65 mmol), and $BF_3 \cdot Et_2O$ (0.08 mL, 0.65 mmol) in anhydrous THF (10 mL) was added dropwise a freshly prepared *t*-BuOH-containing SmI_2 (13 mL, 1.30 mmol) at −60 °C. The reaction mixture was stirred for 30 min and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:6) to afford **29** (120 mg, yield 61%) as a colorless oil: $[\alpha]^{20}_D$ −36.4 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} 2977, 2931, 2864, 1734, 1693, 1454, 1391, 1366, 1255, 1175, 1096, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11−1.18 (m, 3H), 1.25−1.45 (2 m, 9H) 1.81−1.98 (m, 1H), 2.02−2.33 (m, 3H), 3.33−3.43 (m, 1H), 3.61−4.18 (m, 7H), 4.22−4.60 (m, 6H), 7.07−7.30 (m, 15H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 26.1, 27.2, 28.4, and 28.5 (3C), 31.7, 60.4, 62.6 and 62.8, 63.8 and 63.9, 67.9, 68.7, 70.98, 71.04, 71.2, 73.0, 77.4, 79.8 and 79.9, 81.6, 83.0, 83.6, 84.8, 127.47, 127.52, 127.6, 127.7, 127.8, 128.3, 128.4, 128.5, 137.7, 137.9, 138.3, 138.7, 153.8 and 154.0, 172.9, and 173.0. MS (ESI, *m*/*z*): 626 ($M + Na^+$, 100). Anal. Calcd for $C_{36}H_{45}NO_7$: C, 71.62; H, 7.51; N, 2.32. Found: C, 71.21; H, 7.40; N, 2.66.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolizidin-3-one (27). To a solution of pyrrolidine **29** (250 mg, 0.41 mmol) in EtOAc (2.0 mL) was added a 2 N aqueous solution of HCl (2.0 mL, 4.0 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. After warming to rt, the reaction mixture was stirred for another 2 h and concentrated under reduced pressure. The residue was dissolved in MeOH/H_2O (3.0 mL/1.5 mL), and K_2CO_3 (300 mg, 2.2 mmol) was added. The mixture was stirred for 2 days, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:1.5) to afford compound **27** (165 mg, yield 87%) as a colorless oil: $[\alpha]^{20}_D$ −25.6 (*c* 1.2, $CHCl_3$). IR (film) ν_{max} 3030, 2864, 1693, 1454, 1411, 1364, 1313, 1105, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (dddd, *J* = 7.3, 9.8, 10.0, 12.0 Hz, 1H), 2.17 (dddd, *J* = 2.3, 7.3, 10.0, 12.0 Hz, 1H), 2.28 (ddd, *J* = 2.3, 9.8, 16.8 Hz, 1H), 2.51 (ddd, *J* = 10.0, 10.0, 16.8 Hz, 1H), 3.47 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.56 (dd, *J* = 5.6, 9.7 Hz, 1H), 3.63 (dd, *J* = 4.8, 7.3 Hz, 1H), 3.82 (ddd app. q, *J* = 7.3 Hz, 1H), 3.99 (ddd, *J* = 4.2, 4.3, 5.6 Hz, 1H), 4.24 (dd, *J* = 4.2, 4.8 Hz, 1H), 4.38−4.55 (m, 6H), 7.17−7.30 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8 (CH_2), 33.3 (CH_2), 58.6 (CH), 63.8 (CH), 69.4 (CH_2), 72.2 (CH_2), 72.4 (CH_2), 73.3 (CH_2), 87.1 (CH), 89.2 (CH), 127.66 (CH), 127.69 (CH), 127.8 (CH), 127.90 (CH), 127.92 (CH), 128.39 (CH), 128.4 (CH), 128.5 (CH), 137.8 (C), 137.9 (C), 138.0 (C), 174.8 (CO). MS (ESI, *m*/*z*): 458 ($M + H^+$, 100).

(1*R*,2*R*,3*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-pyrrolizidine (34). To a suspension of LAH (9 mg, 0.25 mmol) in anhydrous THF (3.0 mL) was added dropwise a solution of pyrrolizidinone **27** (60 mg, 0.13 mmol) in THF (2.0 mL) at 0 °C under an argon atmosphere. The reaction mixture was refluxed for 5 h and quenched by successive and careful addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (0.5 mL) at −10 °C. After 1 h of stirring, solid Na_2SO_4 was added, and the mixture was stirred for another 1 h. The mixture was filtered through Celite and washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: EtOAc/PE 1:2−1:1) to give **34** (46 mg, yield 79%) as a white solid: mp 48−49 °C (EtOAc/PE 1:1) (lit.[24h] mp 48−49 °C); $[\alpha]^{20}_D$ −2.9 (*c* 0.7, $CHCl_3$) {$[\alpha]^{20}_D$ −5 (*c* 1, $CHCl_3$);[24d] $[\alpha]^{20}_D$ −2.9 (*c* 0.7, $CHCl_3$)[24h]}. IR (film) ν_{max} 3030, 2864, 1496, 1454, 1365, 1206, 1113, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.47−1.58 (m, 1H), 1.60−1.70 (m, 1H), 1.70−1.82 (m, 1H), 1.82−1.92 (m, 1H), 2.66 (ddd, *J* = 6.6, 6.7, 10.6 Hz, 1H), 2.85 (ddd, *J* = 4.6, 5.8, 7.3 Hz, 1H), 2.94 (ddd, *J* = 6.0, 6.2, 10.6 Hz, 1H), 3.36 (ddd, *J* = 5.9, 6.8, 6.9 Hz, 1H), 3.42 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.49 (dd, *J* = 4.6, 9.6 Hz, 1H), 3.70 (dd, *J* = 5.9, 6.1 Hz, 1H), 3.97 (dd, *J* = 6.1, 7.3 Hz, 1H), 4.39−4.61 (m, 6H), 7.11−7.29 (m, 15H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (CH_2), 31.5 (CH_2), 55.0 (CH_2), 67.3 (CH), 68.2 (CH), 71.7 (CH_2), 72.0 (CH_2), 72.4 (CH_2), 73.1 (CH_2), 85.6 (CH), 88.7 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 138.1 (C), 138.35 (C), 138.39 (C). MS (ESI, *m*/*z*): 444 ($M + H^+$, 100). HRESIMS calc for $[C_{29}H_{34}NO_3]^+$ ($M + H^+$): 444.2533; found: 444.2531.

Hyacinthacine A_2 (2). To a solution of pyrrolizidine **34** (120 mg, 0.28 mmol) in methanol (10 mL) was added Pd/C 10% (50 mg). After purging with hydrogen, 10 drops of HCl (6 N) were added. The suspension was stirred for 4 days at room temperature under 1 atm of hydrogen. The mixture was filtered through Celite and washed with MeOH. The filtrate was neutralized with DOWEX 1 × 8 resin (OH^- form) and filtered. The filtrate was concentrated under reduced pressure to give hyacinthacine A_2 (**2**) (38 mg, yield 81%) as a colorless oil: $[\alpha]^{20}_D$ +10.6 (*c* 1.64, H_2O) {$[\alpha]^{25}_D$ +12.5 (*c* 0.4, H_2O);[24a] $[\alpha]^{25}_D$ +12.7 (*c* 0.13, H_2O);[24b] $[\alpha]^{25}_D$ +10.5 (*c* 0.6, H_2O);[24c] $[\alpha]^{20}_D$ +11.2 (*c* 0.52, H_2O)[24e]}. IR (film) ν_{max} 3354, 2956, 2920, 2866, 1124 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 1.67−1.96 (m, 4H), 2.66 (ddd, *J* = 3.9, 6.6, 9.0 Hz, 1H), 2.70 (td, *J* = 5.6, 11.0 Hz, 1H), 2.86 (ddd, *J* = 5.9, 7.1, 11.0 Hz, 1H), 3.11 (td, *J* = 4.4, 7.4 Hz, 1H), 3.61 (dd, *J* = 6.6, 11.6 Hz, 1H), 3.66−3.77 (m, 3H); ^{13}C NMR (100 MHz, D_2O) δ 27.3 (CH_2), 32.6 (CH_2), 57.6 (CH_2), 65.9 (CH_2), 68.8 (CH), 71.9 (CH), 80.1 (CH), 83.0 (CH). HRESIMS calcd for $[C_8H_{16}NO_3]^+$ ($M + H^+$): 174.1125; found: 174.1130.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-[5,6,7,7*a*]-tetrahydropyrrolizin-3-one (28). To a stirring solution of LDA (0.48 mmol) in THF (1.0 mL) [prepared by adding a solution of 2.5 N *n*-BuLi in *n*-hexane (0.19 mL, 0.48 mmol) to *i*-Pr_2NH (0.075 mL, 0.53 mmol)] was added dropwise a solution of pyrrolizidinone **27** (100 mg, 0.22 mmol) in THF (1.0 mL) over 5 min under N_2 atmosphere at −78 °C. After 10 min of stirring, a solution of PhSeBr (57 mg, 0.24 mmol) in THF (1.0 mL) was added rapidly. The mixture was stirred for 30 min and quenched with a saturated aqueous solution of $NaHCO_3$ (1.0 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6.0 mL), and H_2O_2 (30%) was added dropwise until the phenylselenylated intermediate disappeared. The reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 2:3) to afford compound **28** (71 mg, yield 71%) as a colorless oil and recovered starting material **27** (10 mg, 10%): $[\alpha]^{20}_D$ +45.6 (*c* 1.4, $CHCl_3$). IR (film) ν_{max} 3062, 3029, 2864, 1692, 1461, 1360, 1098, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (dd,

J = 6.4, 8.2 Hz, 1H), 3.64 (dd, J = 3.8, 9.9 Hz, 1H), 3.70 (dd, J = 5.0, 9.9 Hz, 1H), 3.97−4.03 (m, 1H), 4.28 (d, J = 8.2 Hz, 1H), 4.72−4.76 (m, 7H), 6.06 (dd, J = 1.5, 5.8 Hz, 1H), 6.96 (dd, J = 1.8, 5.8 Hz, 1H), 7.45- 7.25 (m, 15H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.4 (CH), 68.8 (CH), 70.2 (CH_2), 72.6 (CH_2), 73.1 (CH_2), 73.3 (CH_2), 85.8 (CH), 88.9 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 137.4 (C), 137.8 (C), 137.9 (C), 147.4 (CH), 174.2 (CO). HRESIMS calcd for $[C_{29}H_{30}NO_4]^+$ ($M + H^+$): 456.2169; found: 456.2167.

(1*S*,2*S*/*R*,5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1,2-dihydroxypyrrolizidin-3-one (35 and 36). *Dihydroxylation with OsO_4/NMO.* To a stirring solution of α,β-unsaturated pyrrolizidinone **28** (70 mg, 0.15 mmol) in *tert*-butyl alcohol/water (1:1, 2.0 mL) were added 4-methylmorpholine *N*-oxide (20 mg, 0.17 mmol), citric acid (32 mg, 0.15 mmol), and OsO_4 (0.01 mL, 2 mM in water, 0.02 mmol). The reaction mixture was stirred at rt for 24 h (the color changed from bright green to a pale yellow). The reaction was quenched with a saturated aqueous solution of Na_2SO_3 (2.0 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 3:1) to afford compound **35** (42 mg, yield 56%) and its diastereomer **36** (28 mg, yield 37%) (dr = 60:40). Compound **35** (major diastereomer): white wax; $[\alpha]^{20}_D$ −51.1 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 3333, 2993, 2950, 1678, 1462, 1366, 1261, 1115, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (d, J = 9.0 Hz, 1H), 3.54 (dd, J = 4.6, 9.8 Hz, 1H), 3.61 (dd, J = 6.2, 9.8 Hz, 1H), 3.82−3.88 (m, 2H), 4.01−4.09 (m, 2H), 4.20 (d, J = 6.0 Hz, 1H), 4.27−4.32 (m, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.54 (s, 2H), 4.56 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 5.17 (s br, 1H), 7.42- 7.22 (m, 15H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.9 (CH), 68.3 (CH_2), 71.0 (CH), 71.9 (CH_2), 72.0 (CH), 72.1 (CH_2), 73.2 (CH), 73.3 (CH_2), 86.2 (CH), 86.4 (CH), 127.6 (CH), 127.7 (CH), 127.83 (CH), 127.86 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 137.4 (C), 137.6 (C), 137.8 (C), 172.5 (CO). MS (ESI, m/z): 512 ($M + Na^+$, 100). HRESIMS calcd for $[C_{29}H_{32}NO_6]^+$ ($M + H^+$): 490.2224; found: 490.2239.

Compound **36** (minor diastereomer): white solid; mp 103−105 °C (EtOAc/PE 3:1); $[\alpha]^{20}_D$ −2.5 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 3345, 2993, 2922, 2851, 1688, 1453, 1378, 1130, 1083 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s br, 1H), 3.25 (s br, 1H), 3.52 (dd, J = 4.0, 9.9 Hz, 1H), 3.61 (dd, J = 5.3, 9.9 Hz, 1H), 3.83 (dd, J = 3.5, 6.3 Hz, 1H), 4.03 (dd, J = 4.6, 9.1 Hz, 1H), 4.27−4.42 (m, 4H), 4.27−4.32 (m, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.54−4.67 (m, 4H, PhCH), 7.20−7.42 (m, 15H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.6 (CH), 65.4 (CH), 68.2 (CH_2), 69.4 (CH), 72.4 (CH_2), 72.8 (CH_2), 73.2 (CH_2), 73.4 (CH), 80.7 (CH), 84.3 (CH), 127.65 (CH), 127.71 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.38 (CH), 128.41 (CH), 128.44 (CH), 137.6 (C), 137.86 (C), 137.9 (C), 172.9 (CO). MS (ESI, m/z): 512 ($M + Na^+$, 100). HRESIMS calcd for $[C_{29}H_{32}NO_6]^+$ ($M + H^+$): 490.2224; found: 490.2228.

Dihydroxylation with $KMnO_4$/18-crown-6. A solution of α,β-unsaturated pyrrolizidinone **28** (60 mg, 0.13 mmol) and 18-crown-6 (8.7 mg, 0.033 mmol) in DCM (0.8 mL) was cooled to −10 °C. Next, 12.5 mg (0.08 mmol) of powdered $KMnO_4$ was added in one portion, and the dark mixture was stirred briskly. After 3 h, an additional 12.5 mg (0.08 mmol) of powdered $KMnO_4$ was added in one portion. After being stirred for 13 h, the reaction was quenched at −10 °C by addition of 1.0 mL of saturated aqueous Na_2SO_3 while stirring briskly. The cooling bath was removed, and a saturated aqueous solution of citric acid added dropwise until the brown color disappeared. After 5.0 mL of DCM was added, the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5.0 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 3:1) to afford diastereomer **35** (6 mg, 9%) as a white wax, and diastereomer **36** (35 mg, 55%) as a white solid.

(−)-Uniflorine A (3). To a suspension of LAH (3.8 mg, 0.1 mmol) in anhydrous THF (1.0 mL) was added a solution of compound **35** (20 mg, 0.04 mmol) in THF (1.0 mL) at 0 °C under an argon atmosphere. The reaction mixture was refluxed for 5 h and quenched by successive and careful addition of H_2O (0.1 mL), 15% NaOH (0.1 mL), and H_2O (0.3 mL) at −10 °C. After stirring for 20 min, Na_2SO_4 was added, and the resulting mixture was stirred for 1 h. The mixture was filtered through Celite and washed with EtOAc (2.0 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (1.0 mL), and $PdCl_2$ (11 mg, 0.06 mmol) was added. The mixture was stirred at rt under 1 atm of hydrogen for 12 h, filtered through Celite, washed with MeOH, and concentrated under reduced pressure. The residue was dissolved in water, washed with CH_2Cl_2 (2 × 2.0 mL), and purified through a column of Amberlyst (OH^-) A-26 resin (eluent: H_2O) to afford uniflorine A (**3**) (6.5 mg, yield 78%) as a white solid: mp 177−180 °C (MeOH) (mp 174−178 °C;[25] mp 177−180 °C[27b]); $[\alpha]^{20}_D$ −6.7 (*c* 0.42, H_2O) {lit.[27b] $[\alpha]^{21}_D$ −6.9 (*c* 0.415, H_2O)}. IR (film) ν_{max} 3374, 2963, 2909, 2847, 1379, 1262, 1092, 1022 cm^{-1}. ^{1}H NMR (400 MHz, D_2O) δ 2.76 (m, 1H), 2.98 (dd, J = 5.3, 12.0 Hz, 1H), 3.04 (dd, J = 5.6, 12.0 Hz, 1H), 3.14 (dd, J = 4.8, 7.5 Hz, 1H), 3.62 (dd, J = 6.5, 11.7 Hz, 1H), 3.77 (dd, J = 3.7, 11.7 Hz, 1H), 3.79 (dd, J = 8.3, 8.3 Hz, 1H), 3.94 (dd, J = 7.5, 8.3 Hz, 1H), 4.18 (dd, J = 4.8, 4.8 Hz, 1H), 4.36 (ddd, J = 4.8, 5.3, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 57.8 (CH_2), 63.1 (CH_2), 70.4 (CH), 71.5 (CH), 72.1 (CH), 75.9 (CH), 77.8 (CH), 79.1(CH). MS (ESI m/z): 206 ($M + H^+$, 100%). HRESIMS calcd for $[C_8H_{16}NO_5]^+$ ($M + H^+$): 206.1023; found: 206.1024.

***7-epi*-Casuarine (*7-epi*-Uniflorine B) (37).** To a suspension of LAH (3.8 mg, 0.1 mmol) in anhydrous THF (1.0 mL) was added a solution of compound **36** (20 mg, 0.04 mmol) in THF (1.0 mL) at 0 °C under an argon atmosphere. The reaction mixture was refluxed for 5 h and quenched by successive and careful addition of H_2O (0.1 mL), 15% NaOH (0.1 mL), and H_2O (0.3 mL) at −10 °C. After 20 min of stirring, Na_2SO_4 was added, and the resulting mixture was stirred for 1 h. The mixture was filtered through Celite and washed with EtOAc (2.0 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (1.0 mL), and $PdCl_2$ (11 mg, 0.06 mmol) was added. The mixture was stirred at rt under 1 atm of hydrogen for 12 h. The mixture was filtered through Celite and washed with MeOH, and the filtrate was concentrated under reduced pressure. The residue was dissolved in water, washed with CH_2Cl_2 (2 × 2.0 mL), and purified through a column of Amberlyst (OH^-) A-26 resin (eluent: H_2O) to afford 7-*epi*-casuarine (**37**) (5 mg, yield 60%) as a white wax: $[\alpha]^{20}_D$ +6.1 (*c* 0.62, H_2O) {lit.[35] $[\alpha]^{22}_D$ +6.2 (*c* 0.65, H_2O)}. IR (film) ν_{max} 3443, 2916, 1260, 1092, 1020 cm^{-1}. ^{1}H NMR (400 MHz, D_2O) δ 2.60 (dd app. t, J = 9.8, 9.8 Hz, 1H), 2.79 (ddd, J = 3.5, 6.6, 9.9 Hz, 1H), 3.23 (dd, J = 4.2, 8.0 Hz, 1H), 3.26 (dd, J = 6.5, 9.8 Hz, 1H), 3.58 (dd, J = 6.6, 11.8 Hz, 1H), 3.78 (dd, J = 3.5, 11.8 Hz, 1H), 3.84 (dd, J = 8.0, 9.9 Hz, 1H), 4.14 (dd, J = 3.9, 4.2 Hz, 1H), 2.79 (ddd, J = 3.9, 6.5, 9.8 Hz, 1H), 4.37 (dd, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 56.8 (CH_2), 63.3 (CH_2), 69.0 (CH), 70.6 (CH), 71.6 (CH), 73.9 (CH), 74.1 (CH), 78.6(CH). HRESIMS calc for $[C_8H_{15}NO_5Na]^+$ ($M + Na^+$): 228.0842; found: 228.0840.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of all new compounds; H^1-H^1 COSY and NOESY spectra of compounds **34** and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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