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A Short Route toward Chiral, Polyhydroxylated Indolizidines and Quinolizidines

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In this paper, a rapid route toward functionalized bicyclic alkaloids is presented. In only three steps, an easily accessible carbohydrate derivative was converted into iodomethyl indolizidine **13**, which can equilibrate to the corresponding iodoquinolizidine **15**. We provide strong evidence that this equilibration proceeds via an aziridinium ion intermediate. Furthermore, nucleophilic substitution of the iodomethyl indolizidine as well as the aziridinium intermediate gives access to highly functionalized indolizidine and quinolizidine alkaloids.

Introduction

Azasugars, polyhydroxylated alkaloids such as deoxynojirimicin (**1a**), alexine (**2**), and lentiginosine (**3**), have found wide attraction both as synthetic targets[1,2] and as potential therapeutic agents for the treatment of a variety of diseases (Figure 1).[3] The latter is illustrated by the recent approval of the synthetic azasugar *N*-butyldeoxynojirimicin (**1b**) as a drug for the treatment of the lysosomal storage disorder Gaucher disease.[4]

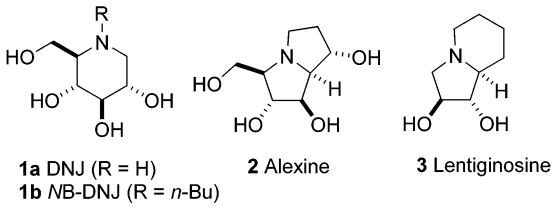

FIGURE 1. Examples of polyhydroxylated alkaloids.

In the past few years, our laboratory demonstrated the merit and potency of ring-closing metathesis (RCM) in the construction of carbocycles,[5] azasugars,[6] spiroketals,[7] and pyranopyran systems[8] starting from readily available sugar derivatives. In a recent publication on analogues of 2-deoxystreptamine,[9] we showed (see Scheme 1) that 1,7-diene **5a** (R^1 = benzyl), obtained from the methyl furanoside **4** via a three-step one pot Vasella−Barbier tandem reaction,[10] could be converted (see pathway a)

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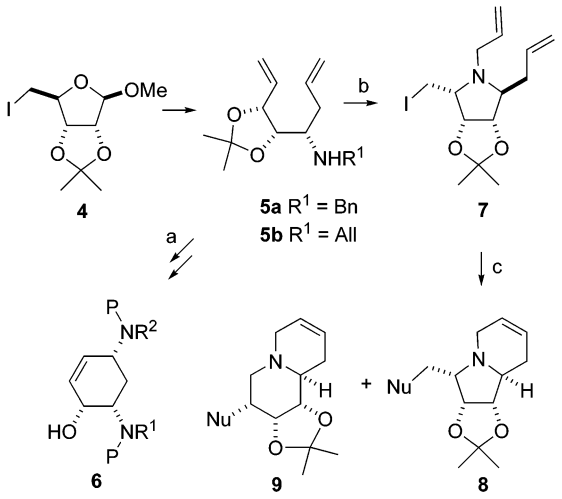
SCHEME 1[a]



[a] P = protective group. Key: (a) RCM and Pd(0)-catalyzed amination; (b) iodoamination; (c) RCM and nucleophilic substitution.

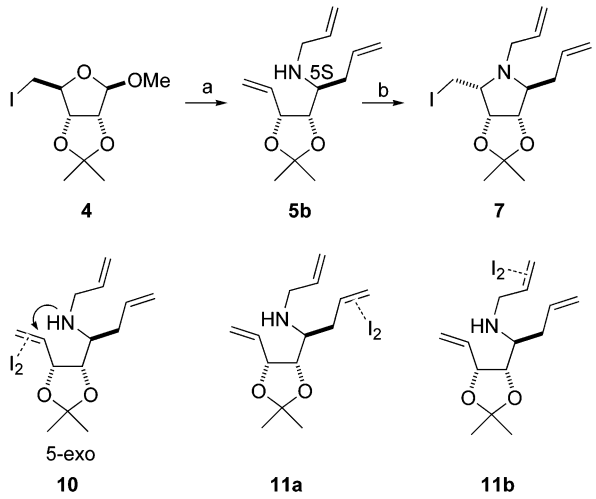
into 4,6-diamino cyclohexene derivatives **6** using RCM followed by a highly stereoselective Pd(0)-catalyzed amination.

We here report that 1,7-diene **5b** (R^1 = allyl) undergoes a regioselective iodoamination resulting in the pyrrolidine derivative **7** that, after RCM and nucleophilic substitution, is readily transformed into the functionalized indolizidines **8** and quinolizidines **9**. Moreover, we provide evidence that the quinolizidines are formed via an aziridinium ion intermediate.

Results and Discussion

The easily accessible[11] methyl 5-iodo-5-deoxy-2,3-isopropylidene-β-D-ribofuranoside **4** was subjected (Scheme 2) under optimal conditions[12] to the Vasella−Barbier tandem reaction to furnish the homogeneous triene **5b** in 63% yield. The configuration of the newly introduced stereogenic center in **5b** was the same as observed for the earlier reported *N*-benzyl-protected diene derivative **5a**[9,10] (see below for assignment by NMR after derivatization). The next step involving intramolecular iodoamination[13,14] of **5b** led to the exclusive isolation of pyrrolidine **7** in a yield of 87%. Selective haloamination of the particular double bond in triene **5b**, proceeding via an *exo-trig* process[15] on π-complex[16] **10**, can be explained by the favorable cyclization of five-membered rings, which excludes the possible formation of three- and four-membered azacycles (aziridines and azetidines) through putative species **11a** and **11b** (Scheme 2). The observed

SCHEME 2[a]



[a] Reagents and conditions: (a) Zn (excess), THF, TMSCl (1 equiv), sonication, 30−40 °C, then allylamine, then allyl bromide (63%); (b) I_2, $NaHCO_3$, dioxane/H_2O, 0 °C (87%).

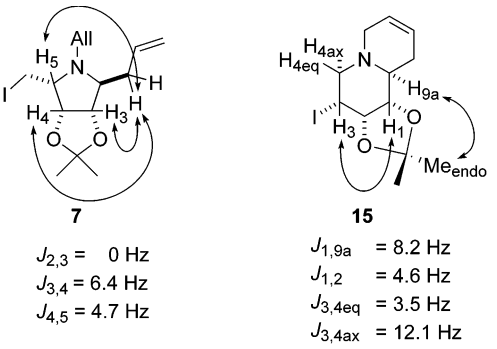


FIGURE 2. ^3J and NOE couplings observed in **7** and **15**.

cis stereoselectivity, assigned by NMR spectroscopy (vide infra), is in accordance with literature studies that describe the directing effect of an allylic hydroxyl or ether functionality during halocyclizations.[17]

The configurations of the newly introduced stereocentra in **7** originating from the Barbier allylation and iodoamination were assigned on the basis of NMR spectroscopy. The values of the proton coupling constants of pyrrolidine **7** (see Figure 2) were in good accord with those of isopropylidene-protected L-lyxose-α-C-glycosides,[18] indicating a 2,3-trans and 4,5-cis relationship. The 2*S*,5*R* configuration was irrefutably corroborated by NOESY experiments, which showed the presence of distinct NOE couplings in compound **7** between the allylic proton and H3, H4, and H5 (Figure 2).

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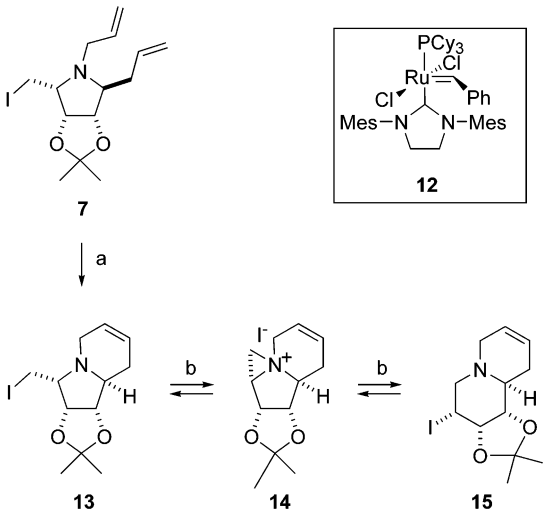
SCHEME 3[a]

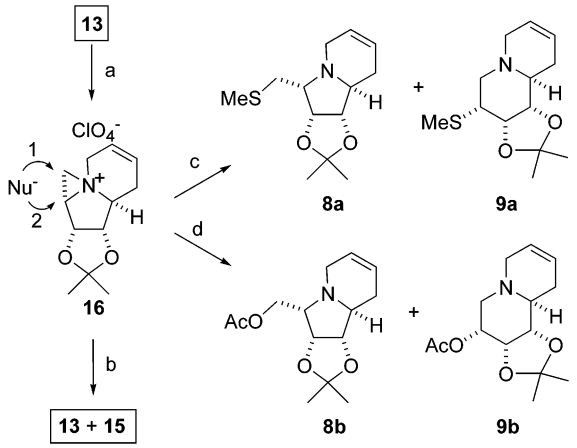


[a] Reagents and conditions: (a) Grubbs' catalyst **12** (1 mol %), camphorsulfonic acid (1.1 equiv), DCM (79%); (b) Δ, DCM (ratio **13**/**15** = 1:2).

At this stage, RCM of **7** using Grubbs' catalyst **12**[19] was undertaken. Free amines are not fully compatible with the ring-closing metathesis reaction due to deactivation of the catalyst by the basic nitrogen. It has been demonstrated, however, that the Grubbs' catalyst **12** tolerates the presence of ammonium salts.[20] Indeed, RCM of **7** using catalyst **12** (1 mol %) in the presence of 1.1 equiv of camphorsulfonic acid proceeded uneventfully at 10−15 °C to give, after purification, the expected indolizidine **13** in 79% yield (Scheme 3).

Interestingly, TLC analysis of a solution of **13** in DCM, accidentally left at room temperature for several days, showed the presence of an additional compound, which could be easily purified by column chromatography. NMR data (see Figure 2)[21] of the homogeneous product were in full accord with the structure of the quinolizidine **15**. Analysis by NMR spectroscopy of the above-mentioned mixture revealed the presence of **13** and **15** in a 1:2 ratio.[22] Moreover, rearrangement of pure **15** under the same conditions gave a similar ratio between **13** and **15**. The thus-established equilibrium may be explained to occur via the intermediate aziridinium[23] ion **14** (Scheme 3) resulting from an intramolecular substitution of the primary iodide by the ring nitrogen in **13**. Ring-opening of the aziridinium ion **14** by attack of the iodide counterion on the most substituted carbon atom will eventually lead to the thermodynamically more stable quinolizidine **15**.

SCHEME 4. Substitution on Aziridinium Perchlorate 16[a]



[a] Reagents and conditions: (a) $AgClO_4$, THF; (b) Bu_4NI (3 equiv), 76%, **13**/**15** = 1:2; (c) NaSMe (3 equiv), 59%, **8a**/**9a** = 1:2; (d) Bu_4NOAc (3 equiv), 53%, **9b**/**9b** = 1:2.

It was envisaged that ring-opening of aziridinium salt **16** (see Scheme 4) with iodide as well as other nucleophiles would provide evidence in support of the proposed aziridinium ion **14**. To this end, we first examined by NMR spectroscopy the feasibility of preparing **16** by exchange of the iodide in the proposed aziridinium **14** with the non-nucleophilic perchlorate ion.[24] Thus, a solution of the indolizidine **13** in $CDCl_3$ was reacted with an excess of $AgClO_4$. After vigorous mixing and sedimentation of precipitated silver iodide, TLC analysis revealed the absence of starting material **13** and the presence of a product with zero mobility, as would be expected for the positively charged compound **16**. The latter was also substantiated by the ^1H NMR spectrum of the sample, which showed a considerable downfield shift of all protons (Figure 3). The presence in **16** of an intact five−six fused ring system is in accord with the splitting pattern and coupling constants which are similar to those observed in the indolizidine **13**. In addition, the ^{13}C spectrum showed a downfield shift of C-9 from 1.7 ppm in indolizidine **13** to 45.9 ppm in **16**, which strongly supports the presence of a bond between N-4 and C-9.[21]

The identity of the aziridinium perchlorate **16** was independently corroborated by analysis of the products resulting from its substitution with different nucleophiles (Scheme 4). It was found that silver perchlorate easily

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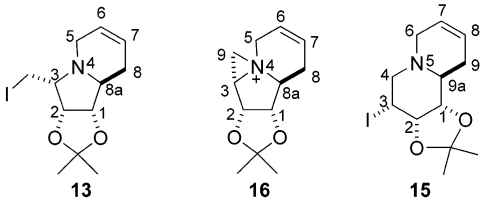
(21) The atom numbering of the bicyclic structures is depicted below. For convenience, the aziridinium ion was numbered in the same manner as compound **13**.



(22) The same ratio was found after refluxing **13** in DCM for 2 days.

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(24) See for a review on the preparation and reactions of aziridinium salts: Crist, D. R.; Leonard, N. J. *Angew. Chem.* **1969**, *81*, 953−1008.

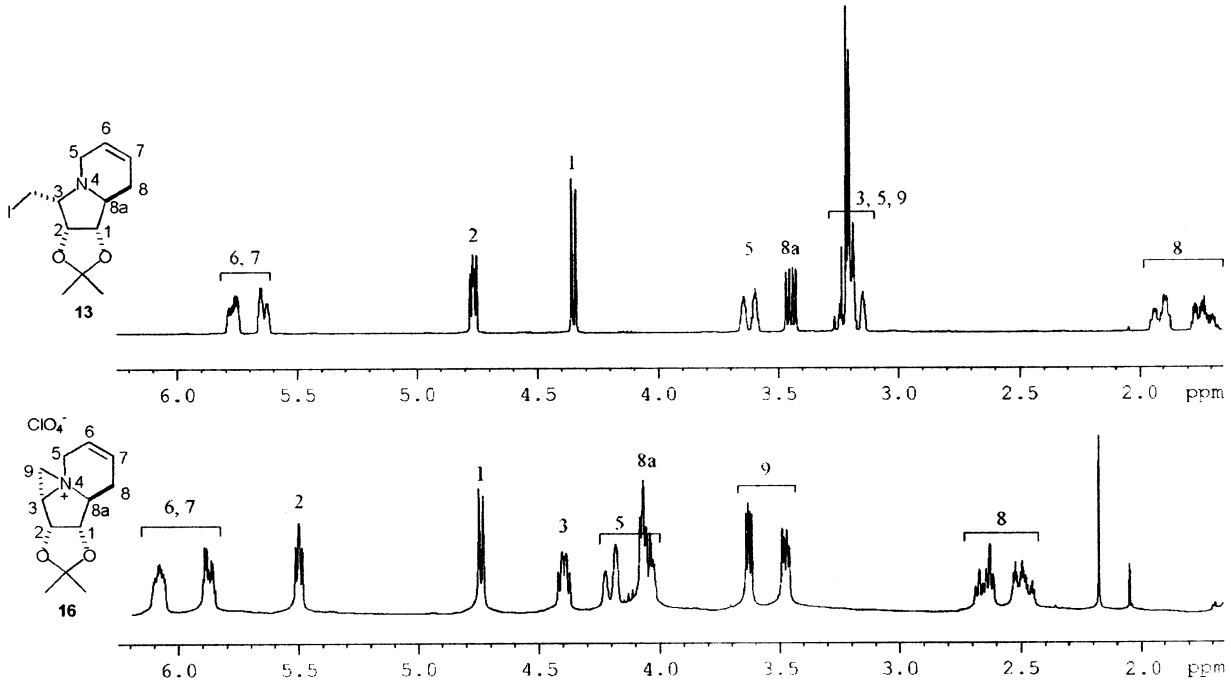


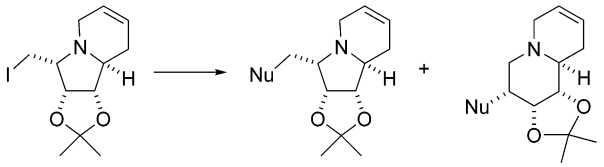
FIGURE 3. ^{1}H NMR spectra (400 MHz) of **13** and **16** in $CDCl_3$.

dissolves in THF and not in chloroform. Therefore, the use of THF allowed the amount of silver perchlorate to be reduced to 1.1 equiv. The addition of tetrabutylammonium iodide to a solution of **16**, obtained after removal of precipitated silver iodide, gave indolizidine **13** and quinolizidine **15** in a 1:2 ratio, the same ratio as earlier observed in the equilibration of **13** and **15**. The outcome of the substitution reaction presents solid evidence for the occurrence of the aziridinium ion **14** as an intermediate species.

Interestingly, the ring-opening of **16** (Scheme 4) with the methylthiolate anion gave indolizidine **8a** and quinolizidine **9a** in a 1:2 ratio, while ring-opening using the acetate ion produced compounds **8b** and **9b** in a similar 1:2 ratio. In these particular cases, the purified substitution products **8a**,**b** and **9a**,**b** were stable during prolonged heating. Therefore, the product distributions reflect the kinetics of substitution of **16** and not the thermodynamic stability of the products. The formation of quinolizidines as major products indicates a preferential attack of the nucleophile at the most substituted carbon atom C-3 (pathway 2, Scheme 4). This can be explained by the development of a partial positive charge in the transition state, which is more stabilized at the most substituted carbon atom in the aziridinium moiety. Moreover, the larger relief of ring strain may well favor pathway 2. On the other hand, the formation of indolizidines **8a**,**b** via pathway 1 (Scheme 4) strongly suggests that transition states of both pathways do not considerably differ in energy.

It occurred to us that nucleophilic displacement of the primary iodide in the indolizidine **13** with different nucleophiles would give access to functionalized indolizidines and quinolizidines. It was anticipated that reaction of **13** with soft nucleophiles would predominantly proceed via direct substitution on the soft electrophilic primary carbon atom. On the other hand, relatively hard nucleophiles may lead to the formation of quinolizidines via aziridinium ion **14** due to competition with the ring nitrogen in **13**.

TABLE 1. Substitution of Indolizidine 13[a]



entry	nucleophile	yield (%)	products	ratio **8**/**9**
1	NaSMe	78	**8a**	1:0
2	CsOAc	79	**8b** + **9b**	1:2.5
3	NaN_3	74	**8c** + **9c**	1:3.5
4	phthalimide, potassium salt	84	**8d** + **9d**	1:1

[a] All reactions were performed with 3 equiv of nucleophile in DMF. The mixtures were stirred for 2 h (entry 1) or overnight (entries 2−4).

Substitution of **13** with the soft nucleophile sodium methylthiolate in DMF produced indolizidine **8a** exclusively and in a satisfactory yield of 78% (Table 1, entry 1). In contrast, the use of cesium acetate (entry 2) led to the formation of indolizidine **8b** and quinolizidine **9b** in a ratio of 1:2.5 in 79% yield. A similar result was obtained using the azide ion as a nucleophile, yielding indolizidine **8c** and quinolizidine **9c** in a 1:3.5 ratio (entry 3). Interestingly, the relatively softer phthalimide anion (entry 4) led to a 1:1 ratio of compounds **8d** and **9d**. The latter ratio is probably a result from direct substitution of the iodide as well as substitution of the aziridinium ion.

Conclusion

In this paper, the application of a Vasella−Barbier tandem reaction in combination with an intramolecular

iodoamination and RCM results in a rapid route toward chiral, polyhydroxylated indolizidines and quinolizidines. First, furanoside **4** was converted into iodomethyl indolizidine **13** in 43% overall yield. Thermal equilibration of indolizidine **13** gives a mixture of **13** and **15** in a 1:2 ratio. The latter process proceeds via an aziridinium ion as demonstrated by the synthesis, NMR characterization and ring-opening of aziridinium perchlorate **16** with different nucleophiles. In addition, functionalization of compound **13** by nucleophilic substitution gave access to several indolizidine and quinolizidine alkaloids.

It is well-known that the Vasella−Barbier tandem reaction is generally applicable on numerous ω-iodoglycosides.[10] Therefore, the route presented in this paper opens the way to the design and synthesis of a wide variety of polyhydroxylated alkaloids comprising different functionalities and stereochemistry.

Experimental Section

(3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-(*N*-allylamino)octa-1,7-diene-3,4-diol (5b). A solution of methyl 5-iodo-5-deoxy-2,3-isopropylidene-β-D-ribofuranoside **4** (1.57 g; 5 mmol) in THF (25 mL) was placed in a sonication bath, and finely powdered Zn (1.5 g; excess) was added. After 15 min, 1.0 equiv of TMSCl was added dropwise. After additional sonication for 5 h, TLC indicated complete conversion of **4** into a lower running product. Allylamine (1.88 mL; 25 mmol; 5 equiv) was added, and sonication was continued for 2 h. Allyl bromide (1.29 mL; 15 mmol; 3 equiv) was added during a 2 h period by the use of a syringe pump. After TLC indicated conversion of the intermediate aldehyde into a higher running product, the reaction mixture was filtered over Hyflo and concentrated. Diluted NH_4Cl was added, and the mixture was extracted with EtOAc (3×). Combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Column chromatography (5 → 25% EtOAc in light petroleum ether) afforded the title compound as a slightly yellow oil (751 mg; 3.17 mmol; 63%). $[\alpha]^{20}_D$: 34.4 (c = 1.0, $CHCl_3$). IR (neat): ν 2985, 1639, 1369, 1215, 995, 914. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_H 5.93−5.74 (m, 3H, H2, H7 and CH All), 5.39−5.01 (m, 6H, H1, H8 and $=CH_2$ All), 4.62 (t, 1H, H3, J = 6.6 Hz), 4.01 (dd, 1H, H4, J = 6.6, 8.0 Hz), 3.30 (dd, 1H C*H*H All, J = 5.8, 13.2 Hz), 3.13 (dd, 1H, CH*H* All, J = 5.8, 13.2 Hz), 2.78−2.69 (m, 1H, H5), 2.42−2.23 (m, 2H, H6), 1.48 (s, 3H, Me isoprop), 1.35 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 136.8, 134.7, 134.2 (C2, C7, CH All), 117.8, 117.2, 115.4 (C1, C8, $=CH_2$ All), 107.9 (C_q isoprop), 78.9, 78.6 (C3, C4), 55.3 (C5), 49.4 (CH_2 All), 34.0 (C6), 27.6, 25.1 (Me isoprop). ES-MS: m/z 238.2 $[M + H]^+$. HRMS: found MH^+ 238.1848, $C_{14}H_{24}NO_2^+$ requires 238.1801.

(2*S*,3*S*,4*R*,5*R*)-1, 2-Diallyl-5-iodomethyl-3,4-*O*-isopropylidenepyrrolidine-3,4-diol (7). To a solution of compound **5b** (1.304 g, 5.50 mmol) in H_2O/dioxane (1/3 v/v; 40 mL) at 0 °C were added I_2 (1.65 g; 1.2 equiv) and $NaHCO_3$ (0.92 g, 2 equiv), and the resulting solution was stirred for 1 h. TLC analysis indicated complete conversion of **5b** to a higher running product. Excess iodine was quenched by addition of 1 M $Na_2S_2O_3$, and the reaction mixture was extracted three times with EtOAc. Combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (2 → 12% EtOAc in light petroleum ether) yielded compound **7** (1.73 g; 4.77 mmol; 87%). $[\alpha]^{20}_D$: 95.2 (c = 1.0, $CHCl_3$). IR (neat): ν 2977, 2931, 1639, 1369, 1207, 1060, 914. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.89−5.80 (m, 1H, CH_{olef}), 5.75−5.65 (m, 1H, CH_{olef}), 5.56 (ddd, 1H, $CH_{2,\ olef}$, J = 1.8, 3.2 Hz, J = 17.2 Hz), 5.13−5.05 (m, 3H, $CH_{2,\ olef}$), 4.71 (dd, 1H, H4, J = 4.7, 6.4 Hz), 4.44 (d, 1H, H3, J = 6.4 Hz), 3.37−3.31 (m, 2H, H2, C*H*H N-All), 3.27 (dd, 1H, C*H*H-I, J = 3.2, 8.6 Hz), 3.22−3.15 (m, 2H, CH*H*-I, CH*H* N-All), 3.10 (ddd, 1H, H5, J = 3.2, 4.5, 10.4 Hz), 2.36−2.29 (m, 1H, C*H*H *C*-All), 1.85−1.77 (m, 1H, CH*H* *C*-All), 1.50 (s, 3H, Me isoprop), 1.34 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 136.2, 134.8 (2 × CH_{olef}), 117.7, 116.5 (2 × $CH_{2,olef}$), 111.5 (Cq isoprop), 80.9, 80.5 (C3, C4), 66.6, 65.9 (C2, C5), 50.4 (CH_2 *N*-All), 28.9 (CH_2 *C*-All), 26.3, 25.3 (Me isoprop), 2.3 (CH_2I). ES-MS: m/z 364.1 $[M + H]^+$. HRMS: found MH^+ 364.0810, $C_{14}H_{23}INO_2^+$ requires 364.0768.

(1*S*,2*R*,3*R*,8a*S*)-3-Iodomethyl-1,2-*O*-isopropylidene-7,8-didehydro-indolizidine-1,2-diol (13). Argon was bubbled through a solution of diene **7** (1.68 g; 4.62 mmol) in DCM (30 mL) cooled in a water bath of approximately 10−15 °C. After 10 min, camphorsulfonic acid (1.16 g; 1.1 equiv) and Grubbs' II catalyst **12** (40 mg; 1 mol %) were added, and the reaction mixture was stirred overnight. TLC indicated the formation of a lower running product. The reaction mixture was neutralized with triethylamine and evaporated to dryness at ambient temperature. Column chromatography (5 → 30% EtOAc in light petroleum ether) furnished indolizidine **13** (1.224 g; 3.65 mmol; 79%). $[\alpha]^{20}_D$: 83.4 (c = 1.0, $CHCl_3$). IR (neat): ν 2916, 2831, 1377, 1056. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.79−5.74 (m, 1H, H_{olef}), 5.67−5.62 (m, 1H, H_{olef}), 4.77 (dd, 1H, H2, J = 4.2, 6.2 Hz), 4.35 (d, 1H, H1, J = 6.2 Hz), 3.62 (dt, 1H, C*H*H H5, J = 5.7, 18.8 Hz), 3.45 (dd, 1H, H8a, J = 5.6, 11.0 Hz), 3.26−3.15 (m, 4H, H3, CH*H* H5, H9), 1.95−1.87 (m, 1H, C*H*H H8), 1.77−1.68 (m, 1H, CH*H* H8), 1.51 (s, 3H, Me isoprop), 1.36 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 125.1, 123.7 (C6, C7), 111.5 (Cq isoprop), 82.4, 80.0 (C1, C2), 64.4, 59.4 (C8a, C3), 44.5 (C5), 26.0, 24.8 (Me isoprop), 22.9 (C8), 1.7 (C9). ES-MS: m/z 336.3 $[M + H]^+$. HRMS: found MH^+ 336.0506, $C_{12}H_{19}INO_2^+$ requires 336.0455.

(1*S*,2*R*,3*R*,9a*S*)-3-Iodo-1,2-*O*-isopropylidene-7,8-didehydro-2*H*-quinolizidine-1,2-diol (15) After refluxing a solution of **13** in DCM for 2 days, a 1:2 equilibrium mixture of indolizidine **13** and quinolizidine **15** was obtained, as judged by NMR. Separation by silica column chromatography (5 → 30% EtOAc in light petroleum ether) provided the title compound in pure form. $[\alpha]^{20}_D$: −30 (c = 0.5, $CHCl_3$). IR (neat): 2986, 2922, 2883, 1379, 1219, 1055. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.78−5.73 (m, 1H, H_{olef}), 5.64−5.59 (m, 1H, H_{olef}), 4.44 (ddd, 1H, H3, J = 3.5, 4.7, 12.1 Hz), 4.39 (t, 1H, H2, J = 4.0 Hz), 3.80 (dd, 1H, H1, J = 4.6, 8.2 Hz), 3.34−3.28 (m, 1H, C*H*H H6), 2.98 (dd, 1H, C*H*H H4, J = 4.7, 11.6 Hz), 2.85−2.76 (m, 2H, CH*H* H4, CH*H* H6), 2.49−2.42 (m, 1H, C*H*H H9), 2.37−2.31 (m, 1H, H9a), 2.01−1.91 (m, 1H, CH*H* H9), 1.56 (s, 3H, Me isoprop), 1.41 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 123.9, 123.5 (C7, C8), 109.2 (C_q isoprop), 79.3, 76.4 (C1, C2), 58.4 (C9a), 58.6, 52.5 (C4, C6), 30.7 (C9), 28.2, 26.4 (Me isoprop), 19.0 (C3). ES-MS: m/z 336.3 $[M + H]^+$. HRMS: found MH^+ 336.0511, $C_{12}H_{19}INO_2^+$ requires 336.0455.

NMR Experiment on Aziridinium Perchlorate 16. $AgClO_4$ (5−6 equiv) was added to a solution of 16 mg of indolizidine **13** in $CDCl_3$ (0.4 mL). When, after vigorous stirring, TLC analysis indicated the absence of starting material **13**, the sample was subjected to NMR experiments. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.11−6.06 (m, 1H, H_{olef}), 5.90−5.85 (m, 1H, H_{olef}), 5.50 (t, 1H, H2, J = 5.5 Hz), 4.73 (d, 1H, H1, J = 6.5 Hz), 4.46−4.41 (m, 1H, H3), 4.18 (bd, 1H, C*H*H H5, J = 17.3 Hz), 4.13−4.01 (m, 2H, CH*H* H5, H8a), 3.62 (dd, 1H, C*H*H H9, J = 3.6, 6.2 Hz), 3.49 (dd, 1H, CH*H* H9, J = 3.1, 7.9 Hz), 2.64 (dt, 1H, C*H*H H8, J = 6.1, 17.3 Hz), 2.54−2.45 (m, 1H, CH*H* H8), 1.54 (s, 3H, Me isoprop), 1.33 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 124.4, 121.6 (C6, C7), 113.8 (C_q isoprop), 85.5 (C1), 76.0 (C2), 65.8 (C8a), 58.8 (C3), 55.9 (C5), 45.9 (C9), 27.0 (C8), 26.1, 24.3 (Me isoprop).

General Procedure for the Substitution Reaction of Indolizidine 13. The appropriate salt (NaSMe, CsOAc, NaN_3 or phthalimide, potassium salt; 3 equiv) was added to a stirred solution of indolizidine **13** in DMF (0.2 M). After TLC indicated complete disappearance of the starting material, the reaction mixture was evaporated to dryness. Silica column chromatography yielded indolizidines **8** and quinolizidines **9**.

General Procedure for the Ring-Opening Reaction of Aziridinium Perchlorate 16. A solution of 1.1 equiv of silver perchlorate in THF was added to a solution of indolizidine **13** in THF. After the yellowish precipitate that was formed immediately was filtered off, an excess of the appropriate nucleophile (3 equiv) was added and the mixture was stirred overnight. After evaporation of the solvent, silica column chromatography yielded indolizidines **8** and quinolizidines **9**.

(1*S*,2*R*,3*R*,8a*S*)-1,2-*O*-Isopropylidene-3-methylsulfanylmethyl-7,8-didehydroindolizidine-1,2-diol (8a). $[\alpha]^{20}_D$: 96.4 (c = 1.0, $CHCl_3$). IR (neat): ν 2982, 2920, 2835, 1369, 1207, 1076, 1057. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.78−5.73 (m, 1H, H_{olef}), 5.68−5.64 (m, 1H, H_{olef}), 4.76 (t, 1H, H2, J = 5.8 Hz), 4.35 (d, 1H, H1, J = 6.3 Hz), 3.60−3.54 (m, 1H, C*H*H H5), 3.36 (dd, 1H, H3, J = 5.6, 11.0 Hz), 3.22 (bd, 1H, CH*H* H5, J = 18.6 Hz), 3.05−3.00 (m, 1H, H3), 2.84 (dd, 1H, C*H*H H9, J = 9.7, 12.7 Hz), 2.58 (dd, 1H, CH*H* H9, J = 3.6, 12.7 Hz), 2.16 (s, 3H, SMe), 1.96−1.89 (m, 1H, CH*H* H8), 1.79−1.70 (m, 1H, CH*H* H8), 1.52 (s, 3H, Me isoprop), 1.35 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 125.2, 123.7 (C6, C7), 111.4 (C_q isoprop), 83.0, 79.8 (C1, C2), 62.2, 58.8 (C3, C8a), 44.0 (C5), 31.9 (C8), 26.0, 24.7 (Me isoprop), 23.0 (CH_2S), 16.7 (SMe). ES-MS: m/z 256.2 $[M + H]^+$, 278.2 $[M + Na]^+$. HRMS: found MH^+ 256.1246, $C_{13}H_{22}NO_2S$ requires 256.1365.

(1*S*,2*R*,3*R*,9a*S*)-1,2-*O*-Isopropylidene-3-methylsulfanyl-7,8-didehydro-2*H*-quinolizidine-1, 2-diol (9a). $[\alpha]^{20}_D$: −109 (c = 0.5, $CHCl_3$). IR (neat): ν 2983, 2916, 2882, 2814, 1379, 1244, 1219, 1057. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.76 (ddd, 1H, H_{olef}, J = 2.4, 4.7, 9.6 Hz), 5.66−5.62 (m, 1H, H_{olef}), 4.39 (t, 1H, H2, J = 4.1 Hz), 3.77 (dd, 1H, H1, J = 4.8, 8.1 Hz), 3.36−3.32 (m, 1H, C*H*H H6), 3.10 (ddd, 1H, H3, J = 3.5, 4.5, 12 Hz), 2.87 (dd, 1H, C*H*H H4, J = 4.5, 11.5 Hz), 2.84−2.70 (m, 1H, CH*H* H6), 2.51−2.42 (m, 2H, CH*H* H4, C*H*H H9), 2.28−2.21 (m, 4H, H9a, SMe), 2.02−1.93 (m, 1H, CH*H* H9), 1.53 (s, 3H, Me isoprop), 1.39 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 124.2, 123.7 (C7, C8), 109.8 (C_q isoprop), 80.1, 74.9 (C1, C2), 58.9 (C9a), 54.6, 53.3 (C4, C6), 42.1 (C3), 30.9 (C9), 28.1, 26.4 (Me isoprop), 14.8 (SMe). ES-MS: m/z 256.2 $[M + H]^+$, 278.0 $[M + Na]^+$, 294 $[M + K]^+$. HRMS: found MH^+ 256.1439, $C_{13}H_{22}NO_2S^+$ requires 256.1365.

(1*S*,2*R*,3*R*,8a*S*)-3-Acetoxymethyl-1,2-*O*-isopropylidene-7,8-didehydroindolizidine-1,2-diol (8b). $[\alpha]^{20}_D$: 39 (c = 0.2, $CHCl_3$). IR (neat): ν 2982, 2932, 2839, 1740, 1369, 1244, 1229, 1209, 1037. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.77−5.73 (m, 1H, H_{olef}), 5.69−5.66 (m, 1H, H_{olef}), 4.74 (t, 1H, H2, J = 5.9 Hz), 4.37−4.33 (m, 2H, H1, C*H*H H9), 4.24 (dd, 1H, CH*H* H9, J = 5.1, 11.3 Hz), 3.48 (bd, 1H, C*H*H H5, J = 18.5 Hz), 3.34−3.27 (m, 2H, CH*H* H5, H8a), 3.15−3.11 (m, 1H, H3), 2.07 (s, 3H, SMe), 2.00−1.94 (m, 1H, C*H*H H8), 1.81−1.71 (m, 1H, CH*H* H8), 1.50 (s, 3H, Me isoprop), 1.34 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 170.9 (CO), 125.4, 123.5 (C6, C7), 111.9 (C_q isoprop), 83.5, 79.5 (C1, C2), 62.8 ($-CH_2OAc$), 60.6, 58.8 (C3, C8a), 44.7 (C5), 26.0, 24.7 (Me isoprop), 21.1 (Me Ac). ES-MS: m/z 268.1 $[M + H]^+$, 290.2 $[M + Na]^+$. HRMS: found MH^+ 268.1585, $C_{14}H_{22}NO_4^+$ requires 268.1543.

(1*S*,2*R*,3*R*,9a*S*)-3-Acetyl-1,2-*O*-isopropylidene-7,8-didehydro-2*H*-quinolizidine-1,2,3-triol (9b). $[\alpha]^{20}_D$: −76 (c = 1.0, $CHCl_3$). IR (neat): ν 2983, 2939, 2897, 2815, 1732, 1377, 1238, 1053, 1034. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.75 (ddd, 1H, H_{olef}, J = 2.5, 4.8, 9.8 Hz), 5.65−5.61 (m, 1H, H_{olef}), 5.22 (ddd, 1H, H3, J = 3.8, 4.9, 11.2 Hz), 4.45 (t, 1H, H3, J = 4.2 Hz), 3.84 (dd, 1H, H1, J = 4.7, 8.0 Hz), 3.34−3.29 (m, 1H, C*H*H H6), 2.87−2.80 (m, 2H, C*H*H H4, CH*H* H6), 2.50−2.41 (m, 2H, CH*H* H4, C*H*H H9), 2.29−2.24 (m, 1H, H9a), 2.14 (s, 3H, Me Ac), 2.01−1.93 (m, 1H, CH*H* H9), 1.57 (s, 3H, Me isoprop), 1.38 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 170.2 (CO), 124.0, 123.8 (C7, C8), 110.4 (C_q isoprop), 80.4, 73.4, 67.4 (C1, C2, C3), 58.7 (C9a), 53.5, 52.0 (C4, C6), 30.7 (C9), 28.1, 26.5 (Me isoprop), 21.1 (Me Ac). ES-MS: m/z 268.0 $[M + H]^+$, 290.0 $[M + Na]^+$. HRMS: found MH^+ 268.1436, $C_{14}H_{22}NO_4^+$ requires 268.1543.

(1*S*,2*R*,3*R*,8a*S*)-3-Azidomethyl-1,2-*O*-isopropylidene-7,8-didehydroindolizidine-1,2-diol (8c). $[\alpha]^{20}_D$: +60 (c = 0.25, $CHCl_3$). IR (neat): ν 2934, 2097, 1371, 1277, 1209, 1107, 1091. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 5.79−5.74 (m, 1H, H_{olef}), 5.68−5.64 (m, 1H, H_{olef}), 4.74 (t, 1H, H2, J = 5.9 Hz), 4.37 (d, 1H, H1, J = 6.3 Hz), 3.67−3.56 (m, 2H, C*H*H H5, C*H*H H9), 3.39−3.32 (m, 2H, H8a, CH*H* H9), 3.18 (bd, 1H, CH*H* H5, J = 19.0 Hz), 3.05 (dt, 1H, H3, J = 5.1, 8.0 Hz), 1.99−1.92 (m, 1H, C*H*H H8), 1.80−1.68 (m, 1H, CH*H* H8), 1.52 (s, 3H, Me isoprop), 1.35 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 75.1 MHz): δ_C 125.2, 123.7 (C6, C7), 111.9 (C_q isoprop), 83.3, 79.6 (C1, C2), 61.2, 58.9 (C3, C8a), 49.9, 44.5 (C5, C9), 26.0, 24.7 (Me isoprop), 23.4 (C8). HRMS: found MH^+, 251.1540, $C_{12}H_{19}N_4O_2^+$ requires 251.1502.

(1*S*,2*R*,3*R*,9a*S*)-3-Azido-1,2-*O*-isopropylidene-7,8-didehydro-2*H*-quinolizidine-1,2-diol (9c). $[\alpha]^{20}_D$: −104 (c = 1.0, $CHCl_3$). IR (neat): ν 2986, 2936, 2098, 1381, 1242, 1219, 1049. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.78−5.73 (m, 1H, H_{olef}), 5.67−5.61 (m, 1H, H_{olef}), 4.42 (t, 1H, H2, J = 4.1 Hz), 3.81−3.75 (m, 2H, H1, H3), 3.36−3.30 (m, 1H, C*H*H H6), 2.89−2.83 (m, 2H, C*H*H H4, CH*H* H6), 2.54−2.42 (m, 2H, CH*H* H4, C*H*H H9), 2.27−2.22 (m, 1H, H9a), 2.00−1.91 (m, 1H, CH*H* H9), 1.54 (s, 3H, Me isoprop), 1.41 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 123.9, 123.6 (C6, C7), 110.3 (C_q isoprop), 80.0, 73.9 (C1, C2), 58.6, 55.3 (C3, C9a), 53.4, 52.3 (C4, C6), 30.8 (C9), 27.9, 26.4 (Me isoprop). ES-MS: m/z 251.2 $[M + H]^+$, 273.2 $[M + Na]^+$. HRMS: found MH^+ 251.1544, $C_{12}H_{19}N_4O_2^+$ requires 251.1502.

(1*S*,2*R*,3*R*,8a*S*)-1,2-*O*-Isopropylidene-3-phthaloylaminomethyl-7,8-didehydroindolizidine-1,2-diol (8d). $[\alpha]^{20}_D$: 63 (c = 0.25, $CHCl_3$). IR (neat): ν 2986, 2924, 1709, 1396, 1377, 1207, 1053. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_H 7.86−7.67 (m, 4H, H_{arom}), 5.78−5.57 (m, 2H, H_{olef}), 4.73 (t, 1H, H2, J = 5.85 Hz), 4.36 (d, 1H, H1, J = 6.6 Hz), 4.18 (dd, 1H, C*H*H H9, J = 6.8, 14,6 Hz), 3.79−3.60 (m, 2H, C*H*H H5, CH*H* H9), 3.44−3.21 (m, 3H, H3, CH*H* H5, H8a), 1.96−1.71 (m, 2H, H8), 1.57 (s, 3H, Me isoprop), 1.35 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 168.3 (CO), 134.2 (CH_{arom}), 132.1 ($C_{q,\ arom}$), 125.5, 123.5, 123.2 (CH_{arom}, C6, C7), 111.8 (C_q isoprop), 83.4, 79.7 (C1, C2), 61.4, 58.3 (C3, C8a), 44.2, 36.6 (C5, C9), 26.1, 24.9 (Me isoprop). 23.1 (C8). ES-MS: m/z 355.1 $[M + H]^+$, 377.0 $[M + Na]^+$. HRMS: found MH^+ 355.1630, $C_{20}H_{23}N_2O_4^+$ requires 355.1652.

(1*S*,2*R*,3*R*,9a*S*)-1,2-*O*-Isopropylidene-3-phthaloylamino-7,8-didehydro-2*H*-quinolizidine-1,2-diol (9d). $[\alpha]^{20}_D$: 10 (c = 0.25, $CHCl_3$). IR (neat): ν 2974, 2924, 1709, 1377, 1218, 1057. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_H 7.87−7.70 (m, 4H, H_{arom}), 5.77−5.58 (m, 2H, H_{olef}), 4.84−4.74 (m, 1H, H3), 4.44−4.40 (m, 1H, H2), 3.89 (m, 1H, H1), 3.74 (t, 1H, C*H*H H4, J = 11.7 Hz), 3.36 (bd, 1H, C*H*H H6), 3.00−2.91 (m, 1H, CH*H* H6), 2.82−2.75 (m, 1H, CH*H* H4), 2.44−2.34 (m, 2H, CH*H* H9, H9a), 2.11−1.96 (m, 1H, CH*H* H9), 1.55 (s, 3H, Me isoprop), 1.28 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 168.1 (CO), 134.0 (CH_{arom}), 131.8 ($C_{q,\ arom}$), 124.1, 123.9, 123.3 (CH_{arom}, C7, C8), 110.5 (C_q isoprop), 80.2, 74.5 (C1, C2), 59.4 (C3), 53.5, 50.6 (C4, C6), 48.8 (C9a), 31.1 (C9), 28.2, 26.4 (Me isoprop). ES-MS: m/z 355.1 $[M + H]^+$, 377.2 $[M + Na]^+$. HRMS: found MH^+ 355.1595, $C_{20}H_{23}N_2O_4^+$ requires 355.1652.

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Supporting Information Available: H−H COSY and ^{13}C spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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