Lewis Acid Assisted Vinylogous Mannich and Mukaiyama Aldol Reactions: A Route to Densely Hydroxylated Indolizidine Alkaloid Analogues

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The hydroxymethyl-substituted indolizidines **6** and **7**, representative members of a ring-B-expanded alexine–australine subclass, are readily accessible by starting with furan-based silyloxydiene **12** and hydroxymethyl hemiaminal **11**, through a synthesis sequence involving a scantily exploited vinylogous version of the Mannich reaction. The key iminium electrophilic acceptor **11** is, in turn, available through a vinylogous intermolecular Mukaiyama aldolization process between pyrrole-based silyloxydiene **8** and (*S*)-glyceraldehyde **9**.

Densely hydroxylated indolizidine and pyrrolizidine alkaloids are a growing progeny of naturally occurring molecules whose relevance is reflected in an impressive number of research papers and review articles dealing with isolation,[1] biological evaluation,[2] and total and analogue syntheses.[3] Representatives of this compound class (Figure 1) are, for example, the indolizidine members castanospermine (**1**)[4] and swainsonine (**2**),[5] and the pyrrolizidines australine (**3**),[6] alexine (**4**),[7] and casuarine (**5**),[8] all of them exhibiting useful therapeutical potential as glycosylation inhibitors, as well as antiviral, and anticancer agents.[2]

We approached the total synthesis of the indolizidine skeleton **A** (Scheme 1) exploiting the vinylogous version of a Lewis acid assisted Mannich reaction[9] of type **C** + **D**, wherein a mechanistically active, chiral *N*-carbamoyliminium intermediate **D** would undergo vinylogous addition to silyloxy-substituted diene **C** in the indicated regiosense (γ attack only) and with complete diastereoface guidance. The *threo,trans*-configured binuclear adduct **B** so formed would be eventually elaborated to an indolizidine **A** by a short sequence consisting of double-bond functionalization (hydrogenation or dihydroxylation), intramolecular lactamization, and carbonyl-to-methylene reduction. The realization of this plan is described herein in the context of total syntheses of 3-(hydroxymethyl)indolizidines **6** and **7**, representative members of a ring-B-expanded alexine-australine alkaloid subclass.

The specific pyrrolidine precursor used to create the operative Mannich acceptor was the chiral nonracemic aminal

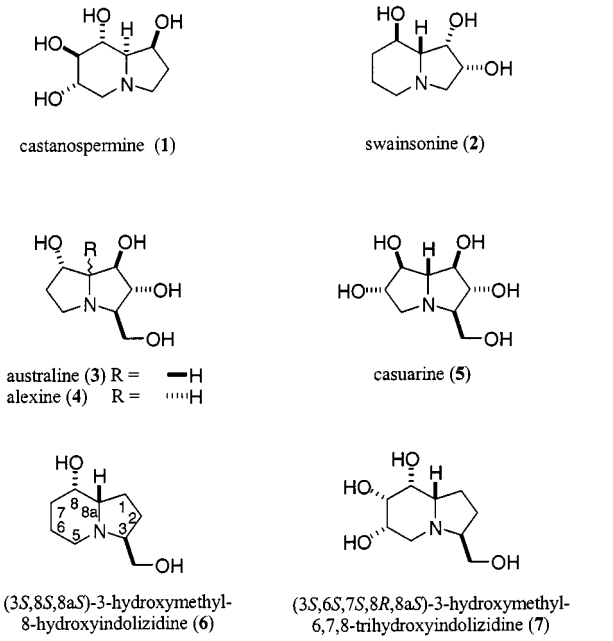

Figure 1. Relevant hydroxylated indolizidine and pyrrolizidine alkaloid compounds

11, whose synthesis was accomplished by starting with 2,3-*O*-isopropylidene-L-glyceraldehyde (**9**, ex commercially available L-gulono-1,4-lactone; Scheme 2). Vinylogous Mukaiyama aldolization[10] of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)pyrrole (**8**) with glyceraldeyde **9** under the conditions indicated, followed by catalytic hydrogenation afforded the hydroxylated pyrrolidinone **10** in 70% yield for the two steps. The triol side chain within **10** was then shortened to a protected hydroxymethyl group, as shown, and the lactam carbonyl group carefully reduced to a hydroxy group (Super Hydride®) to provide, after proper methylation, compound **11** (41% yield from **10**).

The key Mannich reaction between aminal **11** and 2-(*tert*-butyldimethylsilyloxy)furan (**12**) (Scheme 3) was conducted under catalysis by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.6 mol-equiv., CH_2Cl_2). Unsaturated

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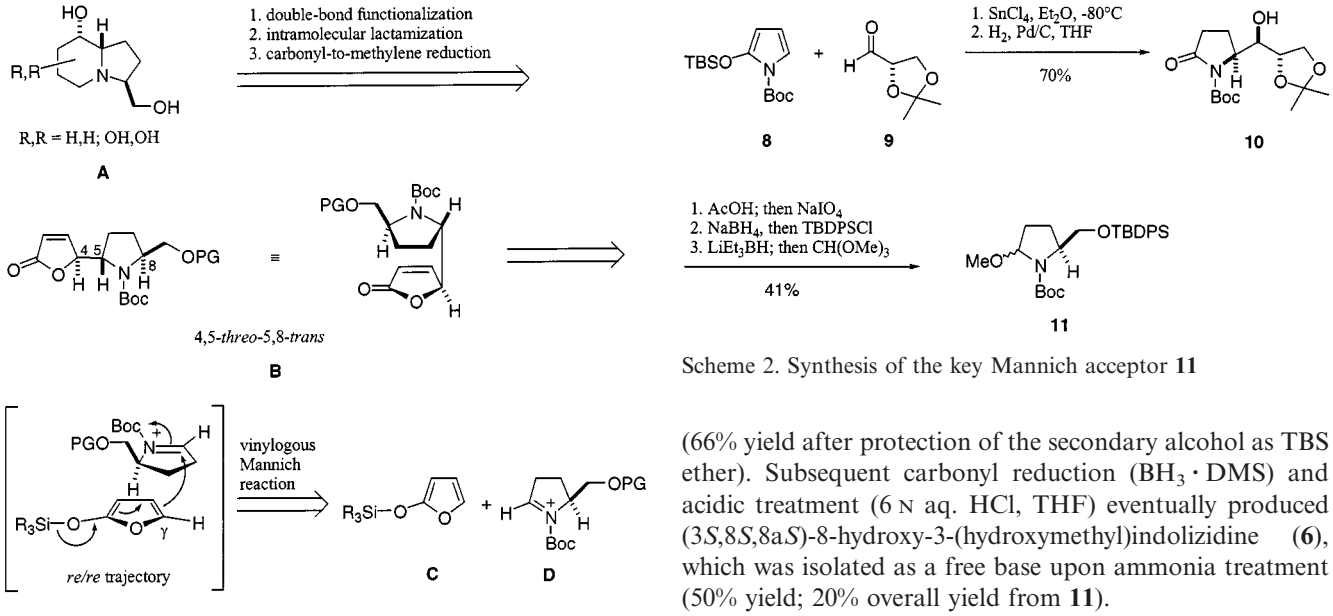
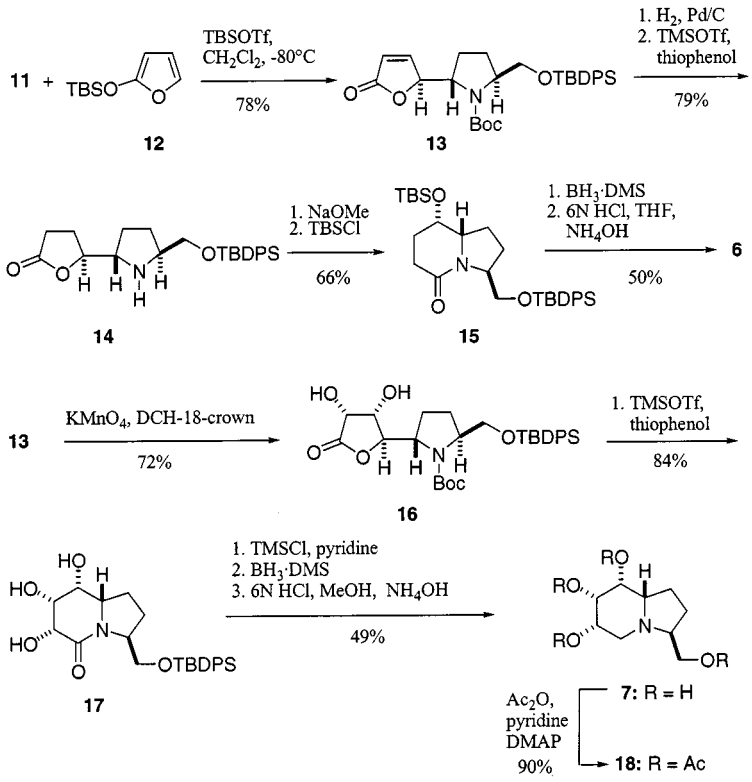


Scheme 2. Synthesis of the key Mannich acceptor **11**

Scheme 1. Synthetic strategy for indolizidines **A**

adduct **13** was then isolated as the single reaction component in 78% isolated yield. From **13**, the synthesis of model indolizidine **6** was first carried out by double-bond hydrogenation followed by selective removal of the *N*-Boc protecting group (TMSOTf, thiophenol), giving rise to the binuclear lactone **14** in 79% yield over the two steps.[11] Following basic treatment (NaOMe, MeOH), the γ-lactone ring in **14** was cleanly rearranged to a δ-lactam, thereby furnishing the requisite fused bicyclic indolizidinone **15** (66% yield after protection of the secondary alcohol as TBS ether). Subsequent carbonyl reduction ($BH_3 \cdot DMS$) and acidic treatment (6 N aq. HCl, THF) eventually produced (3*S*,8*S*,8a*S*)-8-hydroxy-3-(hydroxymethyl)indolizidine (**6**), which was isolated as a free base upon ammonia treatment (50% yield; 20% overall yield from **11**).

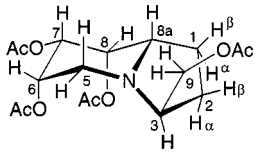
The basic chemistry exploited to transform aminal **11** into **6** was then adopted to arrive at densely hydroxylated indolizidine **7**. Thus, the double bond within intermediate **13** was subjected to *cis*-dihydroxylation by using the well-documented $KMnO_4$/dicyclohexano-18-crown-6 ether phase transfer oxidative protocol,[12] stereoselectively affording diol **16** in 72% yield. Removal of the Boc protecting group under the above selective conditions effected concomitant γ-lactone-to-δ-lactam expansion, straightforwardly furnishing hydroxylated indolizidinone **17** (84% yield). After persilylation (TMSCl, pyridine), the lactam



Scheme 3. Synthesis of hydroxylated indolizidines **6** and **7**

carbonyl group was reduced to a methylene group ($BH_3 \cdot DMS$) and all the silyl ether functions were cleaved (6 N HCl) to provide (3*S*,6*S*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxy-3-(hydroxymethyl)indolizidine (**7**) in 49% yield (23% overall yield from **11**).

The stereostructure of indolizidine **7** could not be simply established on the basis of its ^{1}H-NMR spectrum owing to extensive signal overlap. However, the proton spectrum of the corresponding tetra-*O*-acetyl derivative **18** proved quickly readable, allowing precise assignment of the relative (and hence absolute) stereodisposition of the molecule.



18

Coupling constants:
$^3J_{5ax,6}$ = 2.7 Hz; $^3J_{5eq,6}$ = 2.4 Hz;
$^3J_{6,7}$ = 3.6 Hz; $^3J_{7,8}$ = 3.6 Hz;
$^3J_{8,8a}$ = 2.4 Hz; $^4J_{6,8}$ = 0.9 Hz

NOEs:
H-8a *vs* H-7; H-8a *vs* H-5$_{ax}$; H-8a *vs* H$_2$-9; H-5$_{ax}$ *vs* H-7; H-5$_{ax}$ *vs* H$_2$-9; H-3 *vs* H-5$_{eq}$; H$_2$-9 *vs* H-2β; H-8 *vs* H-1α; H-3 *vs* H-2α; H-8a *vs* H-1β; H$_2$-9 *vs* H-5$_{eq}$

Figure 2. Stereostructure of tetra-*O*-acetyl indolizidine **18** as deduced from ^{1}H-NMR parameters

The spectral parameters are fully consistent with the structure shown in Figure 2, where the piperidine moiety adopts a $^4C_1$ (L) conformation ($^{8a}C_6$ in the figure) with a 1-deoxy-L-*ribo* configuration. In particular, the coupling constant between 8-H and 8a-H ($J_{8,8a}$ = 2.4 Hz) confirms the *cis* relationship for these protons (and hence, the 4,5-*threo* disposition within the precursor adduct **13**), while a strong NOE contact between 8a-H and 9-H$_2$ (not with 3-H) confirms the *cis* relationship between the 8a-H proton and the hydroxymethyl appendage, thus corroborating the 5,8-*trans* arrangement for **13**. The $J_{7,8}$ = $J_{6,7}$ = 3.6 Hz are consistent with an *all-cis* disposition of the piperidine substituents, and confirm the highly diastereoselective *cis-anti* character of the dihydroxylation stage (**13** → **16**). These results also firmly establish the configuration of the model indolizidine **6**, as shown.

To conclude, the chemistry herein disclosed delineates a new, viable entry to the indolizidine nucleus amenable to further adaptations and substituent variations. The successful exploitation of scantily investigated vinylogous versions of the Lewis acid assisted Mannich and Mukaiyama aldolization protocols[9][10] to assemble the key precursors of this synthesis (**13** and **11**) is remarkable and project the silyloxy diene methodology among the reliable tools in the contemporary organic synthesis.

Experimental Section

General: Flash chromatography was performed on ICN Biomedicals silica gel 32−63 μm, using the indicated solvent mixtures. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates (0.25 mm). The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate or in an ethanolic solution of ninhydrin, followed by charring with a heat gun. − ^{1}H-NMR spectra were obtained with a Bruker AC-300 or Varian XL-300 and are reported in parts per million (δ) relative to tetramethylsilane (0.0 ppm) as an internal reference, with coupling constants in Hz. − Rotations were measured with a Perkin−Elmer 241 Polarimeter and are given in units of 10^{-1} deg·cm^2·g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari. − Melting points were determined with an Electrothermal apparatus and are recorded uncorrected. − All the solvents were distilled before use: THF from Na/benzophenone, Et_2O from $LiAlH_4$, CH_2Cl_2 from CaH_2.

***N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (8)** was prepared from pyrrole (Aldrich) according to a described protocol.[13] 2-(*tert*-Butyldimethylsilyloxy)furan (**12**) was obtained from 2-furaldehyde (Aldrich) according to a reported method.[13] 2,3-*O*-Isopropylidene-L-glyceraldehyde (**9**) was prepared from 5,6-*O*-isopropylidene-L-gulonic acid 1,4-lactone (Fluka) according a convenient described procedure.[14]

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-L-*arabino*-heptono-1,4-lactam (10):** To a solution of 2,3-*O*-isopropylidene-L-glyceraldehyde (**9**) (6.0 g, 46 mmol) in anhydrous Et_2O (300 mL) were added silyloxypyrrole **8** (13.6 g, 46 mmol) and $SnCl_4$ (8.1 mL, 69 mmol) under argon at −80°C. The mixture was stirred at this temperature for 3 h, then a saturated aqueous $NaHCO_3$ solution was added at −80°C and, after ambient temperature was reached, the resulting mixture was extracted with Et_2O (3 × 60 mL). After drying ($MgSO_4$), the solution was concentrated under reduced pressure and the crude product was crystallized from CH_2Cl_2/hexane to give 11.3 g (78%) of an α,β-unsaturated lactam intermediate that was subjected to the hydrogenation procedure. Palladium (10% on carbon, 1.1 g) was added to a solution of this α,β-unsaturated lactam (11.2 g, 35.7 mmol) in anhydrous THF (180 mL) in the presence of a small amount of NaOAc (0.46 g) at room temperature. The reaction vessel was evacuated by aspirator and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under hydrogen from a balloon. After 24 h, the hydrogen was evacuated, the catalyst filtered off, and the filtrate was concentrated under vacuum to give a crude residue which was subjected to flash-chromatographic purification (3:2, EtOAc/hexanes). There was obtained 10.2 g (90%) of saturated lactam **10** as a white solid, m.p. 102−105°C. − $[\alpha]_D^{20}$ = −60.14 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.31 (ddd, *J* = 7.7, 5.9, 1.9 Hz, 1 H), 4.09 (m, 2 H), 3.98 (m, 1 H), 3.75 (t, *J* = 6.0 Hz, 1 H), 2.70 (ddd, *J* = 17.7, 12.1, 9.1 Hz, 1 H), 2.39 (ddd, *J* = 17.7, 8.7, 2.2 Hz, 1 H), 2.16 (m, 2 H), 1.75 (br. s,1 H), 1.54 (s, 9 H), 1.40 (s, 3 H), 1.34 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 151.2, 109.3, 83.2, 76.7, 74.0, 67.2, 60.9, 31.9, 27.9 (3 C), 26.5, 25.1, 21.6. − $C_{15}H_{25}NO_6$ (315.37): calcd. C 57.13, H 7.99, N 4.44; found C 57.16, H 8.10, N 4.50.

(2*RS*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5[(*tert*-butyldiphenylsilyl)-oxymethyl]-2-methoxypyrrolidine (11): Lactam **10** (10 g, 31.7 mmol) was dissolved with 50 mL of 80% aqueous acetic acid, and the resulting solution was allowed to react at 50°C. The reaction was monitored by TLC and was judged complete after 8 h. The solution was concentrated to give a crude triol intermediate which was used as such in the subsequent step. The crude triol was then dissolved in CH_2Cl_2 (200 mL) and treated with a 0.65 M aq. $NaIO_4$ solution (108 mL) and chromatography-grade SiO_2 (21 g). The resulting slurry was vigorously stirred for 15 min at which time TLC showed complete consumption of the starting material. The slurry was filtered under suction and the silica gel thoroughly washed with CH_2Cl_2 and ethyl acetate. The filtrates were concentrated to leave the crude aldehyde which was directly subjected to reductive

workup. Thus, crude aldehyde (6.1 g, 28.6 mmol) was dissolved in methanol (140 mL) and the solution treated with $NaBH_4$ (2.13 g, 56.3 mmol) at −30°C. After 30 min, the temperature was allowed to rise to −15°C, while stirring was continued until the starting aldehyde was consumed (1 h). The slurry was quenched by adding acetone and a saturated aqueous citric acid solution. The mixture was concentrated to leave an oily residue, which was subjected to flash chromatographic purification on silica gel (ethyl acetate as an eluant) to furnish a pure alcohol (5.2 g, 85%) as a colorless oil, which was used as such in the subsequent step. Thus, the intermediate alcohol was dissolved in DMF (32 mL), and TBDPSCl (7.3 g, 26.6 mmol) and imidazole (1.8 g, 26.6 mmol) were sequentially added at room temperature. After being stirred for 18 h, the mixture was quenched by addition of an aqueous saturated Na_2SO_4 solution and extracted with ethyl acetate. The extracts were dried and concentrated under vacuum to give an oily residue, from which a pure protected lactam (9.1 g, 83%) was isolated as an oil by silica gel flash chromatography (70:30, hexanes/ethyl acetate). To a solution of the obtained pyrrolidinone (9.0 g, 19.8 mmol) in THF (160 mL) was added a 1.0 M THF solution of $LiEt_3BH$ (21.8 mL, 21.3 mmol) at −78°C, under argon. After 3 h, the reaction was quenched with methanol and water, and, after ambient temperature was reached, the resulting slurry was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and the solvent removed under vacuum to give a crude aminol, which was used in the subsequent step. Thus, the crude product was dissolved in anhydrous diethyl ether (150 mL), and trimethyl orthoformate (5.3 mL, 48.4 mmol), $BF_3 \times OEt_2$ (700 μL) and powdered 4-Å molecular sieves (500 mg) were sequentially added at room temperature. After 30 min, the reaction was quenched with brine and few drops of Et_3N. The mixture was extracted with diethyl ether and, after drying, the solvent evaporated to give crude *O*-methyl derivative **11**, which was purified by silica gel flash chromatography (9:1, hexanes/ethyl acetate). The yield was 6.1 g (65% for the last two steps, 41% from **10**) of **11** as a colorless oil. − $[\alpha]^{20}_D$ = −31.2 (*c* = 1.3, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$) (major anomer): δ = 7.65 (m, 4 H), 7.38 (m, 6 H), 5.17 (m, 1 H), 3.8−4.1 (m, 2 H), 3.6 (m, 1 H), 3.20 (s, 3 H), 2.0−2.2 (m, 2 H), 1.85 (m, 1 H), 1.75 (m, 1 H), 1.41 (s, 9 H), 1.05 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$) (major anomer): δ = 154.9, 135.8 (4 C), 133.7 (2 C), 129.5 (2 C), 127.5 (4 C), 89.6, 79.5, 66.3, 59.1, 55.0, 31.4, 28.2 (3 C), 26.7 (3 C), 22.5, 19.6. − $C_{27}H_{39}NO_4Si$ (469.70): calcd. C 69.04, H 8.37, N 2.98; found C 69.10, H 8.35, N 3.04.

(5*S*,2′*S*,5′*S*)-5-[1′-(*tert*-Butoxycarbonyl)-5′-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidin-2′-yl]-2(5*H*)-furanone (13): To a solution of azafuranose **11** (5.8 g, 12.3 mmol) in anhydrous CH_2Cl_2 (100 mL) cooled to −80°C under N_2 was added TBSOTf (1.7 mL, 7.4 mmol) dropwise. The resulting mixture was stirred at −80°C for 15 min, after which time it was treated with 3.2 g (16.1 mmol) of silylenol ether **12**. After being stirred for an additional hour at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and, after room temperature was reached, the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to provide an oily residue that was purified by flash chromatography (hexanes/EtOAc, 80:20). Pure 2,3-unsaturated butenolide **13** (5.0 g, 78%) was obtained as a 70:30 mixture of rotamers, an oil. − $[\alpha]^{20}_D$ = −117.0 (*c* = 5.0, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, major rotamer): δ = 7.62 (m, 4 H), 7.57 (dd, *J* = 5.8, 1.5 Hz, 1 H), 7.41 (m, 6 H), 6.03 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.42 (dt, *J* = 3.2, 1.7 Hz, 1 H), 4.38 (dd, *J* = 7.9, 3.4 Hz, 1 H), 3.85 (m, 1 H), 3.65 (dd, *J* = 9.7, 2.9 Hz, 1 H), 3.57 (dd, *J* = 9.7, 6.5 Hz, 1 H), 2.0−2.3 (m, 3 H), 1.72 (m, 1 H), 1.24 (s, 9 H), 1.04 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, major rotamer): δ 173.2, 154.8, 153.3, 135.5 (4 C), 133.2 (2 C), 129.7 (2 C), 127.7 (4 C), 120.4, 84.4, 80.1, 64.0, 59.4, 58.3, 28.3, 28.1 (3 C), 27.5, 26.7 (3 C), 19.1. − $C_{30}H_{39}NO_5Si$ (521.73): calcd. C 69.06, H 7.53, N 2.68; found C 69.10, H 7.35, N 2.65.

(5*S*,2′*S*,5′*S*)-5-[5′-(*tert*-Butyldiphenylsilyloxymethyl)pyrrolidin-2′-yl]-tetrahydrofuran-2-one (14): A solution of butenolide **13** (4.8 g, 9.2 mmol) in anhydrous THF (60 mL) in the presence of AcONa (130 mg) was subjected to catalytic hydrogenation with 10% Pd on carbon (486 mg) at room temperature for 24 h. The catalyst was then filtered off and the filtrate concentrated to give, after flash-chromatographic purification (60:40, hexanes/EtOAc), a protected bicyclic compound (4.3 g, 90%) that was then subjected to deprotection at the amino function. To a solution of saturated bicyclic compound (4.2 g, 8.0 mmol) in anhydrous CH_2Cl_2 (200 mL) were added thiophenol (1.2 mL, 12 mmol) and TMSOTf (2.2 mL, 12 mmol) under argon at 0 °C with stirring. After 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was flash-chromatographed on silica gel (90:10, EtOAc/MeOH) to furnish 3.0 g (88%) of pure *N*-deprotected derivative **14** as an oil. − $[\alpha]^{20}_D$ = −11.0 (*c* = 1.4, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.40 (m, 6 H), 4.36 (q, *J* = 7.2 Hz, 1 H), 3.63 (dd, *J* = 10.2, 4.5 Hz, 1 H), 3.53 (dd, *J* = 10.2, 6.0 Hz, 1 H), 3.44 (m, 1 H), 3.28 (q, *J* = 7.2 Hz, 1 H), 2.56 (m, 3 H), 2.25 (m, 1 H), 1.9 (m, 3 H), 1.52 (m, 2 H), 1.04 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 135.5 (4 C), 133.3 (2 C), 129.7 (2 C), 127.7 (4 C), 83.6, 65.7, 61.2, 59.6, 28.7, 27.0, 26.8 (4 C), 25.1, 19.2. − $C_{25}H_{33}NO_3Si$ (423.63): calcd. C 70.88, H 7.85, N 3.30; found C 70.65, H 7.96, N 3.50.

(3*S*,8*S*,8a*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-8-(*tert*-butyldimethylsilyloxy)indolizidin-5-one (15): To a solution of *N*-deprotected compound **14** (2.9 g, 6.8 mmol) in anhydrous methanol (28 mL) was added a catalytic amount of sodium methoxide in methanol under argon at 0°C with stirring. After 1 h, the reaction was quenched with brine, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (90:10, EtOAc/MeOH) gave 2.0 g (69%) of a protected indolizidinone as a white solid, m.p. 58−60°C. − $[\alpha]^{20}_D$ = −83.0 (*c* = 1.2, $CHCl_3$). This compound was subjected to *O*-TBS protection. Thus, TBSCl (2.0 g, 13.5 mmol) and imidazole (0.9 g, 13.5 mmol) were sequentially added to a solution of the bicyclic compound (1.9 g, 4.5 mmol) in anhydrous DMF (20 mL) under stirring at room temperature. After 24 h, further portions of TBSCl (2.0 g, 13.5 mmol) and imidazole (0.9 g, 13.5 mmol) were added, and the resulting solution was stirred for additional 12 h. The reaction was then quenched with 5% aqueous citric acid and the resulting mixture extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to afford a crude residue that was purified by flash chromatography (8:2, hexanes/EtOAc). Protected bicyclic compound **15** (2.3 g, 96%) was obtained as a colorless oil. − $[\alpha]^{20}_D$ = −44.6 (*c* = 2.4, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.40 (m, 6 H), 4.24 (m, 1 H), 4.05 (m, 2 H), 3.78 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.58 (td, *J* = 8.7, 2.7 Hz, 1 H), 2.47 (ddd, *J* = 17.7, 12.6, 6.6 Hz, 1 H), 2.24 (dd, *J* = 17.7, 6.0 Hz, 1 H), 1.7−2.1 (m, 6 H), 1.05 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 168.6, 135.5 (4 C), 133.6 (2 C), 129.5 (2 C), 127.6 (4 C), 64.5, 64.3, 63.9, 57.9, 28.6, 27.1, 26.8 (3 C), 26.3, 25.7 (3 C), 24.5, 19.3, 18.0, −4.6, −5.0. − $C_{31}H_{47}NO_3Si_2$ (537.89): calcd. C 69.22, H 8.80, N 2.60; found C 69.70, H 8.85, N 2.69.

(3*S*,8*S*,8a*S*)-8-Hydroxy-3-(hydroxymethyl)indolizidine (6): To a solution of protected derivative **15** (2.1 g, 3.9 mmol) in dry THF

(15 mL) was added dropwise at room temperature a solution of BH_3·DMS (1.2 mL, 12.0 mmol) under argon. The reaction was stirred for 4 h and was quenched by careful addition of MeOH (8 mL). The residue was concentrated under reduced pressure and purified by flash chromatography on silica gel (90:10, hexanes/EtOAc) to give 1.5 g of a pure reduced derivative (2.8 mmol, 71%) as a glass. To a solution of this compound (1.4 g, 2.8 mmol) in THF (80 mL), a 6 N aqueous HCl solution (2 mL) was added dropwise. The mixture was stirred overnight at room temperature, then the solvent was evaporated to dryness under vacuum. The crude product was flash-chromatographed on silica gel (7:2.5:0.5, EtOAc/MeOH/30% aq. NH_4OH) to afford **6** (325 mg, 68%) as a glassy solid. − $[\alpha]^{20}_D$ = −11.43 (*c* = 0.35, $CHCl_3$). − ^{1}H NMR (300 MHz, D_2O): δ = 4.14 (m, 1 H), 3.7−3.9 (m, 3 H), 3.3−3.6 (m, 2 H), 3.16 (m, 1 H), 1.6−2.3 (m, 8 H). − ^{13}C NMR (75 MHz, CD_3OD): δ = 68.1, 67.1, 65.0, 60.1, 49.0, 28.5, 24.1 (2 C), 18.2. − $C_9H_{17}NO_2$ (171.24): calcd. C 63.13, H 10.01, N 8.18; found C 63.20, H 9.93, N 8.21.

(3*R*,4*R*,5*R*,2′*S*,5′*S*)-5-[1′-(*tert*-Butoxycarbonyl)-5′-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidin-2′-yl]-3,4-dihydroxytetrahydrofuran-2-one (16): To a solution of **13** (4.0 g, 7.6 mmol), dissolved in anhydrous CH_2Cl_2 (50 mL), were added *cis*-dicyclohexano-18-crown-6 ether (335 mg, 0.9 mmol) and powdered $KMnO_4$ (1.3 g, 8.4 mmol). The reaction mixture was stirred for 4 h, and then a saturated Na_2SO_3 aqueous solution was added. After neutralization with saturated aqueous citric acid, the mixture was extracted with CH_2Cl_2 (3 × 40 mL) and EtOAc (3 × 40 mL), dried with $MgSO_4$, and then concentrated in vacuo. The residue was purified by flash chromatography (80:20, ethyl acetate/hexanes) to afford 3.0 g (72%) of pure derivative **16** as a pale yellow glass. − $[\alpha]^{20}_D$ = −32.04 (*c* = 4.5, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (m, 4 H), 7.39 (m, 6 H), 4.60 (br. s,1 H), 4.42 (br. s,1 H), 4.29 (m, 1 H), 4.12 (m, 3 H), 3.90 (m, 1 H), 3.73 (m, 1 H), 3.56 (m, 1 H), 2.20 (m, 3 H), 1.75 (m, 1 H), 1.24 (s, 9 H), 1.04 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 154.4, 135.5 (4 C), 133.2 (2 C), 129.7 (2 C), 127.7 (4 C), 87.4, 80.5, 77.1, 68.5, 63.7, 59.1, 56.7, 28.4, 28.1 (3 C), 26.8 (3 C), 25.8, 19.2. − $C_{30}H_{41}NO_7Si$ (555.75): calcd. C 64.84, H 7.44, N 2.52; found C 64.91, H 7.39, N 2.50.

(3*S*,6*R*,7*R*,8*R*,8a*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-6,7,8-trihydroxyindolizidin-5-one (17): To a solution of dihydroxylated compound **16** (2.9 g, 5.2 mmol) in anhydrous CH_2Cl_2 (150 mL) were added thiophenol (0.8 mL, 7.8 mmol) and TMSOTf (1.4 mL, 7.8 mmol) under argon at 0°C with stirring. After 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was flash chromatographed on silica gel (90:10, EtOAc/MeOH) to furnish 2.0 g (84%) of pure indolizidinone **17** as an oil. − $[\alpha]^{20}_D$ = −44.47 (*c* = 1.5, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (m, 4 H), 7.38 (m, 6 H), 5.20 (br. s,1 H), 4.93 (br. s,1 H), 4.70 (br. s,1 H), 4.20 (m, 1 H), 4.02 (m, 2 H), 3.93 (m, 2 H), 3.69 (bd, *J* = 10.2 Hz, 1 H), 3.49 (br. s,1 H), 1.7−2.1 (m, 4 H), 1.05 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 135.5 (4 C), 133.3 (2 C), 129.7 (2 C), 127.7 (4 C), 67.7, 67.5, 67.3, 63.7, 59.8, 59.1, 29.7, 26.8 (3 C), 25.4, 19.2. − $C_{25}H_{33}NO_5Si$ (455.63): calcd. C 65.90, H 7.30, N 3.07; found C 65.95, H 7.27, N 3.11.

(3*S*,6*S*,7*S*,8*R*,8a*S*)-6,7,8-Trihydroxy-3-(hydroxymethyl)indolizidine (7): Pure indolizidinone **17** (1.9 g, 4.1 mmol) was dissolved in pyridine (5 mL) and TMSCl (3.1 mL, 24.6 mmol) was added under argon at 0°C. The mixture was allowed to react at 25°C for 12 h. Distilled water (30 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water, dried with $MgSO_4$, and concentrated in vacuo furnishing a crude residue that was flash-chromatographed on silica gel (90:10, hexanes/EtOAc) to afford 2.6 g (94%) of a TMS-protected derivative as an oil. To a solution of this TMS-protected intermediate (2.5 g, 3.7 mmol) in THF (15 mL), BH_3 · DMS (1.1 mL, 11.1 mmol) was added dropwise at room temperature. The reaction was stirred for 1 h, quenched by careful addition of methanol (10 mL), and the solvent was evaporated to dryness under reduced pressure. The crude product so obtained (1.7 g, 70%) was dissolved in MeOH (50 mL) and was stirred in the presence of 6 N HCl aqueous solution (2 mL) added overnight at room temperature. The solvent was evaporated to dryness under vacuum to leave a solid residue which was flash chromatographed on silica gel (1:1:1, EtOAc/MeOH/30% aq. NH_4OH) to afford indolizidine **7** (0.4 g, 75%) as a glassy solid. − $[\alpha]^{20}_D$ = −29.5 (*c* = 0.21, $CHCl_3$). − ^{1}H NMR (300 MHz, CD_3OD): δ = 4.08 (m, 1 H), 4.03 (m, 1 H), 3.7−3.9 (m, 4 H), 3.53 (dd, *J* = 12.9, 3.9 Hz, 1 H), 3.49 (m, 1 H), 3.27 (dd, *J* = 12.6, 2.1 Hz, 1 H), 2.1−2.3 (m, 3 H), 2.0−2.1 (m, 1 H). − ^{13}C NMR (75 MHz, CD_3OD): δ = 70.4, 70.2, 68.9, 66.4, 66.0, 61.2, 51.9, 25.5, 24.9. − $C_9H_{17}NO_4$ (203.24): calcd. C 53.19, H 8.43, N 6.89; found C 53.24, H 8.38, N 6.84.

(3*S*,6*S*,7*S*,8*R*,8a*S*)-6,7,8-Triacetoxy-3-(acetoxymethyl)indolizidine (18): Acetic anhydride (1.8 mL, 19 mmol) and a catalytic amount of DMAP (5 mg) were added under argon to a solution of indolizidine **7** (386 mg, 1.9 mmol) in dry pyridine (2 mL). The mixture was stirred for 12 h at room temperature, quenched with water, extracted with CH_2Cl_2 (3 × 15 mL), and dried with $MgSO_4$. Concentration of the solution gave a residue that was flash chromatographed on silica gel eluting with EtOAc to afford 635 mg (90%) of pure protected derivative **18** as a glass. − $[\alpha]^{20}_D$ = −27.8 (*c* = 0.18, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.29 (ddd, *J* = 3.6, 2.4, 0.9 Hz, 1 H, 8-H), 5.20 (dddd, *J* = 3.6, 2.7, 2.4, 0.9 Hz, 1 H, 6-H), 4.98 (t, *J* = 3.6 Hz, 1 H, 7-H), 4.05 (dd, *J* = 11.4, 4.2 Hz, 1 H, 9a-H), 4.00 (dd, *J* = 11.4, 5.4 Hz, 1 H, 9b-H), 3.68 (m, 1 H, 3-H), 3.41 (dd, *J* = 14.1, 2.7 Hz, 1 H, 5-H_{eq}), 3.16 (td, *J* = 6.9, 2.1 Hz, 1 H, 8a-H), 2.98 (dd, *J* = 14.1, 2.4 Hz, 1 H, 5-H_{ax}), 2.16 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.10 (m, 1 H, 2α-H), 2.08 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.90 (m, 1 H, 1β-H), 1.4−1.7 (m, 2 H, 1α-H and 2β-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 170.7, 170.6, 169.2, 69.7, 68.9, 67.3, 65.9, 60.8, 58.9, 48.3, 26.5, 25.1, 21.3, 21.1 (2 C), 20.7. − $C_{17}H_{25}NO_8$ (371.39): calcd. C 54.98, H 6.79, N 3.77; found C 54.90, H 6.75, N 3.73.

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