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Towards Allopumiliotoxins: A Concise Synthesis of the Indolizidine Core

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The common bicyclic indolizidine core present in several allopumiliotoxins was synthesized by the sequential use of a Crimmins' aldol reaction, an $SOCl_2$-mediated S_Ni displacement, and an intramolecular nucleophilic acyl substitution (INAS) as the key transformations.

Introduction

Dendrobates frogs are a rich source for new chemical substances, especially the poisonous materials found in the skin secretions produced for self-defense. These and several interesting compounds from the indolizidine class of natural products have been isolated and characterized.[1] Of more than 40 identified alkaloids, some display potent cardiotonic and myotonic activities.[2] Allopumiliotoxins (i.e., **1a**–**d**) belong to the indolizidine class of alkaloids isolated from the *Dendrobatidae* family of frogs and are 7-hydroxy congeners of pumiliotoxins. The complexity involved in this class of molecules includes a highly substituted 5,6-fused azabicyclic core (indolizidine frame), an (*E*)-geometric exocyclic olefin, and a varied side chain as shown in Figure 1.

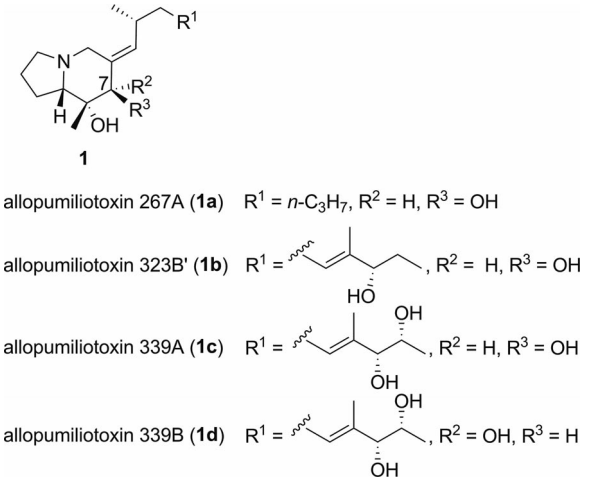

Figure 1. Structure of representative allopumiliotoxin alkaloids.

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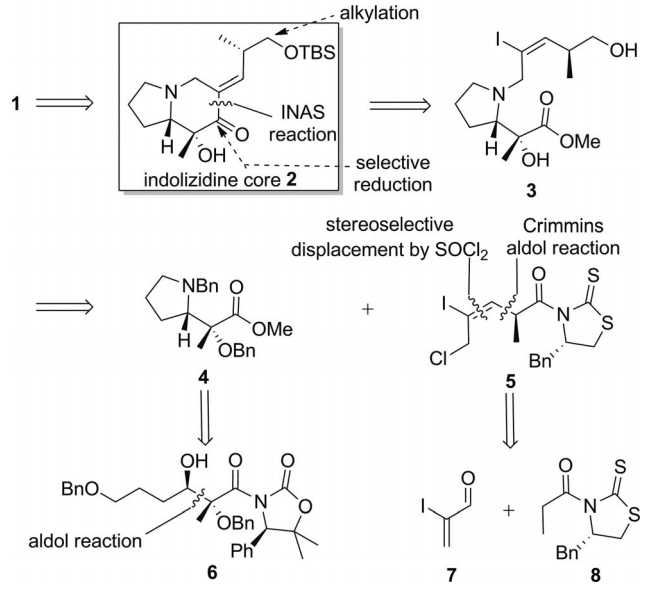
Intrigued by their complexity and activity, several research groups embarked on the synthesis of this class of molecules.[3–5] Interestingly, most of the reported syntheses began with L-proline or its analogs to stitch the second piperidine skeleton leading to the indolizidine core.[3] However, Tan and co-workers[4a,4b] utilized a cycloaddition approach to build the indolizidine moiety. Comins et al.[4c] and Wang et al.[4d] independently reported concise syntheses of allopumiliotoxin 267A (**1a**) using an enantiopure dihydropyridone building block and a (β-aminoalkenyl)lithium reagent, respectively.

Results and Discussion

Our group has been engaged in the total syntheses of alkaloids with various frameworks such as piperidines, pyrrolidines, and indolizidines.[6] We conceived that exploitation of asymmetric aldol reactions and an S_Ni reaction would provide a flexible strategy for the synthesis of the indolizidine core **2** as shown in the retrosynthetic analysis (Scheme 1). Several allopumiliotoxins could be realized from the indolizidine core **2**, which in turn can be constructed from fragments **4** and **5** through **3**. Fragment **4** can be synthesized easily in a stereoselective fashion as a result of an asymmetric aldol reaction through **6**. Allylic chloride **5** can be obtained by a stereoselective S_Ni displacement (by $SOCl_2$) of the aldol adduct obtained by a Crimmins' aldol reaction between aldehyde **7** and propionyl auxiliary **8**.

Thus, the synthesis of pyrrolidine **4** began with an asymmetric aldol reaction[7] between benzyloxybutyraldehyde (**9**) and Evans' auxiliary-appended amide **10** by using $Ti(OiPr)_3Cl$ and ethyldiisopropylamine (DIPEA) to result in aldol adduct **6** in 83% yield and approximately a *dr* of 95:5[8] (Scheme 2).[9] This reaction allowed us to install the tertiary asymmetric carbon atom with the required stereochemistry. Methyl ester **11** was obtained in 92% yield by oxidative cleavage of **6** followed by treatment with diazomethane. The selective debenzylation of the primary ether group of **11** by using Pd/C and H_2 at atmospheric pressure in EtOAc pro-

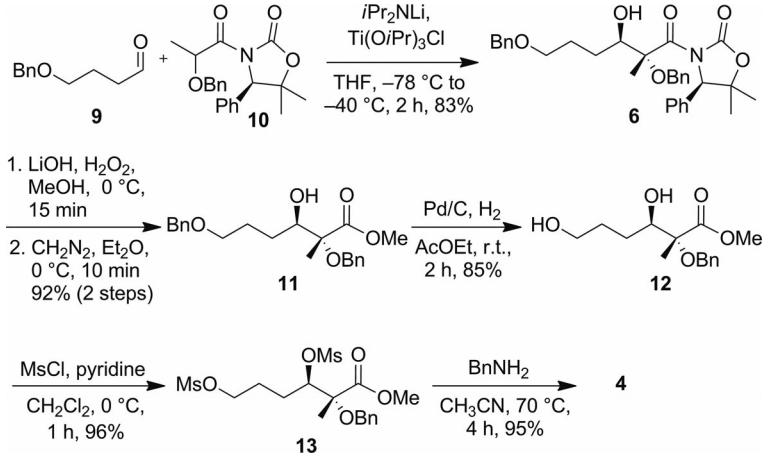


Scheme 1. Retrosynthetic analysis of (+)-allopumiliotoxins.

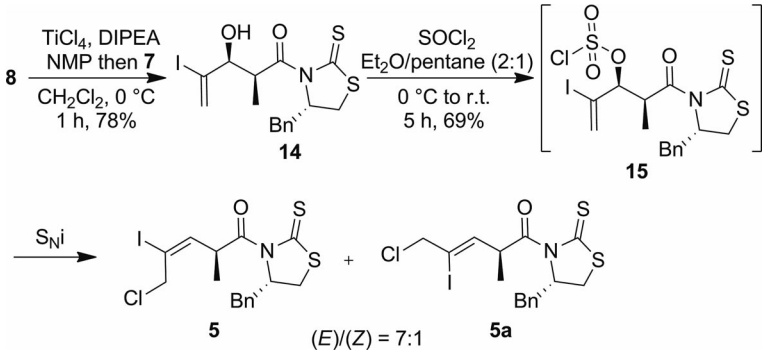
vided diol **12** in 85% yield. The mesylation of **12** to dimesylate **13** was achieved in 96% yield, and upon treatment with $BnNH_2$ in CH_3CN at 70 °C, pyrrolidine **4** was provided in 95% yield.

A highly diastereoselective asymmetric Crimmins' aldol addition[10,11] of the titanium enolate derived from the auxiliary *N*-propionylthiazolidinethione **8** [$TiCl_4$/DIPEA/NMP (*N*-methylpyrrolidone)] to aldehyde **7** [12] gave the Evans *syn*-aldol product **14** as the major isolable diastereomer (*dr* > 98:2)[13] in 78% yield. The newly formed chiral centers in **14** were confirmed by converting it to a known derivative **20** via intermediate **19**.[14,15] This aldol adduct **14** has a peculiar iodoallylic alcohol moiety, and when treated with $SOCl_2$ in a mixture of Et_2O/pentane, **14** underwent a diastereoselective S_Ni displacement reaction to afford a mixture of allyl chlorides **5** and **5a** [(*E*)/(*Z*), respectively] in 69% overall yield (Scheme 3).[16] This reaction facilitated the short synthesis of chiral (*E*)-2-iodoallylic chloride **5** in good selectivity and yield.

The solvent ratio (Et_2O/pentane) and temperature played a key role in the reactivity of $SOCl_2$ with allylic alcohol **14** and in optimizing the product ratio (Table 1). The (*E*)/(*Z*) ratio of allyl chlorides **5**/**5a** was 7:1 by using a mixture of Et_2O/pentane (2:1) at 0 °C and then at room temp. and was confirmed by ^1H NMR spectroscopy and nOe studies (Figure 2).[17] Compound **5** showed an nOe correlation between both the allylic protons (H_a and H_b, see Figure 2) confirming the (*E*) configuration for the olefin, and compound **5a** did not show any nOe correlation between the allylic protons confirming the (*Z*) configuration.



Scheme 2. Synthesis of pyrrolidine **4**.



Scheme 3. Synthesis of (*E*)-2-iodoallylic chloride **5**.

Table 1. Effect of solvents and temperature on the reactivity of $SOCl_2$ with allylic alcohol **14**.

Sample	Et_2O/pentane	Temperature and time	(*E*)/(*Z*)[a]	Yield of **5** and **5a**
1	1:3	–78 °C to 0 °C, 4 h, then room temp., 2 h	1.5:1	70%
2	1:1	–78 °C to 0 °C, 4 h, then room temp., 2 h	2.2:1	64%
3	2:1	–78 °C to 0 °C, 4 h, then room temp., 2 h	7:1	69%

[a] (*E*)/(*Z*) ratios were determined by ^1H NMR spectroscopy.

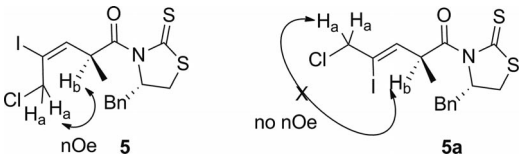


Figure 2. nOe correlation between allylic protons in **5** and **5a**.

On the basis of the above results, the selectivity of rearranged (*E*) isomer **5** over (*Z*) isomer **5a** in the allylic chlorination reaction can be explained by an S_Ni process[18] through a hypothetical chair-like six-membered transition state as shown in Figure 3. The large R group would induce 1,3-diaxial-type interactions in transition state **15**, but not in **15a**. In contrast, the R group is likely to face more steric hindrance from the bulky iodo group at the adjacent carbon atom than 1,3-diaxial-type interactions from the proton at the third carbon atom, which can also be envisaged by Newman projections **15′** and **15a′**. We assume that the strain due to the hindrance between the large R and iodo groups could be relieved by placing them at the maximum possible distance from each other as shown in transition state **15′**, which results in the formation of (*E*)-allylic chloride **5** as the major isomer.

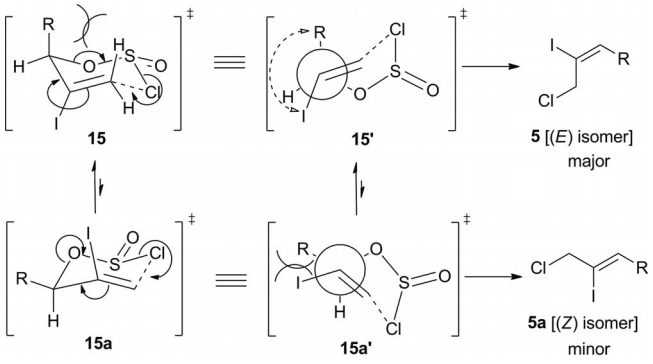


Figure 3. Plausible chlorination transition states for **15**.

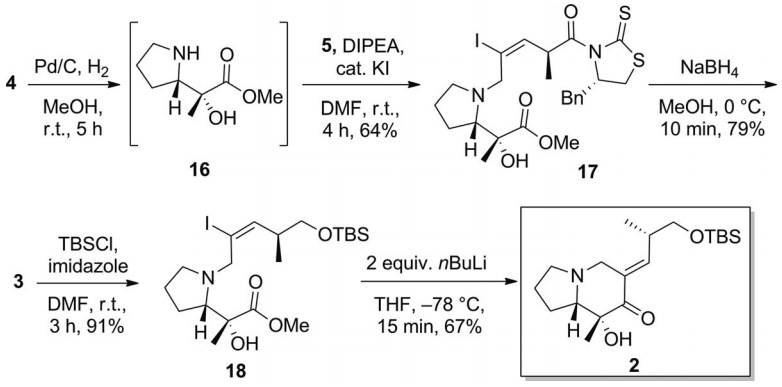
Having both key fragments **4** and **5** in hand, we proceeded to the synthesis of indolizidine core **2** as shown in Scheme 4. The hydrogenation of pyrrolidine **4** by using standard conditions (H_2, Pd/C) in MeOH at room temp. afforded amino alcohol **16**. The filtrate containing amino alcohol **16** was concentrated and then directly subjected to *N*-allylation by treatment with allylic chloride **5** in the presence of DIPEA and a catalytic amount of KI in DMF (*N*,*N*-dimethylformamide) at room temp. for 4 h to afford **17** in 64% yield. After successful allylation of the amine, compound **17** was treated with 1 equiv. of $NaBH_4$ at 0 °C to afford alcohol **3** as a viscous liquid in 79% yield with negligible amounts of the over-reduced product of the methyl ester. The primary alcohol in **3** was selectively converted into silyl ether **18** in 91% isolated yield by using *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF as the solvent at room temp. The deliberate intramolecular nucleophilic acyl substitution (INAS) reaction was performed on vinyl iodoester **18** by treatment with 2 equiv. of *n*BuLi in tetrahydrofuran (THF) at –78 °C to afford enone **2** in 67% yield, which completes the concise synthesis for the indolizidine core of (+)-allopumiliotoxins.[19]

Conclusions

We have achieved a concise synthesis for the indolizidine core **2** of allopumiliotoxins by using asymmetric aldol reactions, an $SOCl_2$-mediated stereoselective S_Ni displacement reaction, and an INAS reaction as the key transformations.

Experimental Section

General Methods: FTIR spectra were recorded as KBr thin films or neat. For low- (MS) and high-resolution mass spectrometry



Scheme 4. Synthesis of allopumiliotoxin core **2**.

(HRMS), *m*/*z* (mass/charge) ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out by using silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under nitrogen in flame- or oven-dried glassware with magnetic stirring. The products were characterized by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry.

(4*R*)-3-[(2*R*,3*R*)-2,6-Bis(benzyloxy)-3-hydroxy-2-methylhexanoyl]-5,5-dimethyl-4-phenyloxazolidin-2-one (6): In a clean, dry 250 mL round-bottomed flask, equipped with magnetic stir bar, under nitrogen, freshly distilled diisopropylamine (0.58 mL, 4.16 mmol) was dissolved in dry THF (15 mL). The resulting clear, colorless solution was cooled to –78 °C in a dry ice/acetone bath. To it was added *n*BuLi (2.5 M solution in hexane, 1.03 mL, 2.57 mmol) dropwise, and the cold reaction mixture was stirred at –78 °C for 20 min. (4*R*)-5,5-Dimethyl-4-phenyloxazolidin-2-one **10** (0.7 g, 1.98 mmol) was dissolved in THF (5 mL), and the resulting solution was added dropwise to the freshly prepared lithium diisopropylamide (LDA) to afford a pale yellow solution that was stirred at –78 °C for 30 min. To it was added Ti(O*i*Pr)$_3$Cl (1 M solution in THF, 6.54 mL, 6.54 mmol) dropwise by syringe to give rise to a dark red/brown solution that was stirred at –40 °C for 1 h. After cooling the reaction mixture to –78 °C, 4-(benzyloxy)butanal (**9**; 1.06 g, 5.95 mmol) in THF (5 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at –40 °C for 2 h. After completion of the reaction, which was monitored by thin layer chromatography, it was quenched under cold conditions by the addition of saturated NH_4Cl (2 mL) and Celite. After warming to room temp., the resulting suspension was filtered through a fritted funnel, the filter cake was rinsed with ethyl acetate, and the filtrate was concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **6** (0.87 g, 83%) as a white solid. R_f = 0.35 (SiO_2, 30% EtOAc in petroleum ether); m.p. 82–84 °C. IR (neat): $\tilde{\nu}_{max}$ = 3445, 2930, 2861, 2360, 1778, 1696, 1508, 1456, 1370, 1217, 1100, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 13 H), 7.18–7.11 (m, 2 H), 5.14 (s, 1 H), 4.54–4.45 (m, 5 H), 3.51–3.45 (m, 2 H), 3.23 (br. s, 1 H), 1.92–1.78 (m, 1 H), 1.75–1.58 (m, 2 H), 1.69 (s, 3 H), 1.54–1.40 (m, 1 H), 1.49 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 151.7, 138.4, 138.2, 136.3, 128.7, 128.5, 128.3, 127.6, 127.4, 127.3, 127.3, 126.3, 85.9, 82.0, 73.5, 72.8, 70.1, 69.0, 66.6, 28.8, 28.5, 26.4, 23.6, 16.8 ppm. HRMS (ESI): calcd. for $C_{32}H_{38}NO_6$ [M + H]$^+$ 532.2694; found 532.2665. $[\alpha]_D^{25}$ = –44.0 (*c* = 1.0, CH_2Cl_2).

Methyl (2*R*,3*R*)-2,6-Bis(benzyloxy)-3-hydroxy-2-methylhexanoate (11): To a solution of compound **6** (0.81 g, 1.52 mmol) in MeOH (10 mL) in a 25 mL round-bottomed flask were added LiOH (10% aqueous solution, 0.73 mL, 3.05 mmol) and H_2O_2 (25% solution, 1.02 mL, 10.88 mmol) very slowly at 0 °C. After 15 min at the same temperature, TLC was used to monitor for the completion of the reaction, and the reaction was quenched by the addition of a saturated solution of Na_2SO_3 (2 mL) followed by aqueous $NaHCO_3$ (2 mL). The solvent, MeOH, was evaporated under reduced pressure at low temperature. The aqueous layer was diluted with water and acidified by the addition of HCl (1 N), and the carboxylic acid was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude acid was dissolved in diethyl ether (5 mL), and the solution was cooled to 0 °C in an ice bath. To a separate 25 mL round-bottomed flask equipped with stir bar were added diethyl ether (5 mL) and aqueous KOH (10% aqueous solution, 2 mL, 3.5 mmol). The mixture was cooled to 0 °C, *N*-nitroso-*N*-methylurea (NMU·HCl; 313 mg, 3.05 mmol) was slowly added, and the mixture was vigorously stirred. After 10–15 min, the diethyl ether layer was separated, dried with anhydrous Na_2SO_4, and slowly added to the carboxylic acid at 0 °C. After complete consumption of the acid, the reaction mixture was concentrated. Purification by flash column chromatography on silica gel (10% EtOAc in hexanes) afforded methyl ester **11** (0.52 g, 92%) as clear, colorless oil. R_f = 0.29 (SiO_2, 30% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3443, 2926, 2857, 1734, 1453, 1373, 1262, 1125, 1118, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 10 H), 4.56–4.44 (m, 2 H), 4.49 (s, 2 H), 3.80 (d, *J* = 10.0 Hz, 1 H), 3.76 (s, 3 H), 3.50 (t, *J* = 6.0 Hz, 2 H), 2.82 (br. s, 1 H), 1.92–1.78 (m, 1 H), 1.77–1.63 (m, 2 H), 1.52 (s, 3 H), 1.51–1.41 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 138.3, 138.2, 128.3, 128.3, 127.6, 127.5, 127.5, 82.9, 75.7, 72.8, 70.0, 66.9, 52.0, 28.1, 26.6, 17.1 ppm. MS (ESI): *m*/*z* (%) = 395 (100) [M + Na]$^+$. $[\alpha]_D^{25}$ = +6.9 (*c* = 1.0, CH_2Cl_2).

Methyl (2*R*,3*R*)-2-(Benzyloxy)-3,6-dihydroxy-2-methylhexanoate (12): To a solution of compound **11** (0.465 g, 1.25 mmol) in EtOAc (10 mL) was added Pd/C (10%, 15 mg, 0.13 mmol). The mixture was stirred under hydrogen. After 2 h, the reaction mixture was filtered through a short bed of Celite to remove the catalyst and washed with EtOAc (2 × 5 mL). The filtrate was concentrated in vacuo. Purification of the crude compound by column chromatography on silica gel (30% EtOAc in hexanes) afforded compound **12** (0.299 g, 85%) as a viscous liquid. R_f = 0.34 (SiO_2, 40% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3390, 2943, 2872, 2360, 1731, 1514, 1453, 1265, 1123, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 4.56–4.45 (m, 2 H), 3.83–3.78 (m, 1 H), 3.78 (s, 3 H), 3.72–3.56 (m, 2 H), 2.76 (br. s, 2 H), 1.79–1.66 (m, 3 H), 1.53 (s, 3 H), 1.51–1.40 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 138.1, 128.3, 127.6, 82.9, 75.9, 67.0, 62.6, 52.1, 29.7, 28.1, 17.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{23}O_5$ [M + H]$^+$ 283.1540; found 283.1513. $[\alpha]_D^{25}$ = +8.0 (*c* = 1.35, $CHCl_3$).

Methyl (2*R*,3*R*)-2-(Benzyloxy)-2-methyl-3,6-bis(methylsulfonyloxy)-hexanoate (13): Diol **12** (0.245 g, 0.86 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and pyridine (346 μL, 4.34 mmol) was added at 0 °C under nitrogen. To the mixture, MsCl (167 μL, 2.17 mmol) was added slowly, and the reaction mixture was stirred at room temp. After confirming the complete consumption of the starting material by TLC, HCl (1 N, 4 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$, separated, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20% EtOAc in hexanes) to afford dimesyl compound **13** (0.365 g, 96% yield) as an oily liquid. R_f = 0.24 (SiO_2, 30% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3026, 2977, 1691, 1516, 1344, 1259, 1164, 1054, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 4.95–4.88 (m, 1 H), 4.5 (q, *J* = 10.3 Hz, 2 H), 4.35–4.20 (m, 2 H), 3.82 (s, 3 H), 2.97 (s, 3 H), 2.92 (s, 3 H), 2.08–1.82 (m, 4 H), 1.57 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 137.3, 128.3, 127.9, 84.6, 82.1, 69.0, 67.1, 52.5, 38.8, 37.2, 25.9, 25.4, 17.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{30}NO_9S_2$ [M + NH$_4$]$^+$ 456.1356; found 456.1318. $[\alpha]_D^{25}$ = +12.5 (*c* = 1.0, $CHCl_3$).

Methyl (2*R*)-2-(Benzyloxy)-2-[(2*S*)-1-benzylpyrrolidin-2-yl]propanoate (4): In a 50 mL round-bottomed flask, compound **13** (0.316 g, 0.72 mmol) was dissolved in CH_3CN (5 mL), and the solution was stirred under nitrogen. Benzylamine (231 mg, 2.16 mmol) was added, and the reaction mixture was heated to reflux until the starting material was consumed (monitored by TLC). After 4 h,

CH_3CN was removed under reduced pressure, and the reaction mixture was diluted with water (10 mL). The compound was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified on silica gel by column chromatography (5% EtOAc in hexanes) to afford pyrrolidine **4** (242 mg, 95%) as an oily, yellow liquid. R_f = 0.44 (SiO_2, 10% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 2950, 2867, 2361, 1734, 1454, 1378, 1259, 1113, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.16 (m, 10 H), 4.55 (d, J = 11.3 Hz, 1 H), 4.46 (d, J = 13.5 Hz, 1 H), 4.35 (d, J = 11.3 Hz, 1 H), 3.73 (s, 3 H), 3.38 (d, J = 13.5 Hz, 1 H), 3.21 (dd, J = 8.8, 4.7 Hz, 1 H), 2.96–2.87 (m, 1 H), 2.28–2.19 (m, 1 H), 1.86–1.73 (m, 1 H), 1.73–1.59 (m, 3 H), 1.56 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 140.8, 138.7, 128.4, 128.1, 128.0, 127.2, 126.4, 85.5, 69.1, 67.0, 61.1, 54.8, 51.8, 27.3, 23.8, 15.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{27}NO_3$ $[M + H]^+$ 354.2064; found 354.2055. $[\alpha]_D^{25}$ = +3.79 (c = 1.45, $CHCl_3$).

2-Iodoacrylaldehyde (7): To a solution of acrylaldehyde (1.0 g, 17.8 mmol) dissolved in diethyl ether (25 mL) was added triethylamine (1.24 mL, 8.9 mmol) at 0 °C. To the mixture was added iodine (1.29 g, 8.9 mmol) in portions at the same temperature. After 15 min, the reaction mixture was filtered through a bed of Celite, and the filtrate was concentrated in vacuo at low temperature. Bulb-to-bulb distillation (b.p. 64 °C/18 mm) of the crude residue afforded 2-iodoacrylaldehyde (**7**; 40%) as a yellow liquid. R_f = 0.60 (SiO_2, 5% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3445, 1634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 7.42 (d, J = 1.5 Hz, 1 H), 7.27 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8, 144.3, 113.0 ppm.

(2*S*,3*S*)-1-[(4*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-hydroxy-4-iodo-2-methylpent-4-en-1-one (14): A solution of the *N*-acylthiazolidinethione **8** (0.548 g, 2.06 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and stirred under nitrogen. $TiCl_4$ (1.08 mL, 2.17 mmol) was added, and the mixture was stirred for 5 min. DIPEA (0.39 mL, 2.27 mmol) was added slowly dropwise to observe a dark brown solution. This solution was stirred at 0 °C for 40 min, and then 1-methyl-2-pyrrolidinone (0.20 mL, 2.06 mmol) was added at the same temperature. After 10 min, freshly distilled 2-iodoacrylaldehyde (**7**; 0.451 g, 2.48 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl, and the mixture was warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded aldol adduct **14** (0.72 g, 78% yield) as a yellow solid. R_f = 0.30 (SiO_2, 20% EtOAc in petroleum ether); m.p. 103–105 °C. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2853, 2356, 1680, 1459, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 6.48 (d, J = 1.5 Hz, 1 H), 5.90 (s, 1 H), 5.12 (ddd, J = 10.5, 6.7, 3.7 Hz, 1 H), 4.61 (quint, J = 6.7 Hz, 1 H), 4.00 (t, J = 5.2 Hz, 1 H), 3.44 (dd, J = 11.3, 6.7 Hz, 1 H), 3.22 (dd, J = 13.5, 3.7 Hz, 1 H), 3.04 (dd, J = 12.8, 10.5 Hz, 1 H), 2.91 (d, J = 11.3 Hz, 1 H), 2.53 (d, J = 5.2 Hz, 1 H), 1.32 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0, 176.4, 136.2, 129.4, 128.8, 127.9, 127.2, 113.1, 79.5, 68.8, 44.3, 36.6, 32.7, 12.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{18}INO_2S_2$ $[M + H]^+$ 447.9896; found 447.9931. $[\alpha]_D^{25}$ = +175.36 (c = 1.0, $CHCl_3$).

(2*R*,3*S*)-4-Iodo-2-methylpent-4-ene-1,3-diol (19): In a 25 mL round-bottomed flask equipped with a stir bar, compound **14** (0.200 g, 0.44 mmol) was dissolved in MeOH (2 mL), and the solution was cooled to 0 °C. $NaBH_4$ (0.034 g, 0.89 mmol) was added slowly. After completion in 15 min (monitored by TLC), the reaction was quenched by the addition of saturated NH_4Cl (1 mL), and MeOH was evaporated under reduced pressure. The aqueous layer was diluted with water (4 mL), and the compound was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (15% EtOAc in hexanes) afforded 1,3-diol **19** (0.104 g, 96%) as a colorless liquid. IR (neat): $\tilde{\nu}_{max}$ = 2928, 2862, 2355, 1444, 1160 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.48 (d, J = 2.0 Hz, 1 H), 5.96 (s, 1 H), 4.19 (d, J = 4.0 Hz, 1 H), 3.74–3.68 (m, 2 H), 2.23 (br. s, 1 H), 2.20–2.13 (m, 1 H), 0.95 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.4, 114.1, 79.2, 65.9, 37.5, 9.4 ppm. MS (ESI): m/z (%) = 243 (100) $[M + H]^+$. $[\alpha]_D^{20}$ = –1.94 (c = 0.72, $CHCl_3$).

(2*S*,3*E*)-1-[(3*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-chloro-4-iodo-2-methylpent-3-en-1-one (5): In a 25 mL round-bottomed flask equipped with a stir bar, compound **14** (0.638 g, 1.42 mmol) was dissolved in Et_2O/pentane (2:1, 50 mL), and the solution was cooled to 0 °C. To this mixture was added $SOCl_2$ in Et_2O/pentane (2:1, 20 mL) at 0 °C, and the reaction mixture was stirred at room temp. for 5 h. The reaction mixture was cooled to –78 °C, and Et_3N (3.97 mL, 28.5 mmol) was added. The resulting mixture was stirred for 30 min followed by the addition of saturated $NaHCO_3$ (10 mL). The compound was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated quickly in vacuo at room temp. The crude residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to afford (*E*)-2-iodoallyl chloride **5** (0.405 g, 61%) as viscous, yellow liquid. R_f = 0.48 (SiO_2, 10% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 2926, 2857, 2360, 1689, 1448, 1344, 1192, 869, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 6.49 (d, J = 10.0 Hz, 1 H), 4.89 (ddd, J = 10.3, 6.9, 3.7 Hz, 1 H), 4.67 (qd, J = 10.1, 6.7 Hz, 1 H), 4.48 (d, J = 12.4 Hz, 1 H), 4.25 (d, J = 12.4 Hz, 1 H), 3.37 (ddd, J = 11.3, 7.1, 0.7 Hz, 1 H), 3.13 (dd, J = 13.0, 3.5 Hz, 1 H), 2.95 (dd, J = 13.2, 10.3 Hz, 1 H), 2.92 (d, J = 11.5 Hz, 1 H), 1.32 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 171.8, 144.1, 136.3, 129.3, 128.8, 127.2, 97.3, 59.9, 49.2, 40.8, 37.3, 28.6, 17.7 ppm. MS (EI): m/z = 449 $[M – OH]^+$, 414 $[449 – Cl]^+$, 322 $[449 – I]^+$, 286 $[322 – Cl]^+$. $[\alpha]_D^{25}$ = +82.16 (c = 1.25, $CHCl_3$).

Methyl (2*R*)-2-[(2*S*)-1-{(2*E*,4*S*)-5-[(4*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-2-iodo-4-methyl-5-oxopent-2-enyl}pyrrolidin-2-yl]-2-hydroxypropanoate (17): To a stirred solution of pyrrolidine **4** (0.183 g, 0.51 mmol) in MeOH (4 mL) was added Pd/C (10%, 0.006 g, 0.05 mmol), and then the mixture was stirred under hydrogen with the help of hydrogen balloons. After 4 h, the reaction mixture was filtered through a short bed of Celite and washed with MeOH (2 × 4 mL). The filtrate was concentrated in vacuo. This crude amino alcohol **16** (0.089 g, 99%) was used directly in the next reaction without further purification; R_f = 0.21 (SiO_2, 20% MeOH in CH_2Cl_2). To a stirred solution of amino alcohol **16** (0.089 g, 0.51 mmol) in dry DMF (1 mL) were added DIPEA (133 μL, 0.77 mmol) and allyl chloride **5** (0.314 g, 0.67 mmol) in dry DMF (1 mL) followed by a catalytic amount of KI (26 mg, 0.15 mmol). The reaction mixture was stirred at room temp. for 4 h. After consumption of the amine (monitored by TLC), water (5 mL) was added to the reaction mixture, and the compound was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford coupled compound **17** (0.199 g, 64%) as viscous, yellow liquid. R_f = 0.34 (SiO_2, 20% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 2926, 2856, 1737, 1692, 1546, 1194,

746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.28–7.24 (m, 3 H), 6.39 (d, J = 9.7 Hz, 1 H), 4.86 (ddd, J = 10.6, 6.7, 3.8 Hz, 1 H), 4.73 (qd, J = 10.6, 6.7 Hz, 1 H), 3.74 (s, 3 H), 3.35 (dd, J = 11.6, 7.7 Hz, 1 H), 3.26 (dd, J = 7.7, 5.8 Hz, 1 H), 3.16 (d, J = 14.5 Hz, 1 H), 3.09 (dd, J = 12.6, 2.9 Hz, 1 H), 3.04–2.88 (m, 4 H), 2.36–2.28 (m, 1 H), 2.23–2.14 (m, 1 H), 1.94–1.85 (m, 2 H), 1.79–1.59 (m, 2 H), 1.32 (s, 3 H), 1.24 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 172.4, 172.3, 140.4, 136.3, 129.3, 128.8, 127.2, 106.9, 75.6, 68.7, 60.2, 59.7, 54.1, 52.4, 40.9, 37.2, 28.6, 26.6, 24.1, 22.6, 17.9 ppm. MS (ESI): m/z = 586 $[M - OH]^+$. $[\alpha]_D^{25.6}$ = +46.33 (c = 1.1, $CHCl_3$).

Methyl (2*R*)-2-Hydroxy-2-{(2*S*)-1-[(2*E*,4*S*)-5-hydroxy-2-iodo-4-methylpent-2-enyl]pyrrolidin-2-yl}propanoate (3): To a solution of **17** (0.188 g, 0.31 mmol) in MeOH (5 mL), $NaBH_4$ (0.013 g, 0.34 mmol) was added at –20 °C under nitrogen, and the mixture was stirred at 0 °C for 5 min. When still cold, the reaction was quenched by the addition of saturated NH_4Cl (3 mL), and the compound was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified on silica gel by column chromatography (15% EtOAc in hexanes) to afford diol **3** (0.098 g, 79%) as a colorless, oily liquid. R_f = 0.20 (SiO_2, 30% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3396, 2956, 2926, 1730, 1623, 1452, 1255, 1117, 1039 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.15 (d, J = 10.0 Hz, 1 H), 3.78 (s, 3 H), 3.51 (dd, J = 10.3, 5.2 Hz, 1 H), 3.38–3.18 (m, 4 H), 3.15–3.05 (m, 1 H), 2.84–2.68 (m, 1 H), 2.42 (dd, J = 16.9, 7.5 Hz, 1 H), 1.94–1.85 (m, 2 H), 1.80–1.66 (m, 2 H), 1.34 (s, 3 H), 0.96 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 146.8, 102.1, 75.7, 69.3, 66.5, 60.7, 54.1, 52.5, 39.2, 26.6, 24.0, 23.1, 16.4 ppm. HRMS (ESI): calcd for $C_{14}H_{25}INO_4$ $[M + H]^+$ 398.0823; found 398.0809. $[\alpha]_D^{25.6}$ = –45.86 (c = 1.0, $CHCl_3$).

Methyl (2*R*)-2-{(2*S*)-1-[(2*E*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-iodo-4-methylpent-2-enyl]pyrrolidin-2-yl}-2-hydroxypropanoate (18): To a solution of diol **3** (0.076 g, 0.19 mmol) in DMF (1.5 mL) were added imidazole (0.039 g, 0.57 mmol) and TBSCl (0.043 g, 0.28 mmol) at room temp. After 2 h, the reaction mixture was diluted with water (2 mL), and the compound was extracted with Et_2O (2 × 3 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified on silica gel by column chromatography (5% EtOAc in hexanes) to afford the silyl ether **18** (0.089 g, 91%) as a colorless, oily liquid. R_f = 0.44 (SiO_2, 10% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 2924, 2855, 1738, 1461, 1106, 839, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.04 (d, J = 10.0 Hz, 1 H), 3.73 (s, 3 H), 3.42–3.29 (m, 2 H), 3.28–3.19 (m, 2 H), 3.04–2.88 (m, 2 H), 2.79–2.68 (m, 1 H), 2.29–2.18 (m, 1 H), 1.92–1.81 (m, 2 H), 1.78–1.60 (m, 2 H), 1.30 (s, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.85 (s, 9 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 146.0, 103.9, 75.5, 68.6, 66.9, 59.8, 53.6, 52.3, 39.1, 26.8, 25.8, 24.1, 22.7, 18.2, 16.4, –5.2, –5.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{39}INO_4Si$ $[M + H]^+$ 512.1688; found 512.1692. $[\alpha]_D^{25.6}$ = –25.40 (c = 1.0, $CHCl_3$).

(8*R*,8a*S*)-6-[(1*E*,2*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-propylidene]-8-hydroxy-8-methylhexahydroindolizin-7(1*H*)-one (2): A solution of **18** (0.077 g, 0.15 mmol) in dry THF (5 mL) was cooled to –78 °C under nitrogen, and *n*BuLi (125 μL, 0.31 mmol) was added. The reaction mixture was stirred at the same temperature for 30 min and was monitored by TLC for the consumption of starting material. The reaction was quenched by the addition of a saturated solution of NH_4Cl (4 mL), and the compound was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified on silica gel by column chromatography (10% EtOAc in hexanes) to afford enone **2** (0.036 g, 67%) as a colorless oil. R_f = 0.25 (SiO_2, 20% EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 3392, 2926, 2856, 1622, 1460, 1384, 1085, 839, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.49 (d, J = 10.1 Hz, 1 H), 4.03 (d, J = 14.3 Hz, 1 H), 3.54–3.34 (m, 2 H), 3.26–3.14 (m, 1 H), 3.04 (dd, J = 14.1, 2.4 Hz, 1 H), 2.63–2.47 (m, 1 H), 2.46–2.25 (m, 1 H), 2.00–1.92 (m, 2 H), 1.90–1.76 (m, 2 H), 1.70–1.45 (m, 2 H), 1.26 (s, 3 H), 1.0 (d, J = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 144.4, 131.3, 73.0, 69.2, 67.0, 55.1, 52.2, 35.9, 31.9, 25.8, 23.5, 22.7, 18.2, 17.8, –5.3, –5.4 ppm. HRMS (ESI): calcd for $C_{19}H_{36}NO_3Si$ $[M + H]^+$ 354.2459; found 354.2434. $[\alpha]_D^{30}$ = –10.65 (c = 1.0, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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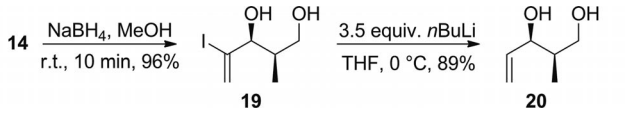

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