cis-5-Amino-6-hydroxycyclohexadiene as a Chiral Building Block: An Asymmetric Synthesis of (−)-Swainsonine

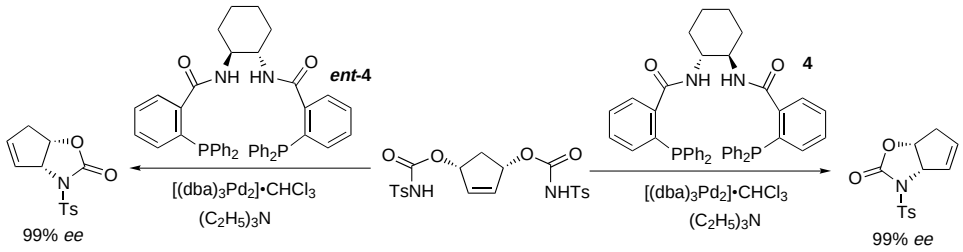
Barry M. Trost* and Daniel E. Patterson[a]

Abstract: A new asymmetric building block, *cis*-5-hydroxy-6-aminocyclohexa-1,3-diene in which the double bonds are differentiated as the Diels–Alder adduct with anthracene, is available in an enantiomerically pure form in three or four steps from anthracence and benzoquinone. The key step is a palladium-catalyzed desymmetrization of a *meso*-2-en-1,4-diol. It serves as a chiral precursor of the anticancer agent swainsonine. Diastereoselective dihydroxylation dictated by the dihydroanthracence unit sets the four stereogenic centers of swainsonine. The sequence then first creates the pyrrolidine ring followed by the piperidine ring. The effectiveness of the synthesis is evident from the overall yield of 15% for the 15-step protocol.

Keywords: alkaloids · asymmetric synthesis · natural products · palladium · swainsonine · total synthesis

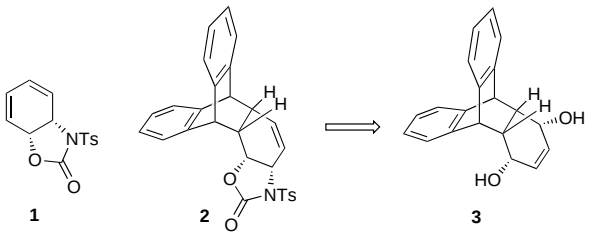
Introduction

Asymmetric synthesis utilizing transition metal catalysis has the advantage of providing equivalent access to either enantiomer of the product. Exploring the properties of both enantiomeric forms becomes increasingly important. For example, in the development of nucleoside analogues as anti-HIV agents, the L-nucleosides sometimes are clinically preferred over the "natural" D-isomers because they have lower toxicity.[1] We have been developing the utility of the AAA (asymmetric allylic alkylation) reaction with palladium, molybdenum, and tungsten catalysis.[2–4] Recently, we established that the bis-urethanes of *meso*-2-ene-1-4-diols can be cyclized to vinyloxazolidin-2-ones with near perfect enantioselectivity as shown in Scheme 1.[5] This reaction serves as the equivalent of an asymmetric and regioselective *cis*-aminohydroxylation of a diene. We envisioned that an equivalent of the oxazolidin-2-one **1**, in which the double bonds were differentiated as in **2**, would be a useful asymmetric building block. Using the method of Scheme 1, the achiral precursor becomes diol **3** which derives in two steps from anthracene and benzoquinone (Scheme 2).[6]



Scheme 1. Enantioselective synthesis of vinyloxazolidin-2-ones.

This strategy was examined in the context of a synthesis of the anticancer agent (−)-swainsonine (**5**). Polyhydroxylated indolizidine alkaloids such as swainsonine have received considerable attention because of their activity as glucosidase inhibitors and because of their structural complexity.[7] These compounds have shown anticancer, antiviral, and immunoregulatory properties. Swainsonine was first isolated from the fungus *Rhizoctonia leguminicola* in 1973.[8] It has shown activity as a potent inhibitor of both lysosomal α-mannosidase and mannosidase II, and has been selected for clinical testing



Scheme 2. The key intermediates.

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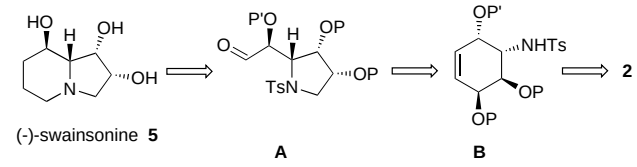
as an anticancer drug.[9] Because of its biological importance, swainsonine has been the focus of extensive synthetic effort. Most of the syntheses reported to date use carbohydrate starting materials,[10] but there have been four total syntheses from achiral starting materials.[11] We report an effective synthesis of (−)-swainsonine starting from achiral starting materials that utilizes the palladium-catalyzed desymmetrization of *meso*-bis-carbamates.

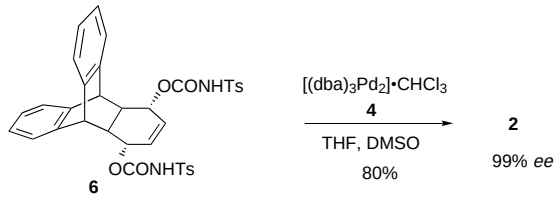
The present strategy for the synthesis of swainsonine is shown in Scheme 3. Swainsonine is available from **A** via a two-carbon homologation followed by ring closure. Aldehyde **A** could arise from **B** by a reductive ozonolysis followed by a Mitsunobu cyclization and oxidation. Cyclohexene **B** was proposed to arise from oxazolidinone **2** by diastereoselective dihydroxylation followed by a retro Diels–Alder reaction.



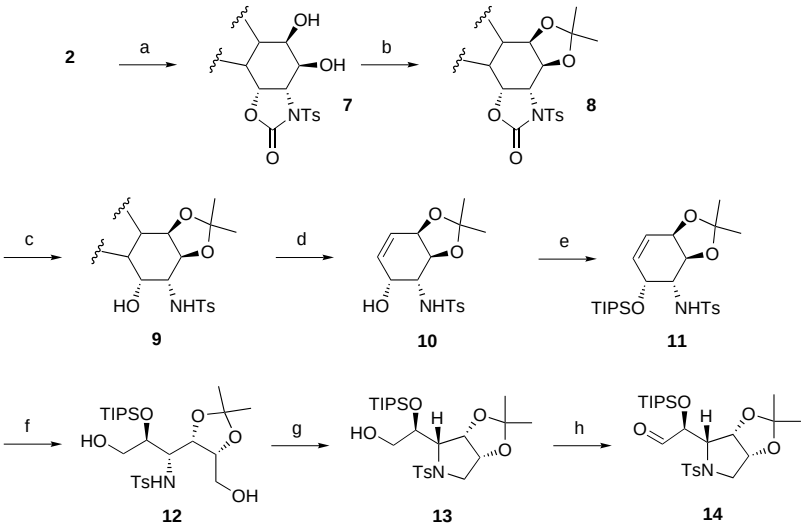
Scheme 3. Retrosynthesis of (−)-swainsonine.

The present synthesis uses the desymmetrization of diol **3** (readily available in two steps from anthracene and benzoquinone in 85% overall yield)[6] to set the stereochemistry of the 1,2-amino alcohol functionality found in swainsonine. Treatment of **3** with tosyl isocyanate (room temperature to 60 °C, THF) provided the desired bis-carbamate **6** in 90% yield. Desymmetrization with $[dba_3Pd_2]\cdot CHCl_3$ (tris-dibenzylideneacetone-bis-palladium, chloroform solvate) and chiral ligand **4** afforded oxazolidinone **2** in 80% yield and >99% *ee* (Scheme 4). The enantiomeric excess was determined to be >95% by chiral shift analysis, and >99% by chiral HPLC analysis on the amino alcohol.[10] Because of the low solubility of **6** in most organic solvents, a mixed solvent system of THF/DMSO (5:1) gave the best results. The bis-carbamate may be formed in situ from diol **3** and the chiral palladium catalyst subsequently added, but the yield was lower although the *ee* was still excellent. It is best to recrystallize the bis-carbamate for reproducible results.

With enantiopure oxazolidin-2-one **2** in hand, its dihydroxylation proceeded from the less hindered face to give a single diastereomer of diol **7** in 95% yield (Scheme 5). Diol **7** contains the four contiguous stereocenters of swainsonine in the correct configuration. Protection of the diol as the acetonide **8** proceeded in 94% yield, and basic hydrolysis of the oxazolidinone provided the desired amino alcohol **9** in 96% yield. The protected double bond of **9** was unmasked by flash vacuum thermolysis (500 °C, 0.05 mm Hg, 91%). The "deblocking" can also be done at the stage of oxazolidin-2-one **8**, but the FVT yields were lower. The choice of the alcohol protecting group is important for the next stage of the synthesis. With many silyl ethers, after ozonolysis and reductive work-up, they had a propensity to migrate from the secondary alcohol to the neighboring primary alcohol. For example, the TBDPS group extensively migrated. We therefore turned to the MOM (methoxymethyl) protecting group but were thwarted as a result to N-alkylation competing with O-alkylation. A satisfactory solution was found in the use of the triisopropylsilyl (TIPS) ether but even here, the temperature during the reduction phase had to be carefully controlled. The hydroxyl group of **10** was protected as the TIPS ether in standard fashion to give cyclohexene **11** in 95% yield. Ozonolysis of **11** followed by treatment with dimethyl sulfide gave the corresponding hemiaminal, which could be isolated if desired. Normally, it was directly reduced to the acyclic amino diol **12** with sodium borohydride in methanol in 62% yield. Exposure of **12** to Mitsunobu conditions closed the five-membered ring in 86%. There is



Scheme 4. Synthesis of **2**.



Scheme 5. Synthesis of fragment **A** (**14**). a) OsO_4, NMO, CH_2Cl_2, RT, 12 h, 95%; b) 2,2-dimethoxypropane, *p*-TsOH·H_2O, acetone, RT, 2 h, 94%; c) K_2CO_3, MeOH/H_2O (9:1), 60 °C, 1.5 h, 96%; d) FVT 500 °C, 0.05 mm Hg, 91%; e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, RT, 3 h, 95%; f) O_3, CH_2Cl_2, −78 °C, 15 min, then Me_2S, −78 °C → RT, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h, 62%; g) DIAD, Ph_3P, THF, 0 °C, 45 min, 86%; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 45 min, 98%.

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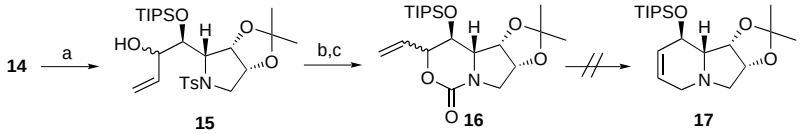
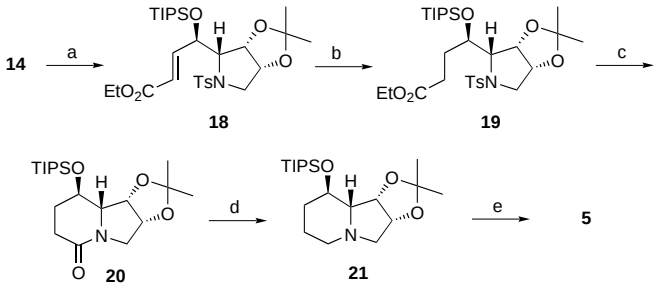
no need to protect the other primary alcohol since azetidine formation is much less favorable than pyrrolidine formation. Oxidation of the primary alcohol **13** with Dess–Martin periodinane afforded key aldehyde **14** nearly quantitatively.

Two routes were investigated for the synthesis of swainsonine from aldehyde **14**. In route A, the six-membered ring of swainsonine was envisioned to be closed by a 6-*endo* palladium-catalyzed allylic amination. To investigate route A (Scheme 6), aldehyde **14** was treated with vinylmagnesium bromide in THF (95%). Conversion of the resulting mixture of diastereomeric allyl alcohols **15** to the methyl carbonate required use of a strong base such as *n*-butyllithium. Removal of the toluenesulfonyl protecting group with sodium–mercury amalgam in methanol buffered with sodium dibasic phosphate[12] effected a cyclization of the amine onto the carbonate to form the bicyclic carbamate **16** directly in 69% yield. All attempts to convert **15** into the desired allyl amine **17** using palladium catalysis however, were unsuccessful and resulted in simply the epimerization of the starting material at the carbamate chiral center, or decomposition. This result suggests that the desired π-allyl palladium intermediate was formed, but the desired decarboxylation and intramolecular amination never occurred. Support for this interpretation derives from the fact that use of an external nucleophile such as *p*-methoxyphenol under otherwise identical conditions does lead smoothly to alkylation of the phenol by the vinylcarbamate **16**.



Scheme 6. Route A: Attempted palladium-catalyzed allylic amination. a) Vinylmagnesium bromide, THF, −78 °C, 10 min, 95%; b) *n*BuLi, methyl chloroformate, THF, −78 °C, 15 min, 62%; c) 3% Na(Hg), Na_2HPO_4, MeOH, RT, 30 min, 68%.

Because of the inability to effect the cyclization of **16** to form **17**, route B was examined (Scheme 7). In route B, olefination followed by lactamization would install the last two carbons and close the ring. Horner–Wadsworth–Emmons olefination[13] of aldehyde **14** provided the *trans*-enoate **18** in 90% yield, which was hydrogenated over platinum oxide to afford ester **19** in 99% yield. Detosylation of **19** with concomitant lactamization gave bicyclic lactam **20** in 72% yield. The final two steps were similar to several previous syntheses of swainsonine.[10, 15] Borane reduction went smoothly in 95% yield to give protected swainsonine **21**. Acidic deprotection afforded (−)-swainsonine **5** in 88% yield.



Scheme 7. Route B: Completion of the synthesis. a) Triethyl phosphonoacetate, LiCl, DBU, CH_3CN, RT, 2 h, 90%; b) PtO_2, H_2 (1 atm), EtOH, RT, 1.5 h, 99%; c) 3% Na(Hg), Na_2HPO_4, MeOH, RT, 3 h, 72%; d) $BH_3 \cdot Me_2S$, THF, RT, 2 h, then EtOH, 95%; e) 6 N HCl, THF, RT, 14 h, 88%.

Conclusion

(−)-Swainsonine of >99% *ee* was synthesized in 15 steps from achiral starting materials in 15% overall yield. The four contiguous stereocenters were efficiently set from a palladium-catalyzed desymmetrization of a *meso*-bis-carbamate followed by a diasteroselective dihydroxylation. Either isomer of swainsonine is readily available depending only on the choice of the chiral ligand. More generally, the adduct **2**, readily available enantiomerically pure in four steps (three steps if urethane formation is done in situ) should prove to be a versatile synthon related to **1** wherein each of the remaining double bonds can be selectively and sequentially modified and with high diastereoselectivity.

Experimental Section

General methods: Reactions were generally conducted under a positive pressure of dry argon or nitrogen in flame-dried glassware. THF was distilled from sodium benzophenone ketyl. Methylene chloride and acetonitrile were distilled from calcium hydride. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide, respectively. Acetone was distilled from calcium sulfate. Dimethyl sulfoxide was distilled at 60 °C at 0.1 mm Hg. Common reagents and materials were purchased from commercial sources and purified by distillation or recrystallization. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed ICN silica gel (Kieselgel 60, 230–400 mesh), analytical TLC was performed with 0.2 mm silica-coated glass plates (E. Merck, DC-Platten Kieselgel 60 F_{254}). Melting points were not corrected. Microanalyses were performed by M-H-W Laboratories, Phoenix AZ.

Synthesis of oxazolidin-2-one (2): Toluenesulfonyl isocyanate (6.56 g, 33.3 mmol) was added to a slurry of diol **3**[6] (5.0 g, 17.24 mmol) in THF (38 mL). The resulting solution was stirred at room temperature for 30 min and at 60 °C for 15 min. The resulting white slurry was cooled to 0 °C and the solid was collected by filtration and dried to give bis-carbamate **6** as a white solid (1:1.8 bis-carbamate/THF, 12.5 g, 90%). M.p. 230–232 °C (THF); IR (neat) 3212, 2927, 1725, 1458, 1347, 1237, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/[D_6]DMSO): $\delta = 7.98$ (d, $J = 8.1$ Hz, 4H), 7.75 (s, 2H), 7.38 (d, $J = 8.3$ Hz, 4H), 7.15 (m, 4H), 7.07 (m, 4H), 5.09 (s, 2H), 4.75 (s, 2H), 4.25 (s, 2H), 2.72 (s, 2H), 2.46 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$/[D_6]DMSO): $\delta = 149.2$, 142.8, 142.3, 139.9, 135.2, 128.1, 126.1, 124.5, 124.3, 123.2, 122.4, 121.8, 69.6, 42.1, 38.8, 19.8. The compound was taken directly to the next step.

DMSO (8 mL) was added to a slurry of the bis-carbamate **6** (7.85 g, 9.751 mmol) in THF (26 mL). An orange solution of [dba_3Pd_2]·$CHCl_3$ (252 mg, 0.252 mmol) and ligand **4** (504 mg, 0.730 mmol) in THF (15 mL) was then added in two portions. The resulting orange solution was stirred at room temperature for 12 h. The reaction was diluted with methylene chloride (100 mL), washed with water (100 mL), and concentrated. Column chromatography on silica (25% petroleum ether/CH_2Cl_2) gave a

white solid which was washed with 20% ethyl acetate/petroleum ether and filtered to give **2** as a white solid (3.7 g, 80%)in >95% *ee* as determined by ^{1}H NMR Eu(hfc)$_3$ chiral shift experiment. $[\alpha]_D^{25} = +76.3$ ($c = 1.54$ in CH_2Cl_2); m.p. 250–252 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} = 3068$, 3041, 2926, 1780, 1596, 1458, 1364, 1316 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.81 (d, $J = 8.3$ Hz, 2H), 7.29 (m, 5H), 7.10 (m, 3H), 6.95 (m, 2H), 5.91 (d, $J = 10.3$ Hz, 1H), 5.63 (d, $J = 10.5$ Hz, 1H), 5.00 (t, $J = 7.3$ Hz, 1H), 4.64 (m, 1H), 4.59 (s, 1H), 4.27 (s, 1H), 2.70 (m, 1H), 2.59 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.9$, 145.3, 144.1, 143.0, 140.9, 140.2, 135.1, 133.7, 129.7, 128.3, 126.4, 126.3, 126.1, 126.0, 125.5, 124.0, 123.7, 123.0, 121.9, 73.9, 54.7, 49.7, 45.5, 38.0, 37.0, 21.7); anal. calcd for $C_{28}H_{23}NO_4S$: C 71.62, H 4.94; found: C 71.86, H 5.08.

Synthesis of diol (7): 4-Methylmorpholine-*N*-oxide (6 g, 51.17 mmol) was added to a solution of oxazolidinone **2** (8.0 g, 17.05 mmol) and osmium tetraoxide (1.08 mL, 4% solution in water, 0.17 mmol) in methylene chloride (70 mL). The resulting solution was stirred at room temperature overnight. Sodium sulfite (19 g) and water (40 mL) were added and the solution was stirred 20 min. The reaction mixture was diluted with methylene chloride (150 mL) and water (100 mL). The aqueous phase was extracted with methylene choride (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Filtration through silica gel (45% EtOAc/petroleum ether) gave diol **7** as a white solid (8.01 g, 95%). $[\alpha]_D^{25} = +55.1$ ($c = 1.7$ in CH_2Cl_2); m.p. 200–205 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} = 3453$, 3069, 2925, 1784, 1596, 1467, 1357 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.27 (m, 4H), 7.09 (m, 4H), 4.93 (m, 1H), 4.43 (s, 1H), 4.40 (s, 1H), 4.24 (d, $J = 8.1$ Hz, 1H), 3.51 (m, 2H), 3.17 (br s, 1H), 2.52 (m, 2H), 2.45 (s, 3H), 2.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.7$, 146.0, 144.1, 143.4, 141.4, 140.4, 134.1, 129.9, 128.4, 126.3, 126.1, 126.0, 125.8, 124.6, 123.6, 123.1, 72.5, 69.2, 65.8, 62.1, 60.4, 46.3, 44.9, 39.8, 38.8, 21.7, 21.0, 15.2, 14.1; HRMS: calcd for $C_{28}H_{25}NO_6S$: 503.1402 $[M]^+$; found: 503.1411.

Synthesis of acetonide (8): A solution of diol **7** (8.0 g, 16.19 mmol), 2,2-dimethoxypropane (9 mL, 73.19 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.525 mmol) in acetone (90 mL) was stirred for 2 h. The solution was concentrated and column chromatography on silica (25% EtOAc/petroleum ether) gave **8** (7.8 g, 94%) as a white solid. $[\alpha]_D^{25} = +67.6$ ($c = 1.92$ in CH_2Cl_2); m.p. 236–237 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} =$ 2987, 2934, 1790, 1732, 1597, 1467, 1379, 1306 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 8.4$ Hz, 2H), 7.1–7.4 (m, 7H), 7.0–7.1 (m, 3H), 4.91 (t, $J = 6.4$ Hz, 1H), 4.41 (s, 2H), 4.34 (dd, $J = 1.5$, 6.4 Hz, 1H), 3.59 (dd, $J =$ 5.1, 7.3 Hz, 1H), 3.40 (dd, $J = 5.1$, 1.5 Hz, 1H), 2.49 (m, 1H), 2.43 (s, 3H), 2.31 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 150.9, 145.8, 144.5, 142.1, 140.8, 140.4, 134.6, 129.8, 128.3, 126.8, 126.6, 126.1, 126.0, 125.9, 124.7, 124.0, 122.7, 108.2, 75.7, 75.6, 75.5, 60.7, 60.3, 46.4, 45.1, 39.4, 38.1, 28.0, 26.1, 21.6, 14.1; HRMS calcd for $C_{31}H_{29}NO_6S$: 543.1715 $[M]^+$; found: 543.1726.

Synthesis of amino alcohol (9): A solution of **8** (4.0 g, 7.35 mmol) and potassium carbonate (2.0 g, 14.5 mmol) in methanol/water (9:1 *v*/*v* 100 mL) was heated to 60 °C for 1.5 h. Acetic acid (1 mL) was added and the reaction was concentrated in vacuo. The resulting residue was diluted with methylene chloride (100 mL) and water (50 mL). The aqueous layer was extracted with methylene chloride (50 mL). The combined organic extracts were dried and concentrated to give **9** as a white solid (3.65 g, 96%). $[\alpha]_D^{25} =$ +10.3 ($c = 1.53$ in CH_2Cl_2); m.p. 185–150 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} = 3529$, 3278, 1466, 1326 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.1$ Hz, 2H), 7.41 (m, 1H), 7.29 (m, 6H), 7.10 (m, 4H), 5.00 (d, $J =$ 7.1 Hz, 1H), 4.41 (s, 1H), 4.32 (s, 1H), 4.26 (s, 1H), 3.73 (t, $J = 6.4$ Hz, 1H), 3.58 (m, 1H), 3.25 (t, $J = 7.6$ Hz, 1H), 2.40 (s, 3H), 2.12 (m, 1H), 2.03 (m, 1H), 1.33 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 144.3$, 143.0, 142.6, 141.9, 141.8, 137.8, 129.2, 127.2, 126.4, 126.2, 125.9, 108.1, 78.5, 76.0, 73.7, 59.3, 46.6, 46.0, 44.4, 41.5, 27.8, 25.0, 21.3; HRMS calcd for $C_{30}H_{31}NO_5S$: 517.1923 $[M]^+$; found: 517.1924.

***N*-(5-Hydroxy-2,2-dimethyl-[3*a*,4,5,7*a*]-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (10)**: Alcohol **9** (500 mg, 0.965 mmol) was subjected to flash vacuum thermolysis (500 °C, 0.05 mm Hg). Column chromatography on silica (30–60% EtOAc/petroleum ether) gave **10** as a white solid (298 mg, 91%) in >99% *ee* as determined by HPLC (Chiralpak AD column), elution time (flow rate 1 mL min^{-1}, 15% isopropyl alcohol in heptane, $\lambda = 254$ nm): (−)-isomer: 13.25 min, (+)-isomer: 14.73 min. $[\alpha]_D^{25} = -99.8$ ($c = 1.50$ in CH_2Cl_2); m.p. 138–141 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} = 3312$, 1599, 1455, 1430, 1375, 1334 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.1$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 5.99 (dd, $J =$ 4.9, 10.0 Hz, 1H), 5.89 (dd, $J = 3.4$, 10.0 Hz, 1H), 5.64 (d, $J = 5.9$ Hz, 1H), 4.54 (m, 1H), 4.33 (s, 1H), 4.25 (m, 1H), 3.24 (m, 1H), 3.17 (s, 1H), 2.38 (s, 3H), 1.25 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 143.6, 136.4, 131.1, 129.6, 127.4, 126.7, 109.6, 73.3, 71.5, 64.9, 56.4, 27.1, 25.7, 21.4; anal. calcd for $C_{16}H_{21}NO_5S$: C 56.62, H 6.24 N 4.13; found: C 56.75, H 6.45, N 4.24.

***N*-(5-Triisopropylsilyloxy-2,2-dimethyl-[3*a*,4,5,7*a*]-tetrahydro-benzo[1,3]-dioxol-4-yl)-4-methyl-benzenesulfonamide (11)**: A solution of alcohol **10** (1.73 g, 5.10 mmol), triisopropylsilyl trifluoromethanesulfonate (1.7 mL, 6.32 mmol), and 2,6-lutidine (0.84 mL, 7.21 mmol) in methylene chloride (20 mL) was stirred at room temperature for 3 h. The reaction was diluted with methylene chloride (50 mL) washed with water (2 × 25 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography on silica (10% EtOAc/petroleum ether) gave the triisopropylsilyl ether **11** as a colorless oil (2.368 g, 95%). $[\alpha]_D^{25} = -83.0$ ($c = 3.10$ in CH_2Cl_2); IR (neat): $\tilde{\nu} = 3290$, 1599, 1453, 1380, 1338 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.1$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 2H), 5.81 (m, 2H), 4.88 (d, $J =$ 5.1 Hz, 1H), 4.59 (m, 1H), 4.53 (t, $J = 6.4$ Hz, 1H), 4.46 (m, 1H), 3.47 (q, $J = 5.1$ Hz, 1H), 2.39 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H), 0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.4$, 136.7, 130.9, 129.5, 127.4, 127.3, 109.4, 73.9, 71.3, 65.6, 56.3, 27.3, 26.0, 21.4, 17.9, 17.8, 12.2; anal. calcd for $C_{27}H_{41}NO_5SSi$: C 60.57, H 8.34 N 2.83; found: C 60.39, H 8.16, N 2.80.

***N*-[3-Hydroxy-1-(5-hydroxylmethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-triisopropylsilyloxy-propyl]-4-methyl-benzenesulfonamide (12)**: Ozone was bubbled through a solution of protected alcohol **11** (1.01 g, 2.07 mmol) in methylene chloride (8 mL) at −78 C for 15 min. Nitrogen was bubbled through the solution for 5 min. Dimethyl sulfide (0.6 mL) was added and the reaction was allowed to warm to room temperature. The reaction was stirred at room temperature for 1 h and concentrated. Methanol (8 mL) was added and the reaction was cooled to 0 °C and sodium borohydride (171 mg, 4.51 mmol) was added slowly. The reaction was stirred at 0 °C for 1 h. The reaction was quenched with water and extracted with methylene chloride (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography on silica (30% EtOAc/petroleum ether) gave diol **12** as a colorless oil (680 mg, 62%). $[\alpha]_D^{25} = -6.7$ ($c = 2.61$ in CH_2Cl_2); IR (neat): $\tilde{\nu} = 3289$, 1600, 1463, 1380, 1337, 1217, 1164 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 5.15 (d, $J = 6.8$ Hz, 1H), 4.41 (t, $J = 4.9$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 1H), 3.91 (m, 2H), 3.68 (dd, $J = 3.2$, 12.2 Hz, 1H), 3.44 (m, 4H), 2.41 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.5$, 137.7, 129.5, 127.3, 107.7, 77.6, 75.3, 73.0, 62.9, 61.0, 52.1, 27.2, 24.9, 21.5, 18.0, 17.9, 12.6; HRMS calcd for $C_{22}H_{38}NO_7SSi$: 488.2138 $[M - iC_3H_7]^+$; found: 488.2140.

2-[2,2-Dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-2-triisopropylsilyloxy-ethanol (13): Triphenylphosphane (228 mg, 0.87 mmol) was slowly added at 0 °C to a solution of diol **12** (338 mg, 0.637 mmol mmol) and diisopropyl azodicarboxylate (DIAD, 0.193 mL, 0.98 mmol) in THF (5 mL). The resulting solution was stirred for 45 min. The reaction was concentrated and column chromatography on silica (25% EtOAc/petroleum ether) gave **13** (281 mg, 86%) as a colorless oil. $[\alpha]_D^{25} =$ −59.8 ($c = 1.52$ in CH_2Cl_2); IR (neat): $\tilde{\nu} = 3541$, 1464, 1382, 1346, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 4.53 (m, 1H), 4.14 (m, 2H), 4.03 (dd, $J = 6.0$, 12.7 Hz, 1H), 3.77 (m, 2H), 3.62 (q, $J = 6.8$ Hz, 1H), 3.17 (m, 1H), 3.03 (dd, $J = 8.6$, 12.9 Hz, 1H), 2.44 (s, 3H), 1.43 (s, 3H), 1.18 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 144.6$, 134.6, 130.2, 127.4, 113.4, 80.4, 77.6, 71.4, 63.6, 62.4, 52.7, 27.9, 25.3, 21.6, 18.2, 18.1, 12.7; anal. calcd for $C_{25}H_{43}NO_6SSi$: C 58.45, H 8.44, N 2.73; found: C 58.60, H 8.45, N 2.96.

[2,2-Dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4]-yl-2-triisopropylsilyloxy-acetaldehyde (14): Dess–Martin periodinane (417 mg, 0.423 mmol) was added at 0 °C to a solution of alcohol **13** (440 mg, 0.858 mmol) and sodium bicarbonate (101 mg, 1.2 mmol) in methylene chloride (8 mL). The resulting white slurry was stirred for 45 min at room temperature. The reaction was concentrated, filtered through silica gel, and concentrated to give aldehyde **14** (430 mg, 98%) as a colorless oil. $[\alpha]_D^{25} =$ −77.3 ($c = 4.19$ in CH_2Cl_2); IR (neat): $\tilde{\nu} = 2728$, 1733, 1598, 1463, 1382, 1354 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.74$ (d, $J = 1.5$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 4.55 (dd, $J = 1.5$, 5.9 Hz, 1H), 4.41 (q, $J = 6.8$ Hz, 1H), 4.36 (q, $J = 6.6$ Hz, 1H), 4.20 (q, $J = 6.6$ Hz, 1H), 3.73 (dd, $J = 7.3$, 12.9 Hz, 1H), 3.36 (dd, $J = 6.6$, 13.2 Hz, 1H), 2.43 (s, 3H),

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1.50 (s, 3H), 1.18 (s, 3H), 1.12 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 202.7, 144.2, 134.5, 130.0, 127.5, 114.7, 79.4, 78.3, 77.7, 64.2, 53.2, 26.7, 24.9, 21.6, 18.0, 12.3; HRMS calcd for $C_{24}H_{38}NO_6SSi$: 496.2186 $[M-CH_3]^+$; found: 496.2200.

1-[2,2-Dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-1-triisopropylsilyloxy-but-3-en-2-ol (15): Vinylmagnesium bromide (1.09 mL, 1M in THF, 1.09 mmol) was added to a solution of aldehyde **14** (430 mg, 0.841 mmol) in THF (8 mL) at −78 °C. After 10 min at −78 °C, the reaction was quenched with wet diethyl ether and water. The reaction was allowed to warm to room temperature and was diluted with diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a 2.1:1 mixture of diastereomers of vinyl alcohol **15** (425 mg, 95%) as a colorless oil. IR (neat): $\tilde{\nu} =$ 3508, 2944, 2867, 1351 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer: $\delta =$ 7.65 (d, $J =$ 8.3 Hz, 2H), 7.32 (d, $J =$ 7.8 Hz, 2H), 6.00 (m, 1H), 5.45 (m, 1H), 5.23 (m, 1H), 4.4–4.6 (m, 3H), 3.6–3.9 (m, 4H), 3.20 (m, 1H), 2.43 (s, 3H), 1.48 (s, 3H), 1.20 (s, 3H), 1.14 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) mixture of diastereomers: $\delta =$ 144.2, 138.9,137.1, 134.4, 130.1, 127.5, 127.4, 115.9, 115.0, 113.6, 80.9, 80.3, 77.9, 75.2, 74.1, 71.6, 63.7, 61.4, 53.0, 52.8, 27.7, 27.5, 25.2, 25.0, 21.5, 18.5, 18.4, 18.2, 18.1, 18.0, 13.4, 12.7, 12.3; HRMS calcd for $C_{24}H_{38}NO_6SSi$ $[M-iC_3H_7]^+$: 496.2189; found: 496.2212.

2,2-Dimethyl-4-triisopropylsilyloxy-5-vinyl-hexahydro-1,3,6-trioxa-[7-*a*]-aza-cyclopenta[*a*]inden-7-one (16): *n*-Butyllithium (2.2 mL, 1.2M in hexane, 2.62 mmol) was added to a solution of vinyl alcohol **15** (430 mg, 0.798 mmol) in THF (5 mL) at −78 °C. Methyl chloroformate (0.40 mL, 5.22 mmol) was added and the reaction was stirred at −78 °C for 15 min. The reaction was quenched with wet diethyl ether and water. The reaction was allowed to warm to RT and was diluted with diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The organic layer was dried ($MgSO_4$), concentrated, and filtered through silica to give the crude methyl carbonate (295 mg, 62%) as a colorless oil which was used directly in the next step.

3% Sodium–mercury amalgam (177 mg, 0.231 mmol) was added to a solution of the above methyl carbonate (23 mg, 0.0385 mmol) and sodium dibasic phosphate (49.2 mg, 0.347 mmol) in methanol (0.5 mL). The resulting slurry was stirred for 30 min. Water (5 mL) and diethyl ether (5 mL) were added. The aqueous layer was extracted with diethyl ether (2×5 mL). The combined ether extracts were concentrated. Column chromatography on silica (15% ethyl acetate/petroleum ether) gave **16** as a colorless oil (11 mg, 68%) of a 5:1 mixture of diastereomers. Major diastereomer: IR (neat): $\tilde{\nu} =$ 2926, 2868, 1720, 1426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 5.96 (m, 1H), 5.55 (dt, $J =$ 1.3, 17.2 Hz, 1H), 5.52 (dt, $J =$ 1.1, 10.6 Hz, 1H), 4.74 (t, $J =$ 5.3 Hz, 1H), 4.69 (m, 1H), 4.48 (m, 1H), 4.19 (dd, $J =$ 7.9, 9.2 Hz, 1H), 4.10 (m, 1H), 3.41 (dd, $J =$ 3.8, 7.9 Hz, 1H), 3.22 (dd, $J =$ 5.1, 13.2 Hz, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 152.5, 132.6, 120.1, 112.2, 80.9, 79.2, 78.5, 66.5, 66.0, 52.3, 26.3, 24.5, 18.1, 17.8, 12.8; HRMS calcd for $C_{21}H_{37}NO_5Si$ $[M]^+$: 411.2441; found 411.2443; minor diastereomer: IR (neat): $\tilde{\nu} =$ 2942, 2868, 1715, 1431, 1217 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.13 (ddd, $J =$ 3.4, 11.0, 17.6 Hz, 1H), 5.45 (d, $J =$ 25.4 Hz, 1H), 5.39 (d, $J =$ 19.0 Hz, 1H), 4.83 (m, 1H), 4.65 (m, 2H), 4.48 (dd, $J =$ 5.1, 8.5 Hz, 1H), 4.04 (d, $J =$ 13.2 Hz, 1H), 3.30 (dd, $J =$ 2.8, 8.3 Hz, 1H), 3.23 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.10 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 151.3, 131.3, 118.3, 112.2, 79.6, 77.9, 64.5, 62.0, 52.8, 26.5, 24.6, 17.9, 12.3; HMRS: calcd for $C_{20}H_{34}NO_5Si$: $[M-CH_3]^+$: 396.2206; found: 396.2207.

Ethyl-(*E*)-4-[2,2-dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo-[4,5-*c*]pyrrol-4-yl]-4-triisopropylsilyloxy-2-butenoate (18): DBU (0.079 mL, 0.527 mmol) and aldehyde **14** (270 mg, 0.527 mmol) were added to a slurry of the triethyl phosphonoacetate (165 mg, 0.738 mmol) and lithium chloride (31.3 mg, 0.738 mmol) in acetonitrile (5 mL). The resulting slurry was stirred at room temperature for 2 h. The reaction was diluted with diethyl ether (50 mL) and water (50 mL). The organic layer was concentrated and subsequent column chromatography on silica (15% EtOAc/petroleum ether) gave enoate **18** as a colorless oil (277 mg, 90%). $[\alpha]_D^{25} =$ −29.3 ($c =$ 2.73 in CH_2Cl_2); IR (neat): $\tilde{\nu} =$ 1720, 1463, 1359, 1270 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.70 (d, $J =$ 8.3 Hz, 2H), 7.28 (d, $J =$ 8.3 Hz, 2H), 7.07 (dd, $J =$ 6.4, 15.6 Hz, 1H), 5.89 (d, $J =$ 15.6 Hz, 1H), 4.77 (t, $J =$ 5.9 Hz, 1H), 4.71 (t, $J =$ 6.6 Hz, 1H), 4.34 (t, $J =$ 5.4 Hz, 1H), 4.20 (m, 3H), 3.80 (dd, $J =$ 7.1, 12.7 Hz, 1H), 2.93 (dd, $J =$ 7.8, 12.7 Hz, 1H), 2.42 (s, 3H), 1.51 (s, 3H), 1.29 (t, $J =$ 7.1 Hz, 3H), 1.26 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 166.1, 147.8, 143.7, 136.4, 129.7, 127.4, 122.6, 114.4, 80.0, 78.5, 71.7, 65.7, 60.3, 52.5, 27.1, 25.0, 21.5, 18.1, 18.0, 14.2, 12.3; HRMS calcd for $C_{26}H_{40}NO_7SSi$ $[M-iC_3H_7]^+$: 538.2295; found: 538.2296.

Ethyl-4-[2,2-dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-4-triisopropylsilyloxy-butyrate (19): A slurry of enoate **18** (266 mg, 0.457 mmol) and platinum oxide (6 mg, 0.023 mmol) in ethanol (4 mL) was stirred under 1 atm of hydrogen for 1.5 h. The reaction was filtered through celite and concentrated to give ester **19** as a colorless oil (265 mg, 99%). $[\alpha]_D^{25} =$ −57.5 ($c =$ 1.62 in CH_2Cl_2); IR (neat): $\tilde{\nu} =$ 1733, 1461, 1353 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.74 (d, $J =$ 8.3 Hz, 2H), 7.32 (d, $J =$ 7.8 Hz, 2H), 4.56 (t, $J =$ 6.4 Hz, 1H), 4.31 (q, $J =$ 6.4 Hz, 1H), 4.13 (q, $J =$ 7.1 Hz, 2H), 4.05 (t, $J =$ 6.6 Hz, 1H), 3.92 (q, $J =$ 6.8 Hz, 1H), 3.76 (dd, $J =$ 7.1, 13.2 Hz, 1H), 3.02 (dd, $J =$ 8.3, 12.9 Hz, 1H), 2.5–2.7 (m, 2H), 2.44 (s, 3H), 2.19 (m, 1H), 2.02 (m, 1H), 1.45 (s, 3H), 1.26 (t, $J =$ 7.1 Hz, 3H), 1.20 (s, 3H), 1.10 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 173.8, 144.6, 135.7, 129.9, 127.4, 113.9, 80.4, 78.1, 70.2, 65.1, 60.2, 52.7, 29.9, 29.5, 27.4, 25.1, 21.5, 18.3, 18.0, 14.2, 12.9; anal. calcd for $C_{29}H_{49}NO_7SSi$: C 59.66, H 8.46, N 2.40; found: C 59.80, H 8.53, N 2.63.

[1*S*,2*R*,8*R*,8*aR*]-8-Triisopropylsilyloxy-1,2-(isopropylidenedioxy) indolizidin-5-one (20): Sodium dibasic phosphate (270 mg, 1.90 mmol) was added to a solution of ester **19** (115 mg, 0.197 mmol) in methanol (0.7 mL), followed by 3% sodium–mercury amalgam (865 mg, 1.13 mmol). The resulting slurry was stirred at room temperature for 3 h. The reaction was poured into diethyl ether (25 mL) and water (25 mL). The aqueous layer was extracted with ether (25 mL). The combined ether extracts were dried ($MgSO_4$), filtered and concentrated to give lactam **20** as a white solid (54 mg, 72%). $[\alpha]_D^{25} =$ −16.9 ($c =$ 1.98 in CH_2Cl_2); m.p. 76–77 °C (EtOAc/hexane); IR (neat): $\tilde{\nu} =$ 2968, 2861, 1655, 1455, 1373, 1214 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 4.69 (m, 2H), 4.28 (m, 1H), 4.12 (d, $J =$ 13.4 Hz, 1H), 3.28 (dd, $J =$ 2.9, 6.8 Hz, 1H), 3.06 (dd, 4.2, 13.7 Hz, 1H), 2.46 (dt, $J =$ 4.9, 17.4 Hz, 1H), 2.31 (m, 1H), 2.00 (m, 1H), 1.84 (m, 1H), 1.37 (s, 3H), 1.27 (s, 3H), 1.06 (s, 18H), 0.9–1.2 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 168.7, 111.6, 79.6, 77.4, 67.3, 65.8, 50.6, 30.7, 29.2, 26.4, 24.5, 17.9, 12.3; HRMS calcd for $C_{17}H_{30}NO_4SSi$: $[M-iC_3H_7]^+$: 340.1944; found: 340.1944.

[1*S*,2*R*,8*R*,8*aR*]-8-Triisopropylsilyloxy-1,2-(isopropylidenedioxy) indolizidine (21): Borane/dimethyl sulfide complex (0.24 mL, 2M solution in THF, 0.48 mmol) was added at 0 °C to a solution of lactam **20** (46 mg, 0.120 mmol) in THF (2.5 mL). The reaction was stirred at 0 °C for 30 min and at room temperature for 2 h. Ethanol (1.5 mL) was added (**Caution**: hydrogen evolution), and the reaction was concentrated to a thick oil which was redissolved in ethanol (3 mL) and refluxed for 2 h. Removal of solvent in vacuo gave **21** as a colorless oil (42 mg, 95%). $[\alpha]_D^{25} =$ −61.9 ($c =$ 1.93, CH_2Cl_2); IR (neat): $\tilde{\nu} =$ 2784, 1463, 1378, 1208, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 4.64 (t, $J =$ 4.6 Hz, 1H), 4.53 (t, $J =$ 4.6 Hz, 1H), 3.93 (m, 1H), 3.09 (d, $J =$ 10.7 Hz, 1H), 2.94 (bd, $J =$ 10.3 Hz, 1H), 2.04 (m, 2H), 1.80 (m, 1H), 1.61 (m, 3H), 1.45 (s, 3H), 1.27 (s, 3H), 1.22 (m, 1H), 1.07 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 110.5, 79.2, 77.7, 74.1, 68.2, 60.4, 51.8, 34.6, 25.9, 24.4, 24.1, 18.1, 12.6; HRMS calcd for $C_{20}H_{39}NO_3Si$ $[M]^+$: 369.2699; found: 369.2691.

[1*S*,2*R*,8*R*,8*aR*]-1,2,8-Trihydroxyindolizidine [(−)swainsonine] (5): A solution of **21** (41 mg, 0.110 mmol) in THF (0.45 mL) was treated with 6N HCl (0.45 mL) at room temperature for 14 h. The reaction was concentrated and the residue was dissolved in methanol and ion-exchange resin (Dowex 1×8–50, HO^-, 2 g) was added and stirred for 15 min. The reaction was filtered and concentrated to give (−)-swainsonine **5** as a white solid (16.8 mg, 88%). $[\alpha]_D^{25} =$ −74.9 ($c =$ 1.15 in MeOH) [lit.: $[\alpha]_D^{25} =$ −75.7 ($c =$ 2.33 in MeOH)][10]; m.p. 136–139 °C (lit.: m.p. 140–142 °C[16], 139–142 °C[10]), 141–143 °C[17]; IR (neat): $\tilde{\nu} =$ 3340, 2931, 2855, 2802, 1654, 1330 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): $\delta =$ 4.20 (ddd, $J =$ 2.8, 5.9, 8.0 Hz, 1H), 4.08 (dd, $J =$ 3.5, 5.8 Hz, 1H), 3.63 (td, $J =$ 4.6, 10.3 Hz, 1H), 2.73 (m, 2H), 2.46 (dd, $J =$ 8.1, 10.8 Hz, 1H), 1.86 (m, 3H), 1.53 (m, 1H), 1.30 (qt, $J =$ 4.1, 13.2 Hz, 1H), 1.06 (qd, $J =$ 4.5, 12.3 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, MeOH internal standard): $\delta =$ 72.5, 69.3, 68.7, 65.9, 60.1, 51.4, 32.1, 22.8; HRMS calcd for $C_8H_{15}NO_3$ $[M]^+$: 173.1052; found: 173.1050. The spectral data agree with those previously reported.[10, 15]

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[1] M. Jurovcik, A. Holy, *Nucl. Acids Res.* **1976**, *3*, 2143; V. Nair, T. S. Jahnle, *Antimicrob. Agents Chemother.* **1995**, *39*, 1017; G. W. Koszalka, S. M. Daluge, F. L. Boyd, *Annu. Rep. Med. Chem.* **1998**, *33*, 163.
[2] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395.
[3] B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355; B. M. Trost, *Isr. J. Chem.* **1997**, *37*, 109.
[4] B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104.
[5] B. M. Trost, D. E. Patterson, *J. Org. Chem.* **1998**, *63*, 1339; see also: B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327.
[6] R. C. Cambie, N. D. Renner, P. S. Rutledge, P. D. Woodgate, *Synth. Commun.* **1989**, *19*, 537.
[7] a) J. P. Michael, *Nat. Prod. Rep.* **1997**, 619; b) J. P. Michael, *Nat. Prod. Rep.* **1995**, 535, and references therein.
[8] F. P. Guengerich, S. J. DiMari, H. P. Broquist, *J. Am. Chem. Soc.* **1973**, *95*, 2055.
[9] a) A. D. Elbein, *FASEB J.* **1991**, *5*, 3055, and references therein; b) I. C. di Bello, G. Fleet, S. K. Namgoong, K. I. Tadano, B. Winchester, *Biochem. J.* **1989**, *259*, 855, and references therein.
[10] W. H. Pearson, E. J. Hembre, *J. Org. Chem.* **1996**, *61*, 7217, and references therein.
[11] a) J. A. Hunt, W. R. Roush, *J. Org. Chem.* **1997**, *62*, 1112; b) W.-S. Zhou, W. G. Xie, Z.-H. Lu, X.-F. Pan, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2559; c) C. E. Adams, F. J. Walker, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 420; d) F. Ferriera, C. Greck, J. P. Genet, *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.
[12] B. M. Trost, H. C. Arndt, P. E. Strege, T. R. Verhoeven, *Tetrahedron Lett.* **1976**, 3477.
[13] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.
[14] T. Hudlicky, M. G. Natchus, G. Sinai-Zingde, *J. Org. Chem.* **1987**, *52*, 4641.
[15] N. M. Carpenter, G. W. J. Fleet, I. C. di Bello, B. Winchester, L. E. Fellows, R. J. Nash, *Tetrahedron Lett.* **1989**, *30*, 7261.
[16] R. B. Bennett III, J.-R. Choi, W. D. Montgomery, J. K. Cha, *J. Am. Chem. Soc.* **1989**, *111*, 2580.
[17] a) B. P. Bashyal, G. W. J. Fleet, M. J. Gough, P. W. Smith, *Tetrahedron* **1987**, *43*, 3083; b) M. Naruse, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1994**, *59*, 1358.

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