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A SYNTHESIS OF (1*S*,2*R*,8*R*,8a*R*)-8-HYDROXY-1,2-(ISOPROPYLIDINEDIOXY)INDOLIZIDIN-5-ONE FROM D-RIBOSE: IMPROVED ACCESS TO (-)-SWAINSONINE AND ITS ANALOGS[†]

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Abstract – A short synthesis of the lactam (**4**), (1*S*,2*R*,8*R*,8a*R*)-8-hydroxy-1,2-(isopropylidenedioxy)indolizidin-5-one, from D-ribose is reported. This compound is a useful intermediate for the synthesis of analogs of the anticancer agent swainsonine (**1**) as well for swainsonine itself.

Swainsonine (**1**) (Scheme 1) is a potent inhibitor of certain α-mannosidases, and has proven useful as a biochemical tool for the study of glycoprotein processing, since it inhibits a key late-stage enzyme in the biosynthesis of glycoproteins.[1-6] That enzyme, Golgi α-mannosidase II (GMII), is necessary for the formation of so-called "complex glycoproteins". The altered distribution of such glycoproteins on the surface of cancer cells is associated with metastasis and disease progression, hence inhibitors of GMII are potentially useful for cancer treatment.[7-10] More selective inhibition of GMII over other mannosidases is a desirable goal for cancer drug development, and makes the synthesis of analogs of swainsonine a significant undertaking.[11-13] Further, swainsonine itself is expensive and difficult to obtain in large quantities, whether by total synthesis or isolation from natural sources.

Many syntheses of swainsonine have been published,[14] including the relatively practical routes of Fleet[15,16] and Cha,[17] as well as our own.[18,19] Nonetheless, improved routes to swainsonine are still needed, as this important compound is still relatively difficult to make. Perhaps more significantly,

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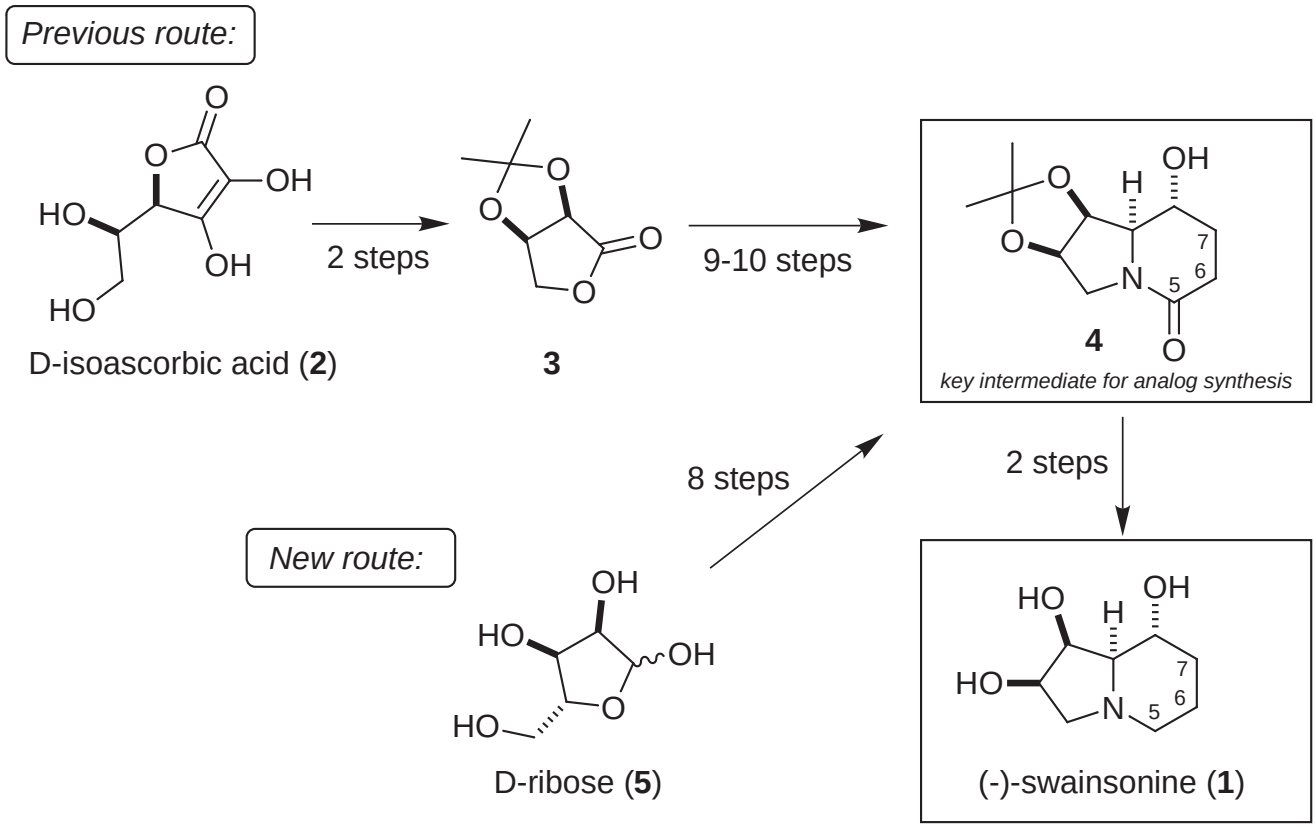
routes to analogs of swainsonine are needed, including those bearing substituents attached at positions 5, 6, and 7 of the swainsonine core.[11,12,20] An attractive compound for preparing such analogs is the lactam (**4**), which is often encountered in syntheses of swainsonine itself. We are exploring the functionalization of **4** at positions 5, 6, and 7, and thus need significant quantities of this compound.[11,12] Herein we report an improved route to **4**, and thus swainsonine (**1**) and certain of its analogs, whereby D-ribose is used as a starting material.

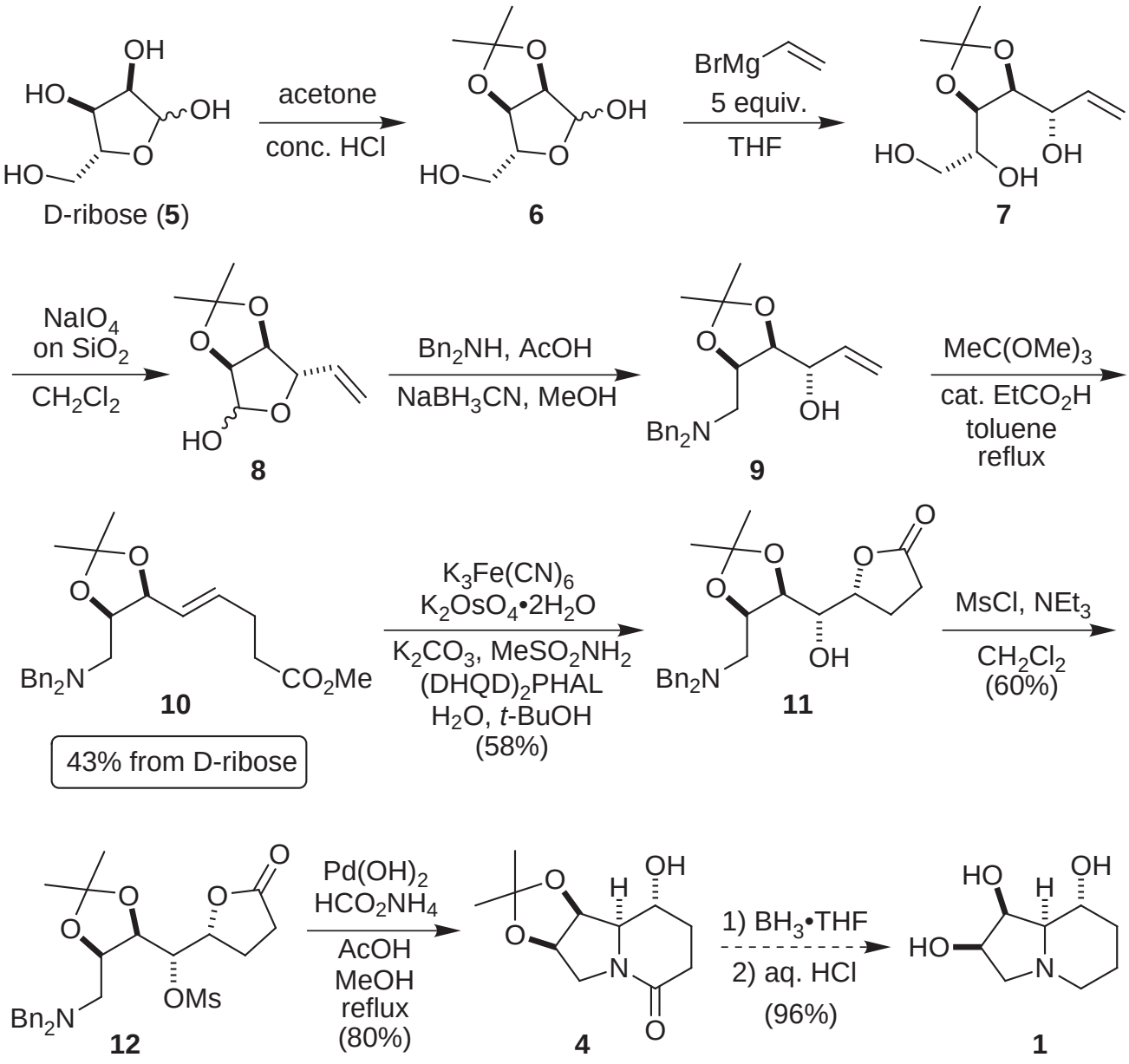
Our previous synthesis of swainsonine (including **4**) was quite practical, allowing multigram quantities of **4** and **1** to be prepared (Scheme 1).[18] The route began with D-isoascorbic acid, which was converted by the literature procedure[21] to the lactone (**3**), which can also be purchased (*ca*. $10/g, Aldrich). This lactone has been used in other routes to swainsonine, e.g. Cha's.[17] After a sequence of 9-10 steps, we were able to convert **3** into **4**. Our need for large quantities of **4** for analog work forced us to examine improvements to this route, since it still required numerous steps and involved DIBAL-H, *t*-$BuMe_2SiCl$, Bu_4NF, azide chemistry, five chromatographies, and three crystallizations. We have now developed a route that uses less exotic and costly reagents, requires only two chromatographies and one crystallization, and involves fewer steps. Further, the inexpensive starting material D-ribose (**5**) is used.



Scheme 1. Overview of (-)-swainsonine syntheses.

RESULTS AND DISCUSSION

The acetonide (**6**) of D-ribose (**5**) was prepared by a modification of the procedure of Levene,[22] and was used without purification in a reaction with vinylmagnesium bromide, providing the triol (**7**). Mekki[23,24] has studied the diastereoselectivity of the addition of organomagnesium reagents to similar carbohydrate-derived lactols. The oxidative cleavage of the 1,2-diol of **7** to the lactol (**8**) was challenging, but was eventually found to be efficient when Shing and Zhong's sodium periodate on silica gel method was used.[25] A reductive amination[26] of **8** with dibenzylamine gave the amino alcohol (**9**), which was subjected to a Johnson orthoester Claisen rearrangement[27] to afford the unsaturated ester (**10**). At this



Scheme 2. Synthesis of swainsonine from D-ribose.

point, the first purification in the sequence was employed, providing **10** in 43% overall yield from D-ribose. A diastereoselective catalytic osmylation of **10** was then carried out using the Sharpless protocol, affording 60% of **11**, 5% of its bis-epimer (not shown), and 4% of starting material, all easily separated by column chromatography. Mesylation of **11** afforded **12** in 60% yield. It was important to rid **12** of impurities by repeated washes with aqueous base before a pass through a short plug of silica gel, since these impurities were found to negatively affect the next reaction. With pure mesylate in hand, hydrogenolysis of the *N*-benzyl groups was carried out using the method of Ram and Spicer[28] to produce the desired crystalline lactam (**4**), a key intermediate in our work on the synthesis of analogs of swainsonine. The lactam (**4**) has previously been converted to swainsonine (**1**) in good yield.[18]

In summary, we have achieved a short and efficient synthesis of the lactam (**4**), and thus swainsonine (**1**) and its analogs, from the inexpensive starting material D-ribose (**5**). Fewer and simpler reactions in conjunction with less purification steps makes for a significant improvement over our previous synthesis,[18] which was already relatively short and practical.

EXPERIMENTAL

2,3-*O*-Isopropylidene-D-ribofuranose (6). This compound was prepared by a modification of the procedure reported by Levene[22] wherein the addition of anhydrous copper sulfate was omitted. Concentrated sulfuric acid (1.3 mL) was added to a suspension of D-ribose (50.0 g) in acetone (500 mL). The mixture was stirred for 4 h until the white solid dissolved, resulting in a brown solution, which was then neutralized to pH 7 by the addition of $Ca(OH)_2$ (~10 g) in small portions. This mixture was filtered through Celite and the filtrate was concentrated to give 63.3 g of crude product, which was dissolved in ether and filtered. Concentration of the filtrate gave the title compound (63.0 g, 99%), which was used without further purification. Although this compound has been prepared numerous times, methods for its purification have not been reported and attempts at purification were unsuccessful in our hands.[23,29-34]

(2*R*,3*R*,4*S*,5*S*)-3,4-Isopropylidenedioxy-6-heptene-1,2,5-triol (7). Vinylmagnesium bromide (600 mL of a 0.96 M solution in THF, 576 mmol) was added in a dropwise fashion *via* addition funnel to a solution of **6** (21.9 g, 115 mmol) in THF (500 mL) at 0 °C. The mixture was stirred at rt for 12 h, then

cooled to 0 °C and treated with saturated aqueous NH_4Cl (400 mL). After 15 min, the mixture was concentrated to leave a pink solid, which was suspended in aqueous HCl (0.25 N) and extracted with EtOAc. The aqueous layer was then acidified to pH 6 with aqueous HCl (6 N) and re-extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 20.2 g (80%) of the title compound as a yellow oil that was used without further purification. A small portion was purified by chromatography (2.5% MeOH/CH_2Cl_2) to provide a pure sample of **7** for characterization. The purified material was found to be a low-melting solid, which was recrystallized with hexanes/EtOAc. R_f to give white needles = 0.34 (2.5% MeOH/CH_2Cl_2); mp 62-63 ºC; $[\alpha]^{23}_D$ –29.5° (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00 (ddd, J = 5.5, 10.3, 16.1 Hz, 1 H), 5.39 (dt, J = 1.5, 15.7 Hz, 1 H), 5.28 (dt, J = 1.5, 10.3 Hz, 1 H), 4.77 (s, 1 H), 4.45 (s, 1 H), 4.31 (br t, J = 7.7, 1 H), 4.13 (dd, J = 5.5, 9.5 Hz, 1 H), 4.04 (dd, J = 5.3, 9.9 Hz, 1 H), 3.90 (m, 2 H), 3.69 (m, 1 H), 3.44 (br t, 1 H), 1.40 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 116.9, 109.0, 80.0, 77.4, 70.5, 69.6, 64.3, 27.8, 25.4; IR (neat) 3682 (m), 3600 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 219 [$(M + H)^+$, 11], 201 (9), 161 (23), 143 (100), 125 (29); HRMS (CI, NH_3) calcd for $C_{10}H_{19}O_5$ [$(M + H)^+$] 219.1154 found 219.1238.

(2*R/S*,3*S*,4*S*,5*S*)-2-Hydroxy-3,4-isopropylidenedioxy-5-vinyltetrahydrofuran (8). Silica gel-supported sodium periodate was prepared according to the procedure reported by Shing and Zhong.[25] Thus, sodium periodate (114.6 g, 536 mmol) was dissolved in water (215 mL) and preheated to 70 °C, then silica gel (400 g) was stirred into the solution to form a free flowing solid, which was added to a solution of **7** (58.4 g 268 mmol) in CH_2Cl_2 (2.5 L) at rt. After 1.5 h, the mixture was filtered and the filtrate was concentrated to give 47.7 g (96 %) of the title compound as a yellow oil that was used without further purification. A small portion was purified by chromatography (2.5% MeOH/CH_2Cl_2) to provide a pure sample of **8** as a yellow oil for characterization. This material was found to be a 6:1 mixture of diastereomers as determined by 400 MHz ^{1}H NMR. R_f = 0.38 (10% MeOH/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$; selected data for major diastereomer) δ 6.00 (ddd, J = 8.1, 10.3, 17.2 Hz, 1 H), 5.48 (d, J = 2.9 Hz, 1 H), 5.29 (dt, J = 1.1, 17.6 Hz, 1 H), 5.16 (dt, J = 1.1, 10.3 Hz, 1 H), 4.65 (m, 3 H), 4.12 (br d, 1 H), 1.50 (3 H, s), 1.32 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 137.8, 117.3, 112.4, 102.8, 88.4, 85.9, 84.5, 77.3, 76.7; IR (neat) 3421 (br s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 204 [$(M + NH_4)^+$, 8], 186 (M^+, 100), 169 (60); HRMS (CI, NH_3) calcd for $C_9H_{18}NO_4$ [$(M + NH_4)^+$] 204.1236 found 204.1226.

(**2*R*,3*S*,4*S*)-1-(*N*,*N*-Dibenzylamino)-2,3-isopropylidenedioxyhex-5-ene-4-ol (9)**. A modification of the method reported by Borch[26] for the reductive amination of aldehydes was used to prepare the title compound. Dibenzylamine (57.5 g, 56 mL, 291 mmol), glacial acetic acid (31.7 g, 26 mL, 522 mmol), and sodium cyanoborohydride (44.4 g, 706 mmol) were added to a solution of **8** (45.2 g, 243 mmol) in MeOH (550 mL) at rt. After 3 d, the mixture was concentrated and the resulting solid was dissolved in saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was dried ($NaSO_4$) and concentrated to ~150 mL, then treated with pyridine (28.8 g, 29.5 mL, 365 mmol) and acetic anhydride (37.2 g, 34.4 mL, 365 mmol). After 3 h at rt, the solution was concentrated and the resulting oil was dissolved in 800 mL of a 1:1 MeOH/saturated aqueous K_2CO_3 solution. After 12 h, the MeOH was evaporated and the remaining liquid partitioned between ether and water. The aqueous layer was extracted with ether and the combined organic layers were washed with water and aqueous HCl (0.1 N). The acidic aqueous layers were collected and extracted with ether, then made basic (pH 8) with aqueous KOH (2 N). The resulting cloudy white solution was extracted with ether, and the organic phase was washed with brine, dried ($NaSO_4$), and concentrated to provide 91.9 g (99%) of the title compound as a yellow oil that was used without further purification. A small portion was purified by chromatography (5% EtOAc/toluene) to provide a pure sample of **9** as a clear oil for characterization, R_f = 0.5 (25% EtOAc/hexanes); $[\alpha]^{23}_D$ –71.02° (c = 1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10 H), 6.67 (s, 1 H), 5.85 (ddd, *J* = 5.9, 10.6, 17.2 Hz, 1 H), 5.18 (m, 2 H), 4.49 (ddd, *J* = 2.6, 5.5, 11.0 Hz, 1 H), 4.02 (dd, *J* = 5.5, 9.5 Hz, 1 H), 3.94 (d, *J* = 12.9 Hz, 2 H), 3.36 (m, 1 H), 3.27 (d, *J* = 13.2 Hz, 2 H), 3.09 (dd, *J* = 11.4, 12.8 Hz, 1 H), 2.36 (dd, *J* = 2.2, 12.8 Hz, 1 H), 1.35 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.3, 129.8, 128.6, 127.8, 116.5, 108.7, 80.9, 74.1, 69.5, 59.1, 54.1, 28.0, 25.3; IR (neat) 3172 (br s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 368 [$(M + H)^+$, 100], 310 (1), 277 (3), 210 (14); HRMS (CI, NH_3) calcd for $C_{23}H_{30}NO_3$ [$(M + H)^+$] 368.2226 found 368.2208.

Methyl (*E*)-(6*S*,7*R*)-8-(*N*,*N*-dibenzylamino)-6,7-isopropylidenedioxy-4-octenoate (10). Trimethyl orthoacetate (160.6 g, 170.8 mL, 1.34 mol) and propionic acid (3.9 g, 4.0 mL, 53 mmol) were added to **9** (89.2 g, 243 mmol) in toluene (500 mL) and the mixture was heated at reflux for 16 h. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The mixture was then concentrated to provide a yellow oil which was purified by chromatography (15% EtOAc/hexanes) to give 44.1 g (43% overall yield from D-ribose) of **10** as a yellow oil, R_f = 0.45 (10% EtOAc/hexanes); $[\alpha]^{23}_D$ -33.4° (c = 1.4, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 10 H), 5.62 (m, 1 H), 5.34 (dd, *J* = 8.1, 15.4 Hz, 1

H), 4.42 (t, *J* = 7.1 Hz, 1 H), 4.32 (dt, *J* = 4.4, 7.3 Hz, 1 H), 3.77 (d, *J* = 13 Hz, 2 H), 3.65 (s, 3 H), 3.52 (d, *J* = 12.9 Hz, 2 H), 2.61 (dd, *J* = 4.0, 13.6 Hz, 1 H), 2.52 (dd, *J* = 7.3, 13.9 Hz, 1 H), 2.30 (br s, 4 H), 1.42 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 139.2, 132.4, 128.8, 128.0, 127.1, 126.7, 108.0, 78.8, 76.8, 58.7, 53.9, 51.5, 33.4, 28.1, 27.4, 25.6; IR (neat) 1739 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 423 (M^+, 11), 306 (10), 210 (100), 181 (5), 91 (70); HRMS (EI, 70 eV) calcd for $C_{26}H_{33}NO_4$ 423.2409 found 423.2395.

(5*R*)-5-[(1*S*,2*R*,3*R*)-4-(*N*,*N*-Dibenzylamino)-1-hydroxy-2,3-isopropylidenedioxybutyl]tetrahydrofuran-2-one (11) and (5*S*)-5-[(1*R*,2*R*,3*R*)-4-(*N*,*N*-Dibenzylamino)-1-hydroxy-2,3-isopropylidenedioxybutyl]tetrahydrofuran-2-one. The method of Sharpless[35] for the asymmetric dihydroxylation of alkenes was used to prepare the title compound. Potassium ferricyanide (9.58 g, 29.1 mmol), potassium carbonate (4.02 g, 29.1 mmol), methanesulfonamide (0.92 g, 9.7 mmol), potassium osmate dihydrate (36 mg, 0.097 mmol), and $(DHQD)_2PHAL$ (75 mg, 0.097 mmol) were added to a mixture of 3:1 water/*t*-butanol (85 mL) at 0 °C, followed by a solution of **10** (4.11 g, 9.7 mmol) in *tert*-butanol (45 mL). After 48 h at rt, sodium sulfite (15.9 g, 126 mmol) was added and the mixture was stirred for 1 h then extracted with EtOAc. The combined organic layers were washed with aqueous KOH (2 M), dried (Na_2SO_4), and concentrated. Chromatography (20% EtOAc/hexanes) gave 2.44 g (60%) of **11** as a white foam, 0.22g (5%) of (5*S*)-5-[(1*R*,2*R*,3*R*)-4-(*N*,*N*-dibenzylamino)-1-hydroxy-2,3-isopropylidenedioxybutyl]tetrahydrofuran-2-one as a white foam, and 0.15 (4%) of recovered starting material. Data for **11**: R_f = 0.45 (40% EtOAc/hexanes); $[\alpha]^{23}_D$ –63.2° (c = 0.73, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10 H), 4.52 (m, 2 H), 4.36 (dd, *J* = 5.9, 9.9 Hz, 1 H), 3.96 (d, *J* = 12.9 Hz, 2 H), 3.18 (d, *J* = 13.2 Hz, 2 H), 2.99 (dd, *J* = 11.4, 12.8 Hz, 1 H), 2.71 (m, 2 H), 2.37 (m, 2 H), 2.06 (m, 2 H), 1.33 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 178.1, 136.2, 130.0, 128.6, 127.9, 108.7, 79.4, 76.8, 73.4, 70.0, 59.2, 53.6, 37.1, 28.5, 28.0, 25.2, 23.6; IR (neat) 3200 (br s), 1771 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 426 [$(M + H)^+$, 1], 340 (8), 210 (100), 91 (55); HRMS (CI, NH_3) calcd for $C_{25}H_{32}NO_5$ [$(M + H)^+$] 426.2280 found 426.2283. Data for (5*S*)-5-[(1*R*,2*R*,3*R*)-4-(*N*,*N*-dibenzylamino)-1-hydroxy-2,3-isopropylidenedioxybutyl]tetrahydrofuran-2-one: R_f = 0.28 (40% EtOAc/hexanes); $[\alpha]^{23}_D$ –24.9° (c = 2.25, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10 H), 4.42 (dd, *J* = 7.1, 12.9 Hz, 1 H), 4.36 (dt, *J* = 3.8, 6.6 Hz, 1 H), 3.93 (dd, *J* = 2.7, 6.6 Hz, 1 H), 3.82 (d, *J* = 12.8 Hz, 2 H), 3.54 (d, *J* = 13.1 Hz, 2 H), 2.95 (m, 2 H), 2.77 (dd, *J* = 3.8, 14.0 Hz, 1 H), 2.58-2.34 (m, 2 H), 2.14 (m, 1 H), 1.93 (m, 1 H), 1.51 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 137.9, 129.6, 128.4, 127.4, 108.6, 80.7, 76.5, 75.7, 70.4, 59.9,

51.7, 28.4, 26.7, 25.1, 23.9; IR ($CHCl_3$) 3532 (br s), 1773 (s), 1732 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 426 [$(M + H)^+$, 100], 334 (3), 210 (14), 198 (17), 91 (4); HRMS (CI, NH_3) calcd for $C_{25}H_{32}NO_5$ [$(M + H)^+$] 426.2280 found 426.2265.

(5*S*)-5-[(1*R*,2*R*,3*R*)-4-(*N*,*N*-Dibenzylamino)-2,3-isopropylidenedioxy-1-methanesulfonyloxybutyl]tetrahydrofuran-2-one (12). Methanesulfonyl chloride (3.68 g, 2.48 mL, 32 mmol) and triethylamine (3.69 g, 5.08 mL, 36.5 mmol) were added sequentially to a solution of **11** (6.20 g, 14.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After warming to rt for 4 h, the mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (15x), dried (Na_2SO_4), and concentrated to give a pale yellow foam. Before the product could be carried on to the next reaction, all of the mesylate impurities had to be removed with basic aqueous washes, which were done until the singlet at δ 3.14 (s) in the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum had disappeared. Finally, passing the crude product through a silica plug (25% EtOAc/hexanes) gave 4.19 g (60%) of the title compound as a white foam, R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]^{23}_D$ +17.6° (c = 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (br d, 4 H), 7.26 (br t, 4 H), 7.17 (br t, 2 H), 4.80 (dd, *J* = 5.5, 4.0 Hz, 1 H), 4.60 (m, 1 H), 4.45 (br s, 1 H), 4.17 (t, *J* = 5.7 Hz, 1 H), 3.66 (br s, 4 H), 3.00 (s, 1 H), 2.78 (s, 3 H), 2.64 (dd, *J* = 9.2, 13.2 Hz, 1 H), 2.52 (ddd, *J* = 6.2, 10.3, 17.9 Hz, 1 H), 2.35 (m, 1 H), 2.16 (m, 1 H), 2.06 (m, 1 H), 1.28 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 129.1, 128.2, 127.0, 108.7, 79.2, 77.8, 76.0, 58.8, 53.3, 38.9, 37.1, 31.5, 27.6, 27.5, 25.5, 24.0; IR (neat) 2800 (s), 1784 (s), 1360 (s), 1178 (s); MS (CI, NH_3) *m/z* (rel intensity) 504 [$(M + H)^+$, 4], 318 (100), 293 (6), 228 (7), 204 (46), 108 (8); HRMS (CI, NH_3) calcd for $C_{26}H_{34}NO_7S$ [$(M + H)^+$] 504.2056 found 504.2040.

(1*S*,2*R*,8*R*,8a*R*)-8-Hydroxy-1,2-(isopropylidenedioxy)indolizidin-5-one (4). A modification of the method reported by Ram and Spicer[28] for the debenzylation of *N*-benzylamines was used to prepare the title compound. Ammonium formate (4.53 g, 72 mmol), 20 wt.% $Pd(OH)_2$/C (500 mg), and glacial acetic acid (3.15 g, 3 mL) were added to a solution of **12** (4.55 g) in MeOH (200 mL). After heating at reflux for 18 h, the mixture was cooled and filtered through Celite. The filtrate was concentrated and the resulting solid was dissolved in a minimal amount of water and the pH was adjusted to 8 with aqueous NaOH (1 N). The water was removed *in vacuo* and the residue was extracted with $CHCl_3$. The remaining solid was dissolved in a minimal amount of water and also extracted with $CHCl_3$. The organic layers were then combined, dried ($NaSO_4$), and concentrated. Upon standing at rt for 12 h, the

resulting oil became a low-melting orange solid, which was recrystallized from EtOAc to provide 1.63 g (80%) of the title compound as white rhomboid crystals, R_f = 0.3 (10% MeOH/EtOAc); mp 129-130 ºC (lit., 126-128 ºC,[15] 129 ºC[18]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 4.5, 6.0 Hz, 1 H), 4.75 (dd, *J* = 5.0, 5.2 Hz, 1 H), 4.20 (d, *J* = 11.0 Hz, 1 H), 4.15 (m, 1 H), 3.34 (dd, *J* = 4.8, 8.4 Hz, 1 H), 3.14 (dd, *J* = 4.8, 13.5 Hz, 1 H), 2.53 (ddd, *J* = 2.5, 6.2, 17.9 Hz, 1 H), 2.43 (m, 1 H), 2.14 (m, 1 H), 2.05 (br s, 1 H), 1.88 (m, 1 H), 1.43 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 112.4, 80.0, 77.8, 66.3, 65.7, 50.8, 29.9, 29.9, 26.5, 24.9.

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