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Enantioselective ring expansion of prolinol derivatives. Two formal syntheses of (−)-swainsonine

Ingrid Déchamps, Domingo Gomez Pardo* and Janine Cossy*

Laboratoire de Chimie Organique, Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI)—ParisTech, CNRS, 10, rue Vauquelin, 75231 Paris Cedex 05, France

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Dedicated to Professor Miguel Yus on the occasion of his 60th anniversary

Abstract—Two enantioselective formal syntheses of (−)-swainsonine have been achieved from L-proline by using an enantioselective ring enlargement of substituted prolinols as the key step. The more efficient synthesis has been achieved in 14 steps with an overall yield of 14%.

1. Introduction

Polyhydroxylated indolizidines belong to an important class of alkaloids with antimestatic, antitumor-proliferative and anticancer properties.[1] The most studied of these indolizidine is (−)-swainsonine **1**, the (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine (Fig. 1), which had been first isolated from the fungus *Rhizoctonia leguminicola* in 1973,[2] and was later isolated from more than 30 other plants and fungi. (−)-Swainsonine acts as an inhibitor of lysosomal α-mannosidase[3] and Golgi complex mannosidase II,[4] its activity has been shown to be specific of cancer cells. Moreover, this alkaloid improves the natural antitumoral defenses[5] and its ability to facilitate the proliferation of bone marrow cells might enable recovery of the hematopoietic system during the treatment of cancers by chemotherapy.[6] In 2002, (−)-swainsonine entered in phase II of clinical tests by GLYCODesign Inc. as an anticancer drug.

Since the first total syntheses in 1984,[7] over 35 syntheses of (−)-swainsonine have been described in the literature.[8,9] Many of these syntheses used carbohydrates as starting material in order to control the four stereogenic centers of the final structure. To the best of our knowledge, α-amino-acids have never been used to synthesize (−)-swainsonine. Here, we would like to report two approaches to (−)-swainsonine using L-proline as the starting material and an enantioselective ring expansion of substituted prolinols[10,11] as the key step.

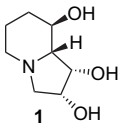
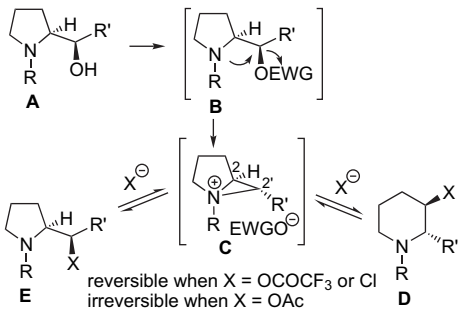


Figure 1. (−)-Swainsonine.

The stereospecific ring expansion of a prolinol into a piperidine is now a well-known process: when the hydroxy group of a prolinol of type **A** is transformed into a good leaving group, an aziridinium intermediate of type **C** is formed by intramolecular nucleophilic substitution (S_Ni). Two positions are then possible for a nucleophilic attack (S_N2) and when the attack occurs at the fused carbon (C2), a ring expanded product of type **D** is obtained. When the nucleophile is a trifluoroacetate[10,11] or a chloride,[11g,12] the reaction is reversible and the formation of the expanded product **D** and/or non-expanded product **E** is the result of their relative thermodynamic stability. However, if the nucleophile is not a good leaving group (for example, $X^- = AcO^-$),[13] the ring opening of the aziridinium is irreversible and the ratio **D/E** is controlled by kinetic factors (Scheme 1).



Scheme 1. Ring expansion of prolinols.

* Corresponding authors. Tel.: +33(0)140794663; fax: +33(0)140794660 (D.G.P.); tel.: +33(0)140794429; fax: +33(0)140794660 (J.C.); e-mail addresses: domingo.gomez-pardo@espci.fr; janine.cossy@espci.fr

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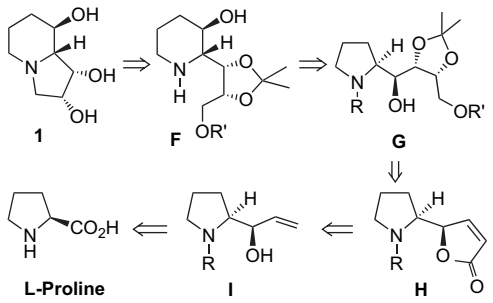
2. Results and discussion

2.1. First strategy

The synthesis of (−)-swainsonine **1** was hypothesized from the substituted 3-hydroxypiperidine **F**, which would be obtained by applying an enantioselective ring expansion to prolinol **G**. This latter compound would be obtained by dihydroxylation and reduction of the lactone present in the substituted pyrrolidine **H**, which would be synthesized by using a ring closing metathesis applied to a prolinol derivative of type **I**.[14] A diastereoselective addition of an organometallic species on a prolinal prepared from L-proline would provide prolinol **I** (Scheme 2).[15]

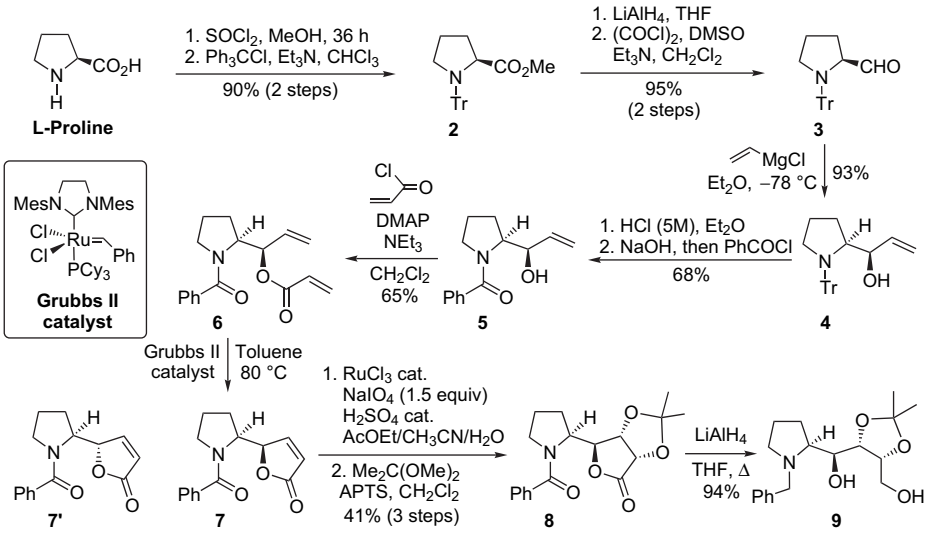


Scheme 2. Retrosynthesis of (−)-swainsonine.

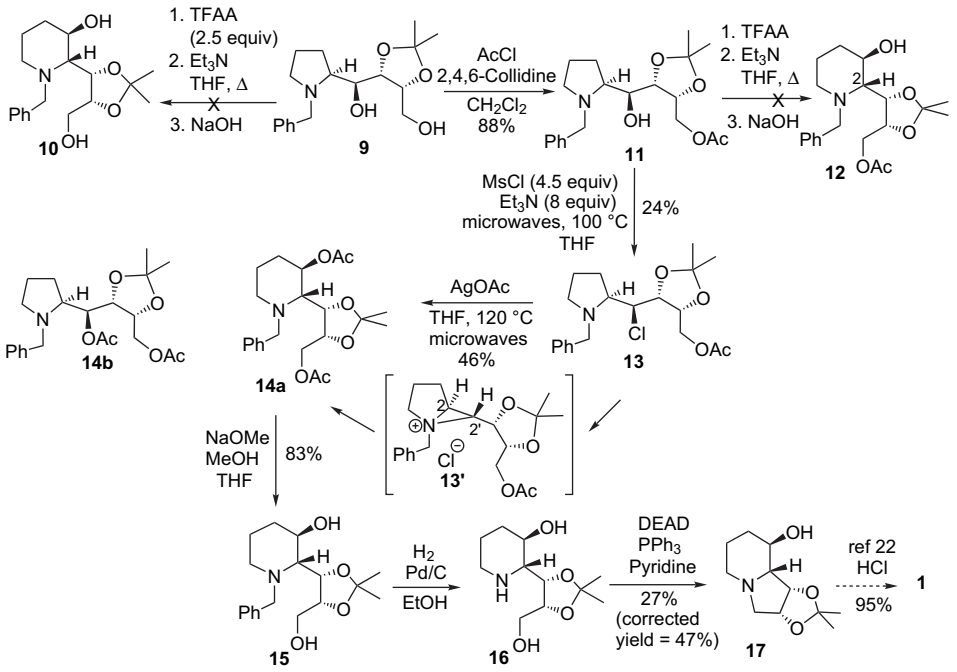
The synthesis of (−)-swainsonine started with the preparation of prolinol **4**, obtained in four steps from L-proline.[15] After esterification ($SOCl_2$, MeOH) and N-alkylation by using trityl chloride, aminoester **2**[15] was obtained in 90% yield. A reduction by $LiAlH_4$ in THF followed by a Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2] provided aldehyde **3**[15] in 95% yield over the two steps. The addition of vinylmagnesium chloride to aldehyde **3** gave allylic alcohol **4**[15] with a diastereomeric excess superior to 98/2 (93% yield). It is worth noting that the presence of the *N*-trityl group is of great importance, as prolinal of this type is known to be configurationally unstable[16] and the addition of organometallic reagents to these compounds usually led to a low diastereoselectivity.[17] In order to gain access to the substituted prolinol of type **G**, the allylic alcohol **4** was transformed to the unsaturated lactone **7** in three steps. After a detritylation–benzoylation step (HCl, then NaOH, PhCOCl, 68%), the resulting pyrrolidine **5** was treated with acryloyl chloride (DMAP, Et_3N, CH_2Cl_2) to afford diene **6** in 65% yield.

This latter compound was heated at 80 °C with the second generation Grubbs catalyst[18] (Grubbs II) in toluene and transformed to the desired lactone **7**. We have to point out that any attempt of purification either on silica gel or on alumina led to the partial isomerization of lactone **7**. To avoid the formation of the isomerized lactone **7′**, crude lactone **7** was filtered on Celite® and used without further purification. After a diastereoselective dihydroxylation[19] of **7** using $RuCl_3/NaIO_4$[20] (H_2SO_4 cat., MeCN/AcOEt/H_2O: 3/3/1), the diol obtained was protected ($Me_2C(OMe)_2$, APTS, CH_2Cl_2) to afford acetonide **8** with a diastereomeric excess superior to 90%.[21] After reduction by $LiAlH_4$ (in refluxing THF), prolinol **9** was obtained in 94% yield (Scheme 3).

In agreement with our previous results on the ring expansion,[11] prolinol **9** was then treated with trifluoroacetic anhydride and Et_3N in THF. However, after saponification, the ring expanded product **10** was not detected and only degradation of the starting material was observed whatever were the conditions used (classical reflux or microwave irradiations at 120 °C). As the non-protected primary alcohol can interfere with the rearrangement process and be responsible for the degradation of the starting material, compound **9** was converted to the monoacetate **11** in 88% yield. However, when this latter product was submitted to the ring expansion conditions, prolinol **11** was recovered unchanged. The use of microwaves also failed to provide piperidine **12** (Scheme 4). The failure of this ring expansion can be explained by thermodynamic considerations. Due to the presence of the bulky alkyl chain at C2 in piperidine **12**,



Scheme 3. Synthesis of prolinol **7**.



Scheme 4. Synthesis of indolizidine **17**, precursor of (−)-swainsonine.

the latter compound is probably less stable than prolinol **11** and under thermodynamic conditions, the ring enlargement cannot take place.[11n]

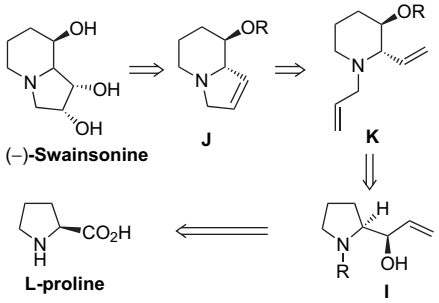
The use of kinetic conditions was then applied.[11n] At first, prolinol **11** was converted to the more reactive chloro compound **13** by using mesyl chloride (MsCl, Et_3N, THF, microwaves, 100 °C). It is worth noting that under these conditions a prolinol usually leads to a ring expansion product via an aziridinium species of type **13′**.[11g,12] The obtention of pyrrolidine **13** proves that for this compound, the pyrrolidine is more stable than the piperidine. The low yield of the chloro compound **13** (24%) was probably related to a decrease of the reactivity of the alcohol due to steric hindrance in prolinol **11**. The chloro compound **13** was then treated with silver acetate (THF, microwave irradiations, 120 °C)[11n] and piperidine **14a** was the unique product isolated in 46% yield (Scheme 4). As the acetate is not a good leaving group, a ring expansion under kinetic control should occur and two ring opening products issued from the same aziridinium intermediate **13′** are expected: piperidine **14a** and pyrrolidine **14b**.[13] The formation of piperidine **14a** as the unique product is probably due to steric hindrance around the C2′ carbon in aziridinium **13′**.

The diacetate **14a** was then transformed to diol **15** (83% yield) by treatment with NaOMe (MeOH/THF). After debenzylation (H_2, Pd/C, EtOH), the piperidine alcohol **16** was submitted to a cyclization under Mitsunobu conditions (DEAD, PPh_3, pyridine) to provide the known indolizidine **17**,[7b,9b–d,22] precursor of (−)-swainsonine, with an overall yield of 27% for the two steps (Scheme 4).

A formal synthesis of (−)-swainsonine in 18 steps was achieved from L-proline with an overall yield of 0.3%. Due to this low efficiency, another strategy was pursued to obtain (−)-swainsonine.

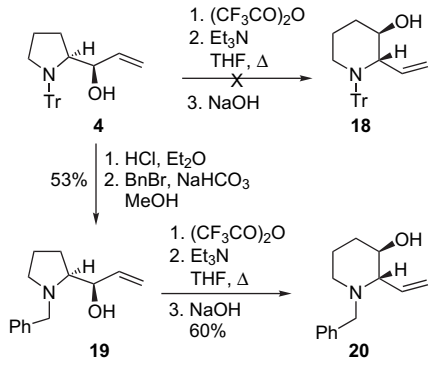
2.2. Second strategy

The second route also utilized the type **I** prolinol by using a ring expansion at an earlier stage in the synthesis to produce the piperidinol ring of (−)-swainsonine. The synthesis of this alkaloid was envisaged from the unsaturated indolizidine **J**, which would be formed by a ring closing metathesis applied to diene **K**. This compound would be synthesized by applying a ring expansion to prolinol **I** (Scheme 5).



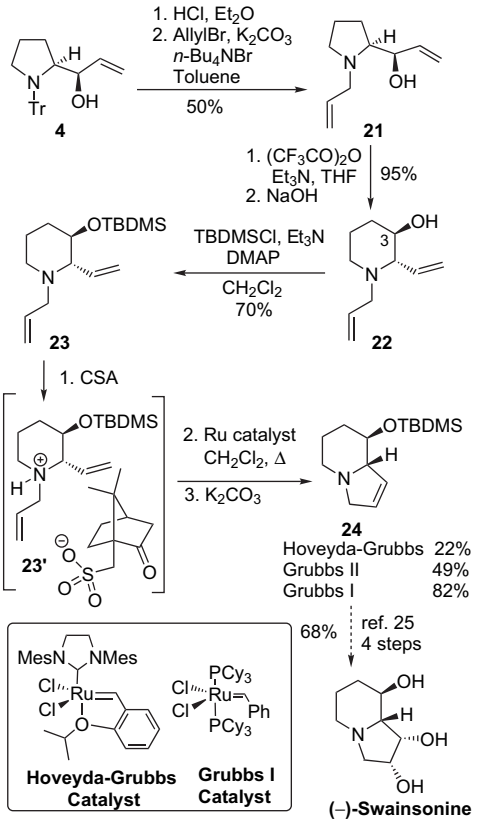
Scheme 5. Second retrosynthetic approach of (−)-swainsonine.

In order to access the 3-hydroxypiperidine of type **K**, the previously synthesized prolinol **4** was treated under the ring expansion conditions (trifluoroacetic anhydride, Et_3N, THF, Δ). Unfortunately, after saponification, piperidine **18** was not detected and prolinol **4** was recovered unchanged. As the presence of a trityl group can reduce the nucleophilic properties of the nitrogen, its replacement by a benzyl group was investigated. *N*-Benzylated prolinol **19** was obtained in two steps by a classical detritylation–benzylation sequence. When treated under the ring expansion conditions, prolinol **19** was converted to piperidine **20** in 60% yield (Scheme 6). This result shows that an *N*-benzylprolinol containing an allylic alcohol functionality is compatible with the ring expansion reaction.



Scheme 6. Ring expansion applied to prolinols containing an allylic alcohol.

The ring expansion of *N*-allylprolinol was then examined and the trityl group in prolinol **4** was removed (HCl, Et_2O) and replaced by an allyl group (AllylBr, *n*-Bu_4NBr, K_2CO_3, toluene) to produce the substituted prolinol **21** in 50% yield. Treatment of prolinol **21** under the ring enlargement conditions (trifluoroacetic anhydride, Et_3N, THF, Δ) provided, after saponification, 3-hydroxy-piperidine **22** in 95% yield with a diastereomeric excess superior to 95%. As ring closing metathesis applied to diene **22** revealed to be difficult, the free hydroxy group at C3 was protected as a *tert*-butyldimethylsilyl group (TBDMSCl, DMAP, Et_3N, CH_2Cl_2) and piperidine **23** was isolated in 70% yield (Scheme 7). As ruthenium catalysts can be poisoned by amino groups, piperidine **23** was transformed to the ammonium salt **23′** by treatment with commercially available



Scheme 7. Formal synthesis of (−)-swainsonine.

camphorsulfonic acid (CSA). Three different metathesis ruthenium catalysts were then tested to perform the ring closing metathesis on **23′**. Hoveyda–Grubbs catalyst[23] revealed to be rather inefficient as the total conversion could not be reached and indolizidine **24** was obtained in poor yield (22%). When second generation Grubbs catalyst was used, the conversion in **23** was complete and the bicyclic compound **24** was isolated in 49% yield. The best result was obtained with the commercially available first generation Grubbs catalyst[24] (Grubbs I) as the unsaturated indolizidine **24** was obtained in 82% yield (Scheme 7). The spectroscopic data of **24** are in agreement with those previously reported in literature.[25] As the transformation of **24** into (−)-swainsonine had been described in 4 steps, this approach constitutes a formal synthesis of (−)-swainsonine in 14 steps from L-proline with an overall yield of 14%.[26]

3. Conclusion

In conclusion, two formal syntheses of (−)-swainsonine have been developed from L-proline by using a diastereoselective addition of vinyl Grignard reagent on *N*-trityl-prolinal, an enantioselective ring expansion of a substituted prolinol into a 3-hydroxypiperidine, and a ring closing metathesis as the key steps. A greater efficiency was observed when the ring expansion was performed at an early stage in the synthesis. This approach will be used to prepare swainsonine analogues for biological testing.

4. Experimental

4.1. General procedures

Commercially available reagents were used as received. Solvents were distilled. Tetrahydrofuran and diethyl ether were dried by distillation from sodium and benzophenone, methylene chloride was dried by distillation from CaH_2. TLC was performed on Merck 60 F_{254} silica gel plates and visualized either with a UV lamp (254 nm), or by using a solution of $KMnO_4/K_2CO_3$/NaOH in water followed by heating. Flash chromatography was performed with Merck Geduran Si60 silica gel (40–63 μm). Microwave irradiation experiments were performed using a single-mode Initiator™ EXP (0–300 W, 2.45 GHz) from Biotage.[27] Infrared (IR) spectra were recorded on a Bruker TENSOR™ 27 (IRFT); wavenumbers are indicated in cm^{-1}. ^1H NMR spectra at 400 MHz and ^{13}C NMR spectra at 100 MHz were recorded on a Bruker AVANCE 400. ^1H NMR spectra at 300 MHz and ^{13}C NMR spectra at 75 MHz were recorded on a Bruker AC 300. Data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of non-equivalent resonances) and integration. ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett–Packard tandem 5890A GC

(12 m capillary column)—5971 MS (70 eV). Mass spectra with chemical ionization (MS-CI) and high resolution mass spectra (HRMS) were performed at the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm (Paris). Optical rotations were measured on a Perkin–Elmer 343 polarimeter in a 10 cm cell.

4.1.1. [(*S*)-2-((*R*)-1-Hydroxyallyl)pyrrolidin-1-yl]phenylmethanone (5). To a stirred solution of prolinol **4**[15] (3.34 g, 9.1 mmol, 1.0 equiv) in Et_2O (40 mL), cooled to 0 °C, was added dropwise HCl (5 M aqueous solution) (18 mL, 91 mmol, 10 equiv). After 18 h of vigorous stirring at rt, the two phases were separated and the aqueous phase was washed with Et_2O (3×30 mL). Et_2O (40 mL) was added to the aqueous phase and the mixture was cooled to 0 °C, and NaOH (2.5 M aqueous solution) (121 mmol, 48.4 mL, 13.3 equiv) was then added until the obtention of a basic pH. Benzoyl chloride (3.17 mL, 27.3 mmol, 3.0 equiv) was then added. After 7 h of vigorous stirring at rt, the organic solvents were evaporated to dryness in vacuo and ethanol was added (25 mL). After 2 h at rt, the organic solvents were evaporated to dryness in vacuo and the resulting aqueous phase was extracted with AcOEt (3×60 mL). The organic phases were dried over Na_2SO_4 and the solvents were evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 50/50). Compound **5** (1.41 g, 6.1 mmol, 68%) was obtained as a yellow oil.

$[\alpha]_D^{20}$ −155.1 (*c* 4.33, $CHCl_3$). IR (film): 3370, 2960, 2886, 1720, 1605, 1570, 1492, 1425, 1336, 1270, 1210, 1140, 990 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.52–1.84 (3H), 2.10 (m, 1H), 3.30 (m, 1H), 3.40 (m, 1H), 4.26 (d, *J*=5.0 Hz, 1H), 4.43 (dd, *J*=8.0, 8.0 Hz, 1H), 5.18 (ddd, *J*=10.3, 1.5, 1.5 Hz, 1H), 5.32 (ddd, *J*=17.0, 1.5, 1.5 Hz, 1H), 5.39 (br s, 1H), 5.85 (ddd, *J*=17.0, 10.6, 6.0 Hz, 1H), 7.28–7.35 (2H), 7.36–7.42 (3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.0 (t), 27.9 (t), 51.8 (t), 63.8 (d), 75.0 (d), 116.8 (t), 127.0 (d), 128.3 (d), 130.2 (d), 136.0 (d), 136.7 (s), 171.9 (s). MS (EI, 70 eV): *m*/*z* (relative intensity): 231 ($M^{+\bullet}$, 1), 175 (8), 174 (50), 146 (11), 106 (8), 105 (100), 77 (30), 51 (4). HRMS: found: *m*/*z* 254.1151. Calcd for $C_{14}H_{17}NO_2Na$: $(MNa)^+$, 254.1151.

4.1.2. (*R*)-1-((*S*)-1-Benzoylpyrrolidin-2-yl)allylacrylate (6). To a solution of prolinol **5** (1.52 g, 6.8 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL), cooled to −78 °C, DMAP (40 mg, 0.32 mmol, 0.05 equiv), Et_3N (1.85 mL, 13.2 mmol, 2.0 equiv), and acryloyl chloride (0.80 mL, 9.9 mmol, 1.5 equiv) were added. The reaction mixture was slowly warmed up to rt, and after 3 h, the mixture was quenched with a saturated $NaHCO_3$ aqueous solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 40/60) to give **6** (1.26 g, 4.42 mmol, 65%) as a colorless oil.

$[\alpha]_D^{20}$ −144.3 (*c* 1.15, $CHCl_3$). IR (film): 2978, 2876, 1722, 1629, 1576, 1449, 1410, 1295, 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.75 (m, 1H), 1.85–2.20 (3H), 3.33–3.49 (2H), 4.61 (m, 1H), 5.28 (m, 1H), 5.39 (m, 1H), 5.85–5.99 (2H), 6.17 (m, 1H), 6.22 (dd, *J*=17.2, 10.4 Hz, 1H), 6.50 (m, 1H), 7.35–7.50 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.8 (t), 25.2 (t), 50.7 (t), 59.2 (d), 74.0 (d), 117.5 (t), 127.3 (d), 128.2 (d), 128.5 (d), 130.0 (d), 131.1 (t), 133.6 (d), 137.0 (s), 164.9 (s), 170.3 (s). MS (EI, 70 eV) *m*/*z* (relative intensity): 285 ($M^{+\bullet}$, 1), 230 (1), 175 (7), 174 (52), 106 (8), 105 (100), 77 (26), 55 (7), 51 (3). Anal. Calcd for $C_{17}H_{19}NO_3$ C: 71.56, H: 6.71, N: 4.91. Found C: 71.28, H: 6.75, N: 4.99.

4.1.3. (*S*)-6-((*S*)-*N*-Benzoylpyrrolidin-2-yl)-2,2-dimethyldihydro-furo[3,4-*d*][1,3]dioxol-4-one (8). To a solution of diene **6** (930 mg, 3.26 mmol, 1.0 equiv) in toluene (80 mL) second generation Grubbs catalyst was added (55 mg, 0.064 mmol, 0.02 equiv), and the reaction mixture was heated to 80 °C for 2 h. Two portions of second generation Grubbs catalyst (25 mg, 0.029 mmol, 0.01 equiv) were added again, each addition was followed by a 2 h reflux. The reaction mixture was then filtered on Celite®. The solvent was removed in vacuo. The crude lactone **7** was obtained as a black oil and used in the dihydroxylation step without purification.

To a suspension of $NaIO_4$ (1.05 g, 4.9 mmol, 1.5 equiv) in water (4 mL), cooled to 0 °C, were added three drops of concentrated H_2SO_4, then a solution of $RuCl_3$ (40 mg, 0.16 mmol, 0.05 equiv) in water (4 mL) was added followed by the addition of MeCN/AcOEt: 50/50 (20 mL). After 5 min, a solution of unsaturated lactone **7** (1.0 equiv) in MeCN/AcOEt: 50/50 (40 mL) was quickly added. After 1.5 min at 0 °C, the reaction is quenched by addition of solid $Na_2S_2O_3$ (5 g). The mixture was then filtered and the solvents were removed in vacuo. The crude oil can be purified by flash column chromatography (CH_2Cl_2/MeOH: 90/10) to give a brown solid (64%) but the crude material was generally used without purification.

To a solution of the obtained diol (1.0 equiv) in CH_2Cl_2 (30 mL), APTS (56 mg, 0.33 mmol, 0.1 equiv) and dimethoxypropane (4.05 mL, 32.6 mmol, 10 equiv) were successively added. After 18 h at rt, the reaction mixture was quenched by a saturated solution of $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The crude oil was purified by flash column chromatography (cyclohexane/AcOEt/Et_3N: 30/70/0.1). Compound **8** (640 mg, 1.9 mmol, 60%) was obtained as a brown solid. The synthesis of compound **8** was also achieved in 41% yield from diene **6** without purifications.

Mp: 118 °C. $[\alpha]_D^{20}$ −119.3 (*c* 0.67, $CHCl_3$). IR (neat): 2986, 1784, 1624, 1576, 1405, 1384, 1175, 1152, 1086 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 3H), 1.30 (s, 3H), 1.68–2.03 (4H), 3.34–3.55 (2H), 4.43 (m, 1H), 4.74–4.80 (3H), 7.32–7.50 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.7 (t), 25.6 (q), 26.3 (t), 26.8 (q), 50.5 (t), 57.9 (d), 74.7 (d), 77.3 (d), 83.0 (d), 113.7 (s), 127.5 (d), 128.4 (d), 130.6 (d), 136.1 (s), 171.6 (s), 174.0 (s). MS (EI, 70 eV) *m*/*z* (relative intensity): 331 ($M^{+\bullet}$, 1), 316 (3), 273 (3), 256 (6), 204 (3), 175 (9), 174 (57), 124 (2), 106 (8), 105 (100), 77 (24). Anal. Calcd for $C_{18}H_{21}NO_5$ C: 65.24, H: 6.39, N: 4.23. Found C: 65.35, H: 6.63, N: 3.92.

4.1.4. (*S*)-((*S*)-*N*-Benzylpyrrolidin-2-yl)-((4*S*,5*R*)-5-hydroxymethyl-2,2-dimethyl[1,3]dioxolan-4-yl)methanol (9). To a suspension of $LiAlH_4$ (275 mg, 7.2 mmol, 4.0 equiv) in THF (20 mL), cooled to 0 °C, was added a solution of compound **8** (600 mg, 1.8 mmol, 1.0 equiv) in THF (15 mL). After 20 min, the reaction mixture was heated at reflux for 2.5 h. The mixture was then quenched carefully at 0 °C by addition of a saturated solution of Rochelle salt (sodium potassium tartrate, 25 mL). The mixture was then extracted with Et_2O (3×50 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH: 95/5). Prolinol **9** (548 mg, 1.7 mmol, 94%) was isolated as a yellow oil.

$[\alpha]_D^{20}$ −64.3 (*c* 0.96, $CHCl_3$). IR (film): 3317, 2935, 1457, 1371, 1216, 1167, 1048 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.43 (s, 3H), 1.66 (m, 1H), 1.76 (m, 1H), 1.83–1.98 (2H), 2.37 (ddd, *J*=9.3, 9.3, 7.5 Hz, 1H), 2.92 (ddd, *J*=7.9, 7.9, 2.7 Hz, 1H), 3.04 (ddd, *J*=9.5, 7.1, 2.8 Hz, 1H), 3.42 (d, *J*=13.0 Hz, 1H), 3.57 (br s, 1H), 3.77–3.90 (4H), 4.01 (d, *J*=13.0 Hz, 1H), 4.09 (dd, *J*=9.8, 5.8 Hz, 1H), 4.40 (ddd, *J*=8.5, 5.4, 5.4 Hz, 1H), 7.21–7.27 (3H), 7.33–7.38 (2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1 (t), 23.5 (t), 25.4 (q), 27.9 (q), 54.4 (t), 58.2 (t), 60.6 (t), 65.0 (d), 65.7 (d), 77.7 (d), 77.7 (d), 108.5 (s), 127.5 (d), 128.5 (d), 128.9 (d), 132.3 (s). HRMS: found: *m*/*z* 322.2013. Calcd for $C_{18}H_{28}O_4N$: $(MH)^+$, 322.2013.

4.1.5. Acetic acid (4*R*,5*S*)-5-[(*S*)-((*S*)-*N*-benzyl-pyrrolidin-2-yl)hydroxymethyl]-2,2-dimethyl[1,3]dioxolan-4-ylmethyl ester (11). To a solution of prolinol **9** (70 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) cooled to −78 °C, acetyl chloride (16.3 μL, 0.23 mmol, 1.05 equiv) and 2,4,6-collidine (58 μL, 0.44 mmol, 2.0 equiv) were added. After 2.5 h at −78 °C and 1 h at rt, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH: 95/5). Prolinol **11** (70 mg, 0.19 mmol, 88%) was isolated as a yellow oil.

$[\alpha]_D^{20}$ −13.3 (*c* 1.16, $CHCl_3$). IR (film): 3449, 2936, 1738, 1454, 1371, 1217, 1167, 1076, 1041 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (s, 3H), 1.36 (s, 3H), 1.42–1.88 (4H), 2.01 (s, 3H), 2.21 (ddd, *J*=9.4, 9.2, 9.2 Hz, 1H), 2.78 (m, 1H), 2.90 (ddd, *J*=9.5, 6.9, 2.4 Hz, 1H), 3.27 (d, *J*=13.2 Hz, 1H), 3.62 (dd, *J*=9.8, 2.6 Hz, 1H), 3.88 (d, *J*=13.2 Hz, 1H), 3.93 (dd, *J*=9.8, 6.0 Hz, 1H), 4.05 (dd, *J*=12.0, 8.7 Hz, 1H), 4.34 (ddd, *J*=8.7, 6.0, 2.6 Hz, 1H), 4.48 (dd, *J*=11.8, 3.0 Hz, 1H), 7.13–7.27 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1 (q), 23.1 (t), 23.2 (t), 25.5 (q), 28.0 (q), 54.3 (t), 58.2 (t), 63.7 (t), 65.2 (d), 65.6 (d), 76.0 (d), 77.3 (d), 109.1 (s), 127.2 (d), 128.4 (d), 128.7 (d), 138.9 (s), 171.0 (s). MS (EI, 70 eV) *m*/*z* (relative intensity): 348 $((M-Me)^+$, 4), 190 (4), 161 (13), 160 (100), 115 (2), 92 (4), 91 (47), 65 (2), 59 (1). Anal. Calcd for $C_{20}H_{29}NO_5$: C: 66.09, H: 8.04, N: 3.85. Found C: 65.97, H: 8.25, N: 4.12.

4.1.6. Acetic acid (4*R*,5*R*)-5-[(*S*)-((*S*)-*N*-benzylpyrrolidin-2-yl)chloromethyl]-2,2-dimethyl[1,3]dioxolan-4-ylmethyl ester (13). To a solution of prolinol **11** (138 mg, 0.38 mmol, 1.0 equiv) in THF (10 mL), cooled to 0 °C, were added mesyl chloride (44.1 μL, 0.57 mmol, 1.5 equiv) and Et_3N (106.9 μL, 0.76 mmol, 2.0 equiv). After 20 min, the reaction mixture was heated to 100 °C by microwave irradiations for 1 h. Five portions of MsCl (12.5 μL, 0.16 mmol, 0.6 equiv) and Et_3N (30 μL, 0.3 mmol, 1.2 equiv) followed by 1 h heating at 100 °C by microwave irradiations are needed to reach total conversion. The reaction mixture is then quenched by addition of water (3 mL) and the aqueous layer was extracted with AcOEt (3×10 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (cyclohexane/AcOEt: 80/20). Chloropyrrolidine **13** (25 mg, 0.065 mmol, 24%) was isolated as a yellow oil.

$[\alpha]_D^{20}$ +1.6 (*c* 0.91, $CHCl_3$). IR (film): 2939, 1742, 1454, 1370, 1217, 1169, 1074, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H), 1.37 (s, 3H), 1.58–1.90 (4H), 2.02 (s, 3H), 2.22 (m, 1H), 2.96 (m, 1H), 3.05 (m, 1H), 3.43 (d, *J*=12.9 Hz, 1H), 3.82 (d, *J*=12.9 Hz, 1H), 3.88 (dd, *J*=10.5, 2.3 Hz, 1H), 3.97 (dd, *J*=11.6, 7.7 Hz, 1H), 4.10 (dd, *J*=10.6, 5.6 Hz, 1H), 4.22 (dd, *J*=11.6, 3.6 Hz, 1H), 4.30 (ddd, *J*=7.7, 5.5, 3.6 Hz, 1H), 7.16–7.30 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.0 (q), 22.9 (t), 24.6 (t), 25.7 (q), 28.0 (q), 54.4 (t), 58.7 (t), 59.2 (d), 62.9 (t), 64.1 (d), 71.6 (d), 78.1 (d), 109.6 (s), 127.2 (d), 128.3 (d), 129.0 (d), 139.0 (s), 170.8 (s). MS (EI, 70 eV) *m*/*z* (relative intensity): 366 $((M-Me)^+$, 2), 269 (2), 210 (2), 208 (7), 161 (13), 160 (100), 115 (2), 92 (5), 91 (62), 77 (2), 65 (4), 60 (2), 58 (4), 55 (2).

4.1.7. Acetic acid (2*R*,3*R*)-2-((4*S*,5*R*)-5-acetoxymethyl-2,2-dimethyl[1,3]dioxolan-4-yl)-*N*-benzylpiperidin-3-yl ester (14a). To a solution of the chloropyrrolidine **13** (25 mg, 0.065 mmol, 1.0 equiv) in THF (5 mL), was added AgOAc (33 mg, 0.19 mmol, 3.0 equiv). The reaction mixture was then heated at 120 °C by microwave irradiations for 1 h. Additions of AgOAc (33 mg, 0.19 mmol, 3.0 equiv) and heating for 1 h at 120 °C (repeated three times) were necessary to reach total conversion. The reaction mixture was then quenched by addition of water (3 mL). The aqueous layer was extracted with AcOEt (3×10 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by preparative TLC on silica gel (cyclohexane/AcOEt: 60/40). Piperidine **14a** (12 mg, 0.030 mmol, 46%) was isolated as a yellow oil.

$[\alpha]_D^{20}$ +34.0 (*c* 0.35, $CHCl_3$). IR (film): 2935, 1736, 1454, 1371, 1247, 1139, 1075, 1044 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 3H), 1.53 (s, 3H), 1.58 (m, 1H), 1.73–1.94 (3H), 2.04 (s, 3H), 2.11 (s, 3H), 2.61 (ddd, *J*=13.2, 4.3, 4.3 Hz, 1H), 2.96 (ddd, *J*=12.9, 9.6, 3.3 Hz, 1H), 3.05 (dd, *J*=10.0, 4.0 Hz, 1H), 3.83 (d, *J*=14.0 Hz, 1H), 4.04 (d, *J*=14.0 Hz, 1H), 4.08 (dd, *J*=11.5, 8.2 Hz, 1H), 4.22 (ddd, *J*=8.2, 5.3, 3.7 Hz, 1H), 4.37 (dd, *J*=11.4, 3.7 Hz, 1H), 4.58 (dd, *J*=10.0, 5.4 Hz, 1H), 4.80 (m, 1H), 7.20–7.39 (5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (t), 20.9 (q), 21.3 (q), 25.8 (q), 26.7 (t), 28.3 (q), 45.1 (t), 57.2 (t), 59.0 (d), 63.6 (t), 69.2 (d), 74.6 (d), 75.3

(d), 108.5 (s), 126.8 (d), 128.1 (d), 128.5 (d), 140.4 (s), 170.5 (s), 170.9 (s). MS (EI, 70 eV) *m/z* (relative intensity): 404 ($(M-H)^+$, 1), 390 (2), 233 (16), 232 (100), 190 (5), 173 (2), 160 (3), 92 (3), 91 (37). HRMS: found: *m/z* 406.2224. Calcd for $C_{22}H_{32}O_6N$: $(MH)^+$, 406.2224.

4.1.8. (2*R*,3*R*)-*N*-Benzyl-2-((4*S*,5*R*)-5-hydroxymethyl-2,2-dimethyl[1,3]dioxolan-4-yl)piperidin-3-ol (15). To a solution of diacetate **14a** (6.0 mg, 0.015 mmol, 1.0 equiv) in THF (2 mL), was added a solution of NaOMe (8.0 mg, 0.15 mmol, 10.0 equiv) in MeOH (0.5 mL). After 3 h at rt, the reaction mixture is quenched by addition of a saturated solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with AcOEt (3×5 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by preparative TLC on silica gel (CH_2Cl_2/MeOH: 95/5). Diol **15** (4.9 mg, 0.012 mmol, 83%) was isolated as a yellow oil.

$[\alpha]_D^{20}$ +82.1 (*c* 0.12, $CHCl_3$). IR (film): 3383, 2932, 2857, 1453, 1370, 1245, 1219, 1049 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 3H), 1.46–1.58 (5H), 1.68 (m, 1H), 1.83 (m, 1H), 2.23 (m, 1H), 2.79 (ddd, *J*=12.0, 7.6, 3.0 Hz, 1H), 2.91 (dd, *J*=7.6, 6.7 Hz, 1H), 3.56–3.64 (2H), 3.78 (dd, *J*=11.3, 7.7 Hz, 1H), 3.91 (m, 1H), 3.97 (d, *J*=13.0 Hz, 1H), 4.34 (dd, *J*=12.6, 6.0 Hz, 1H), 4.85 (dd, *J*=7.8, 5.5 Hz, 1H), 7.25–7.34 (5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (t), 25.5 (q), 28.4 (q), 29.7 (t), 48.3 (t), 59.2 (t), 61.4 (t), 64.4 (d), 67.4 (d), 76.2 (d), 77.9 (d), 108.3 (s), 127.5 (d), 128.5 (d), 129.2 (d), 138.6 (s). HRMS: found: *m/z* 322.2013. Calcd for $C_{18}H_{28}O_4N$: $(MH)^+$, 322.2013.

4.1.9. (2*R*,3*R*)-2-((4*S*,5*R*)-5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)piperidin-3-ol (16). To a solution of piperidine **15** (3.0 mg, 0.009 mmol, 1.0 equiv) in EtOH (2 mL), was added Pd/C (5%) (0.5 mg). After 3 h of vigorous stirring under a hydrogen atmosphere, the mixture was filtered on Celite®. The solvent was removed in vacuo and piperidine **16** (1.9 mg, 0.008 mmol, 93%) was obtained and used without further purification.

$[\alpha]_D^{20}$ −82.3 (*c* 0.09, $CHCl_3$). IR (film): 3317, 2931, 2858, 1454, 1380, 1247, 1212, 1165, 1140, 1065, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 3H), 1.41–1.54 (5H), 1.78 (m, 1H), 2.15 (m, 1H), 2.49–2.58 (2H), 3.03 (m, 1H), 3.53 (ddd, *J*=10.0, 10.0, 4.6 Hz, 1H), 3.69 (dd, *J*=13.0, 1.5 Hz, 1H), 3.84 (dd, *J*=13.0, 4.8 Hz, 1H), 4.25 (ddd, *J*=7.5, 4.7, 1.5 Hz, 1H), 4.68 (dd, *J*=7.7, 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.4 (q), 26.6 (t), 26.8 (q), 34.6 (t), 44.6 (t), 60.2 (d), 60.3 (t), 69.1 (d), 74.4 (d), 77.7 (d), 107.4 (s). HRMS: found: *m/z* 232.1543. Calcd for $C_{11}H_{22}O_4N$: $(MH)^+$, 232.1543.

4.1.10. (1*S*,2*R*,8*R*,8a*R*)-1,2-*O*-Isopropylidenedioxy-8-hydroxyindolizidine [(−)-swainsonine acetonide] (17).[7b,9b–d,22] To a solution of piperidine **16** (1.6 mg, 0.007 mmol, 1.0 equiv) in pyridine (0.25 mL), cooled to 0 °C, were added PPh_3 (2.18 mg, 0.008 mmol, 1.2 equiv) in a pyridine solution (0.5 mL), and DEAD (1.3 μL, 0.008 mmol, 1.2 equiv). After 2.5 h at 0 °C, the solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (cyclohexane/AcOEt: 60/40), indolizidine **17** (0.4 mg, 0.002 mmol, 27%) was isolated along with the unreacted piperidine **16** (0.7 mg, 0.003 mmol, 43%). The ^1H NMR data are in agreement with those described in literature.[22b]

^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H), 1.51 (s, 3H), 1.60–1.70 (4H), 1.85 (m, 1H), 2.06 (m, 1H), 2.14 (dd, *J*=10.8, 4.0 Hz, 1H), 3.00 (m, 1H), 3.16 (d, *J*=11.0 Hz, 1H), 3.85 (m, 1H), 4.62 (dd, *J*=6.2, 4.2 Hz, 1H), 4.71 (dd, *J*=6.2, 4.7 Hz, 1H). MS (EI, 70 eV): *m/z* (relative intensity): 213 ($M^{+\bullet}$, 45), 198 (20), 156 (18), 155 (10), 138 (100), 126 (30), 120 (28), 113 (58), 99 (37), 96 (57), 84 (18), 71 (18), 70 (11), 68 (14), 55 (13).

4.1.11. (*R*)-1-((*S*)-*N*-Benzylpyrrolidin-2-yl)prop-2-en-1-ol (19). To a solution of prolinol **4** (515 mg, 1.4 mmol, 1.0 equiv) in Et_2O (5 mL), cooled to 0 °C, was added dropwise HCl (5 M aqueous solution) (2.2 mL, 11.3 mmol, 8.0 equiv). The cooling bath was removed and, after 6 h of vigorous stirring at rt, the two phases were separated and the aqueous phase was washed with Et_2O (3×5 mL). The aqueous phase was cooled to 0 °C, and NaOH (solid) was added until basic pH. The aqueous phase was then extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were dried over Na_2SO_4 and the solvents were evaporated to dryness in vacuo. To a solution of this resulting product in MeOH (5 mL), were added K_2CO_3 (170 mg, 1.2 mmol, 1.2 equiv) and benzylbromide (122 μL, 1.15 mmol, 1.15 equiv). After 45 min at rt, the reaction mixture was quenched by KOH (1 M) (4 mL). The aqueous phase was extracted with ethyl acetate (3×5 mL). The organic phases were dried over Na_2SO_4 and the solvents were evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/AcOEt/Et_3N: 80/20/0.1). Compound **19** (160 mg, 0.74 mmol, 53%) was obtained as a yellow oil.

$[\alpha]_D^{20}$ −70.2 (*c* 1.1, $CHCl_3$). IR (film): 3420, 3025, 2960, 2795, 1643, 1604, 1492, 1451, 1421, 1351, 1280, 1211, 1148, 1112, 1029 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.58–1.77 (3H), 1.88 (m, 1H), 2.31 (m, 1H), 2.67 (m, 1H), 3.01 (m, 1H), 3.37 (d, *J*=13.0 Hz, 1H), 4.09 (d, *J*=13.0 Hz, 1H), 4.31 (dddd, *J*=5.0, 3.3, 1.7, 1.5 Hz, 1H), 5.20 (ddd, *J*=10.5, 1.7, 1.7 Hz, 1H), 5.38 (ddd, *J*=17.1, 1.7, 1.7 Hz, 1H), 5.83 (ddd, *J*=17.3, 10.7, 5.2 Hz, 1H), 7.24–7.38 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2 (t), 23.8 (t), 54.3 (t), 58.0 (t), 67.5 (d), 69.7 (d), 115.4 (t), 127.0 (d), 128.2 (d), 128.6 (d), 137.4 (d), 138.9 (s). MS (EI, 70 eV) *m/z* (relative intensity): 216 ($(M-H)^+$, 1), 198 (1), 184 (1), 161 (12), 160 (100), 159 (3), 158 (2), 130 (2), 104 (2), 92 (6), 91 (96), 89 (3), 77 (2), 70 (4), 65 (7). HRMS: found: *m/z* 218.1536. Calcd for $C_{14}H_{20}ON$: $(MH)^+$, 218.1539.

4.1.12. (2*S*,3*R*)-*N*-Benzyl-2-vinylpiperidin-3-ol (20). To a solution of prolinol **19** (150 mg, 0.7 mmol, 1.0 equiv) in THF (5 mL), cooled to 0 °C, trifluoroacetic anhydride (146 μL, 1.04 mmol, 1.5 equiv) was added dropwise. After 15 min at 0 °C, Et_3N (491 μL, 3.5 mmol, 5.0 equiv) was added. The reaction mixture was heated to reflux for 24 h. Trifluoroacetic anhydride (59 μL, 0.35 mmol, 0.5 equiv) and Et_3N (123 μL, 0.7 mmol, 1.0 equiv) were added and the mixture was heated again for 18 h. Another 5 equiv of

trifluoroacetic anhydride and 3 h at 65 °C were necessary to reach total conversion. The reaction mixture was then cooled to 0 °C and quenched by addition of NaOH (2.5 M aqueous solution) (5 mL). After 2 h, the aqueous phase was extracted with ethyl acetate (3×30 mL). The organic phases were dried over Na_2SO_4 and the solvents were evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/AcOEt/Et_3N: 80/20/0.1). Compound **19** (90 mg, 0.41 mmol, 60%) was obtained as a yellow oil.

$[\alpha]_D^{20}$ +49.7 (*c* 2.1, $CHCl_3$). IR (film): 3365, 2930, 2785, 1645, 1602, 1496, 1451, 1368, 1262, 1092, 1070 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.36 (m, 1H), 1.53 (m, 1H), 1.69 (m, 1H), 2.08–1.94 (2H), 2.23 (s large, 1H), 2.63 (dd, *J*=8.3, 8.2 Hz, 1H), 2.75 (m, 1H), 3.20 (d, *J*=13.6 Hz, 1H), 3.43 (m, 1H), 3.97 (d, *J*=13.6 Hz, 1H), 7.36–7.22 (m, 2H), 5.89 (ddd, *J*=17.0, 10.6, 9.2 Hz, 1H), 7.36–7.22 (5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3 (t), 30.3 (t), 50.5 (t), 59.4 (t), 69.6 (d), 72.9 (d), 120.2 (t), 126.7 (d), 128.0 (d), 128.8 (d), 138.0 (d), 138.8 (s). MS (EI, 70 eV) *m/z* (relative intensity): 217 ($M^{+\bullet}$, 4), 200 (2), 172 (6), 158 (6), 144 (5), 127 (6), 126 (100), 104 (5), 91 (68), 71 (8).

4.1.13. (*R*)-1-[(*S*)-1-Allylpyrrolidin-2-yl]prop-2-en-1-ol (21). To a stirred solution of prolinol **4** (5.33 g, 14.4 mmol, 1.0 equiv) in Et_2O (40 mL) cooled to 0 °C, was added HCl (5 M aqueous solution, 29 mL) dropwise. The cooling bath was removed and, after 24 h of vigorous stirring at rt, the two phases were separated and the aqueous phase was washed with Et_2O (3×30 mL). Toluene (150 mL) was added to the aqueous phase and the mixture was cooled to 0 °C, and K_2CO_3 (26 g), *n*-Bu_4NBr (0.93 g, 2.9 mmol, 0.2 equiv), and allyl bromide (3.75 mL, 43.3 mmol, 3.0 equiv) were added. After 24 h of vigorous stirring at rt, the two phases were separated. The aqueous phase was extracted with AcOEt (2×50 mL). The organic phases were dried over Na_2SO_4 and the solvents were evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/Et_2O: 50/50). Compound **21** was obtained as a yellow oil (1.2 g, 7.2 mmol, 50% yield).

$[\alpha]_D^{20}$ −54.3 (*c* 1.0, $CHCl_3$). IR (film): 3405, 3075, 2960, 2795, 1642, 1604, 1444, 1419, 1351, 1280, 1205, 1150 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.58–1.72 (m, 3H), 1.82 (m, 1H), 2.30 (m, 1H), 2.53 (m, 1H), 2.92 (dd, *J*=13.7, 7.5 Hz, 1H), 3.15 (m, 1H), 3.36 (br s, 1H), 3.48 (dd, *J*=13.7, 5.2 Hz, 1H), 4.24 (m, 1H), 5.08–5.24 (m, 3H), 5.33 (ddd, *J*=17.1, 1.8, 1.8 Hz, 1H), 5.77 (ddd, *J*=16.9, 10.7, 5.4 Hz, 1H), 5.89 (dddd, *J*=17.2, 10.0, 7.5, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (t), 24.0 (t), 54.3 (t), 56.5 (t), 67.2 (d), 69.8 (d), 115.4 (t), 116.9 (t), 135.8 (d), 137.7 (d). MS (CI, CH_4): *m/z* (relative intensity): 168 (MH^+, 100), 128 (8), 150 (12), 126 (4), 110 (47), 98 (3). HRMS: found: *m/z* 168.1390. Calcd for $C_{10}H_{18}NO$: $(M+H)^+$, 168.1388.

4.1.14. (2*S*,3*R*)-1-Allyl-2-vinylpiperidin-3-ol (22). To a solution of prolinol **21** (1.2 g, 7.1 mmol, 1.0 equiv) in THF (60 mL), cooled to 0 °C, was added dropwise trifluoroacetic anhydride (1.5 mL, 10.6 mmol, 1.5 equiv). After 1 h, Et_3N (3.0 mL, 21.2 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred for 20 min at 0 °C and then heated to reflux for 15 h. After addition of NaOH (2.5 M aqueous solution, 15 mL), the mixture was stirred for 2 h at rt and then extracted with EtOAc (3×30 mL), dried over Na_2SO_4, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 80/20) to give piperidine **22** (1.1 g, 6.7 mmol, 95% yield) as a yellow oil.

$[\alpha]_D^{20}$ +50.2 (*c* 1.03, $CHCl_3$). IR (film): 3415, 3076, 2936, 2861, 2793, 1643, 1441, 1419, 1261, 1090, 994, 916, 889 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (m, 1H), 1.56 (m, 1H), 1.71 (m, 1H), 1.98–2.04 (m, 2H), 2.23 (br s, 1H), 2.50 (dd, *J*=8.4, 8.4 Hz, 1H), 2.76–2.90 (m, 2H), 3.31–3.39 (m, 2H), 5.10–5.19 (m, 2H), 5.31–5.37 (m, 2H), 5.70–5.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.7 (t), 30.8 (t), 50.9 (t), 58.3 (t), 69.9 (d), 73.1 (d), 117.8 (t), 120.3 (t), 134.8 (d), 137.9 (d). MS (EI, 70 eV) *m/z* (relative intensity): 167 (M^+, 9), 140 (9), 126 (100), 122 (16), 110 (17), 108 (21), 96 (14), 94 (18), 82 (17), 71 (16), 68 (18), 56 (14). HRMS: found: *m/z* 168.1384. Calcd for $C_{10}H_{18}NO$: $(M+H)^+$, 168.1388.

4.1.15. (2*S*,3*R*)-1-Allyl-3-(*tert*-butyldimethylsilanyloxy)-2-vinylpiperidine (23). To a solution of piperidine **22** (0.670 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at rt, DMAP (0.049 g, 0.4 mmol, 0.1 equiv), Et_3N (1.13 mL, 8.0 mmol, 2 equiv), and TBDMSCl (1.20 g, 8.0 mmol, 2.0 equiv) were successively added. After 18 h at rt, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution until pH∼10. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 90/10) to give **23** (0.788 g, 2.8 mmol, 70% yield) as a colorless oil.

$[\alpha]_D^{20}$ +64.2 (*c* 0.665, $CHCl_3$). IR (film): 2928, 2857, 2790, 1643, 1462, 1361, 1253, 1101 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ −0.02 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 1.28 (m, 1H), 1.52 (m, 1H), 1.65 (m, 1H), 1.88–1.95 (2H), 2.42 (dd, *J*=8.6, 8.6 Hz, 1H), 2.74 (dd, *J*=8.0, 13.9 Hz, 1H), 2.88 (m, 1H), 3.35–3.49 (m, 2H), 5.07–5.14 (2H), 5.19 (dd, *J*=4.4, 1.9 Hz, 1H), 5.22 (m, 1H), 5.58 (m, 1H), 5.82 (dddd, *J*=17.0, 10.3, 8.0, 5.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.3 (q), −4.2 (q), 18.1 (s), 23.4 (t), 25.9 (q), 34.0 (t), 51.6 (t), 58.2 (t), 71.8 (d), 73.7 (d), 117.6 (t), 119.4 (t), 135.1 (d), 138.9 (d). MS (EI, 70 eV) *m/z* (relative intensity): 281 ($M^{+\bullet}$, 4), 241 (20), 240 (100), 224 (15), 185 (9), 150 (10), 122 (10), 110 (56), 108 (23), 73 (28). HRMS: found: *m/z* 282.2257. Calcd for $C_{16}H_{32}NOSi$: $(M+H)^+$, 282.2253.

4.1.16. (8*R*,8a*S*)-8-(*tert*-Butyldimethylsilanyloxy)-3,5,6,7,8,8a-hexahydroindolizine (24).[25] To a solution of piperidine **23** (79 mg, 0.28 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) cooled to 0 °C, (+)-camphorsulfonic acid (72 mg, 0.31 mmol, 1.1 equiv) was added. After 10 min at 0 °C, the cooling bath was removed and first generation Grubbs catalyst was added in three portions (3×8 mg, 0.035 mmol, 12.5 mol %), each addition was followed by 2 h reflux. The reaction mixture was then treated with K_2CO_3 and filtered. The solvent was removed in vacuo.

The crude oil was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH: 90/10) to give **24** (58 mg, 0.23 mmol, 82% yield) as a yellow oil. The spectroscopic data are in agreement with those described in literature.

$[\alpha]_D^{20}$ −88.9 (*c* 0.70, C_6H_6) [lit.:[25] $[\alpha]_D^{20}$ −91.7 (*c* 0.955, C_6H_6)]. IR (film): 2931, 2886, 2857, 2778, 1467, 1368, 1253, 1148, 1095 cm^{-1}. ^1H NMR (C_6D_6, 400 MHz): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.99 (s, 9H), 1.27 (m, 1H), 1.41 (m, 1H), 1.59 (m, 1H), 1.89 (ddd, *J*=12.2, 7.9, 4.0 Hz, 1H), 2.25 (ddd, *J*=11.6, 11.6, 2.9 Hz, 1H), 2.72 (dd, *J*=11.2, 4.8 Hz, 1H), 3.04 (m, 1H), 3.13 (dddd, *J*=12.5, 6.5, 2.0, 2.0 Hz, 1H), 3.54 (dddd, *J*=12.5, 3.9, 1.9, 1.9 Hz, 1H), 3.60 (ddd, *J*=10.2, 8.8, 4.4 Hz, 1H), 5.69 (ddd, *J*=6.2, 4.0, 2.1 Hz, 1H), 6.18 (m, 1H). ^{13}C NMR (C_6D_6, 100 MHz): δ −4.5 (q), −4.1 (q), 18.3 (s), 25.2 (t), 26.1 (q), 35.1 (t), 49.1 (t), 58.3 (t), 72.5 (d), 74.8 (d), 128.9 (d), 131.5 (d). MS (CI, CH_4) *m*/*z* (relative intensity): 254 (MH^+, 100), 144 (3), 120 (24), 111 (3).

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