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Asymmetric Synthesis of *gem*-Difluoromethylenated Dihydroxypyrrolizidines and Indolizidines

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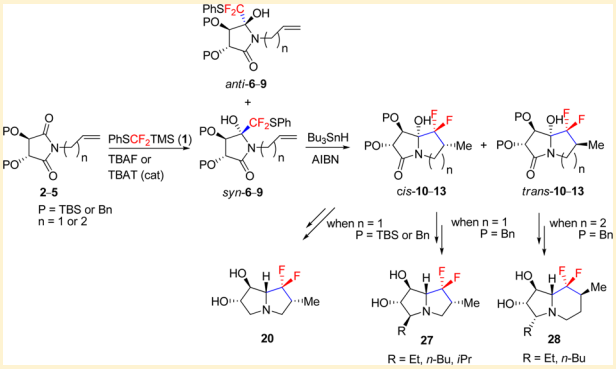
Supporting Information

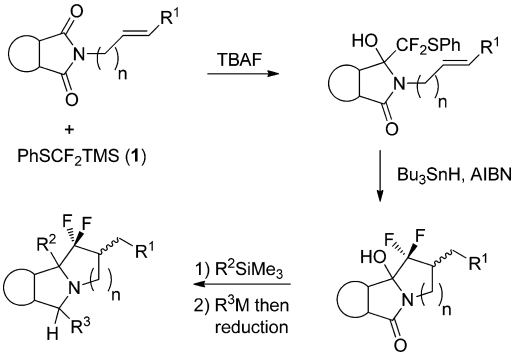
ABSTRACT: An asymmetric synthesis of *gem*-difluoromethylenated dihydroxypyrrolizidines and indolizidines is described. The fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ (**1**) to chiral imides was achieved in satisfactory yields to provide mixtures of *syn*- and *anti*-isomers **6**−**9** with moderate to good diastereoselectivities. Reductive cleavage of the phenylsulfanyl group followed by intramolecular radical cyclization of the *syn*-isomers **6**−**9** occurred under refluxing conditions to afford the corresponding *gem*-difluoromethylenated 1-azabicyclic compounds **10**−**13** in moderate yields as a separable mixture of *cis*- and *trans*-isomers. The *cis*-isomers of compounds **10** and **12** and *trans*-**13** were readily transformed to *gem*-difluoromethylenated dihydroxypyrrolizidines **20** and **27** and indolizidine **28**, respectively, by reductive cleavage of the hydroxyl group and organometallic addition followed by hydrogenolysis.



INTRODUCTION

Organic molecules containing *gem*-difluoromethylene moiety have been shown to have unique physical, chemical and biological properties. The presence of the *gem*-difluoromethylene can enhance pharmacological activities of drug molecules including their stability, lipophilicity and bioavailability.[1] In this respect, there is a growing trend for development of efficient methodology for the preparation of *gem*-difluoromethylenated compounds, particularly analogues of natural products for use in pharmaceutical industry.[2] In the course of our continuous research on employing $PhSCF_2SiMe_3$ (**1**) as a *gem*-difluoromethylene building block,[3] we have recently demonstrated a general method for the preparation of *gem*-difluoromethylenated 1-azabicyclic derivatives (Scheme 1).[4] The synthesis involved fluoride-catalyzed nucleophlilic difluoro(phenylsulfanyl)methylation reaction of $PhSCF_2SiMe_3$ (**1**) to *N*-alkenyl succinimide derivatives followed by sequential intramolecular radical cyclization. The resulting adducts were employed as useful precursors for the preparation of *gem*-difluoromethylenated pyrrolizidines and indolizidines by reductive cleavage of the hydroxyl group and subsequent organometallic addition to the carbonyl group followed by reduction. In view of the important biological properties of polyhydroxylated pyrrolizidine and indolizidine alkaloids, e.g., lentiginosine, swainsonine and catanospermine as potent glycosidase inhibitors,[5] numerous reports described the syntheses of these classes of natural products and their analogues.[6] In the present paper, we report an asymmetric synthesis of *gem*-difluoromethylenated dihydroxypyrrolizidines and indolizidines starting from readily available chiral *N*-alkenyl-3,4-dihydroxylated succinimides.

Scheme 1. Preparation of *gem*-Difluoromethylenated 1-Azabicyclic Derivatives



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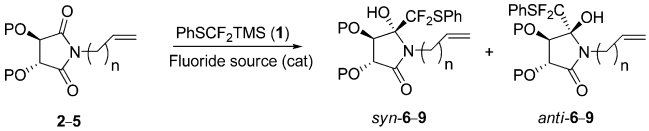
RESULTS AND DISCUSSION

At first, suitable chiral imides **2**–**5** were synthesized starting from L-tartaric acid (see the Experimental Section).[7] With the chiral imides in hand, we then commenced our study by examining the stereoselective fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ (**1**) to chiral imides **2**–**5** (Scheme 2).

Scheme 2. Adducts 6–9 Obtained via Fluoride-Catalyzed Reaction of $PhSCF_2SiMe_3$ (1) with Chiral Imides 2–5



Treatment of **1** with imide **2** in the presence of 10 mol % of tetrabutylammonium fluoride (TBAF) in THF at −78 to 0 °C for 3 h gave adduct **6** as a mixture of *syn*- and *anti*-isomers in 58 and 7% yields, respectively. Gratifyingly, better yield and higher stereoselectivity of adduct **6** were obtained (*syn*-**6** = 72% yield, *anti*-**6** = 8% yield) when tetrabutylammonium triphenyldifluorosilicate (TBAT) was employed as a fluoride source (10 mol % TBAT, DMF, 0 °C, 2 h) (Table 1, entries 1 and 2). Under similar reaction conditions, the reaction of imide **3** with **1** also gave rise to a formation of a mixture of *syn*-**7** (76% yield) and *anti*-**7** (4% yield) (Table 1, entry 3). Poor results (lower yield and stereoselectivity) were observed when the benzyl protected imides **4** were employed as a substrate (Table 1, entry 4). However, slightly higher yield was obtained when the reaction was performed in THF at low temperature (−78 °C) albeit with low stereoselectivity (Table 1, entry 5). Imide **5** gave comparable results to those of imide **4** (Table 1, entry 6). The diastereomeric mixtures of the obtained adducts **6**–**9** can be separated by column chromatography.

A proposed transition state for fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ (**1**) to chiral imides is illustrated in Figure 1. The nucleophile ("$PhSCF_2^-$") preferentially attacked the carbonyl group of the imide in the direction that steric repulsion to the −OP group is minimized, affording the *syn*-isomer as the major isomer. The stereoselectivity of the reduction was realized, and the stereochemical outcomes can be rationalized as those previously reported by Speckamp and Takabe.[8]

When the *syn*-adducts **6**–**9** were treated with Bu_3SnH/AIBN in refluxing toluene, the corresponding *gem*-difluoromethyl radicals[9] were formed and subsequently underwent intramolecular cyclization to the alkenyl moiety, affording *gem*-difluoromethylenated 1-azabicyclic compounds **10**–**13** as mixtures of *cis*- and *trans*-isomers (Scheme 3).[10,11] Separation

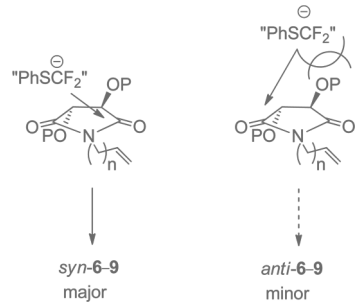
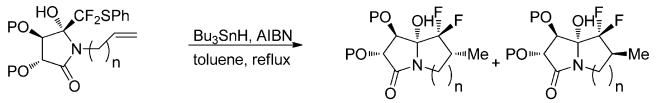


Figure 1. Proposed transition state for the addition of $PhSCF_2SiMe_3$ (**1**) to chiral imides.

Scheme 3. Reductive Cyclization of the *Syn* Isomers of Adducts 6–9 to Bicyclic Derivatives 10–13



syn-**6**; n = 1, P = TBS
syn-**7**; n = 2, P = TBS
syn-**8**; n = 1, P = Bn
syn-**9**; n = 2, P = Bn

cis-**10** (37%)
cis-**11** (12%)
cis-**12** (39%)
cis-**13** (15%)

trans-**10** (15%)
trans-**11** (34%)
trans-**12** (13%)
trans-**13** (43%)

of each isomer can readily be achieved by preparative thin-layer chromatography on silica gel. The relative stereochemistries of *cis*-**10**, *trans*-**11** and *cis*-**13** were established by X-ray crystallography (see the Supporting Information). On the basis of the X-ray structures of *cis*-**10**, *trans*-**11** and *cis*-**13**, the stereochemistries of *syn*-**6**, *syn*-**7** and *syn*-**9** could be confirmed as depicted in Scheme 3.

The stereochemical outcome of compounds **10**, **11**, **12** and **13** can be rationalized as shown in Scheme 4. The radical cyclization was proposed to proceed via 5-*exo* or 6-*exo* cyclization mode.[12] Half-chair transition state **A** for the radical intermediate derived from *syn*-**6** or *syn*-**8** is energetically more favorable due to minimized steric interaction between the vinylic group and the −CHOP group, giving rise to *cis*-**10** or *cis*-**12** as the major isomer. Similarly, the radical cyclization of *syn*-**7** or *syn*-**9** proceeded via the favorable chair like transition state **C**, of which the vinylic group is at quasi-equatorial position, leading to *trans*-**11** or *trans*-**13** as the major product.

Having established an efficient strategy to chiral *gem*-difluoromethylenated 1-azabicyclic compounds **10**–**13**, we further demonstrated their conversion to chiral substituted *gem*-difluoromethylenated dihydroxypyrrolizidines and indolizidines. Indeed, reductive cleavage of the hydroxyl group of *cis*-**10** was examined. When *cis*-**10** was allowed to react with Et_3SiH/$BF_3{\cdot}OEt_2$ in CH_2Cl_2[13] at −78 °C to room temperature for 24 h, compound **15** of which the hydroxyl group is opposite to that

Table 1. Results Obtained for the Formation of Adducts 6–9[a]

	imides						adducts (% yield)[b]	
entry		*n*	P	F^-	temp (°C)	time (h)	*syn*-	*anti*-
1	**2**	1	TBS	TBAF[c]	−78 to 0	3	**6** (58)	**6** (7)
2	**2**	1	TBS	TBAT[d]	0	2	**6** (72)	**6** (8)
3	**3**	2	TBS	TBAT[d]	0	2.5	**7** (76)	**7** (4)
4	**4**	1	Bn	TBAT[d,e]	0	2	**8** (28)	**8** (23)
5	**4**	1	Bn	TBAT[c]	−78	8	**8** (48)	**8** (31)
6	**5**	2	Bn	TBAT[c]	−78	10	**9** (40)	**9** (31)

[a]In all cases, 10 mol % of fluoride source were used. [b]Isolated yields. [c]THF was used as the solvent. [d]DMF was used as the solvent. [e]β-Elimination product derived from adduct **8** was isolated in 18% yield.

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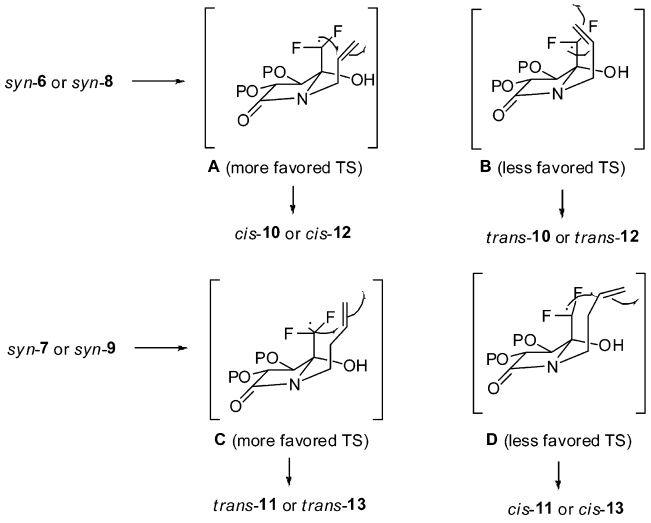
Scheme 4. Proposed Transition States of the Radical Cyclization for the Formation of Bicyclic Derivatives 10−13

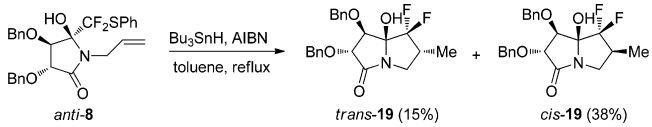


of the starting compound *cis*-**10** was obtained in 71% yield. However, when the reaction was carried out at higher temperature (refluxing CH_2Cl_2) for 24 h, a mixture of products were obtained including expected reduction product **14**, accompanied with desilylated compounds **16** and **17** in 20, 12, and 13% yields, respectively (Scheme 5). Similar results were obtained when *cis*-**12** was employed as the substrate. Treatment of *cis*-**12** with $Et_3SiH/BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 24 h afforded the expected reduction product **18** accompanied by compound **19** in 18 and 34% yields, respectively. To our delight, it was discovered that the reaction of *cis*-**12** with $Et_3SiH/BF_3{\cdot}OEt_2$ proceeded to completion either at room temperature within 48 h or refluxing CH_2Cl_2 within 24 h, affording **18** as a single product in 73 and 62% yield, respectively. The relative stereochemistries of compounds **14**, **16** and **18** were established by the NOE experiments (see the Supporting Information).

The formation of compounds **14**, **15**, **18** and **19** could be rationalized as shown in Scheme 6. The initially formed iminium intermediate **E** was trapped by a hydride from Et_3SiH or by $HOBF_3$, which upon hydrolysis, leading to compounds **14** or **18** and **15** or **19**, respectively. As mentioned earlier, the reductive cleavage of *cis*-**10** and *cis*-**12** conducted either at prolonged reaction time or at refluxing temperature provided exclusively the reduction products (**14** and **16**−**18**). This implies that the step of intermediate **F** formation is reversible. Thus, intermediate **F** was able to undergo elimination, converting back to the intermediate **E**, which could then be trapped by the hydride.

The structure and relative stereochemistry of *trans*-**19** was established by comparing its spectral data with those of *trans*-**19** obtained from the radical cyclization of *anti*-**8** (Scheme 7),

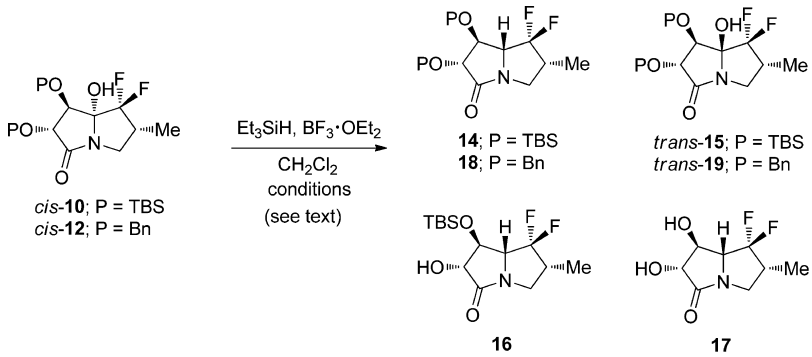
Scheme 7. Radical Mediated Cyclization of *anti*-8



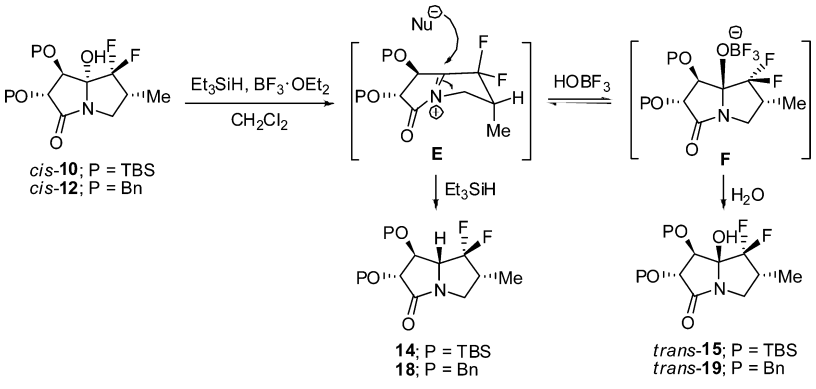
which provided *cis*-**19** as the major isomer. The relative stereochemistry of *cis*-**19** was finally confirmed by X-ray crystallography (see the Supporting Information).

Having compounds **14** and **16** in hand, we then carried out the hydrolytic deprotection of the *t*-butyldimethylsilyl group by using DOWEX 50 WX8 ($H^{\oplus}$-form) in methanol[14] and obtained

Scheme 5. Reductive Cleavage of the Hydroxyl Group of *cis*-10 and *cis*-12



Scheme 6. Proposed Transition States for the Formation of Compounds 14, 15, 18 and 19



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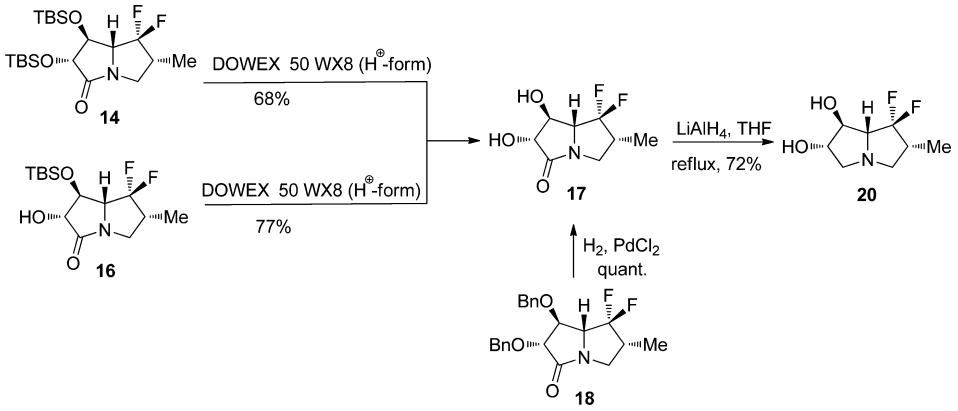
Scheme 8. Preparation of *gem*-Difluoromethylenated Dihydroxypyrrolizidine 20



the corresponding dihydroxy derivative **17** in good yields. Compound **18**, on the other hand, was subjected to hydrogenolysis (H_2, $PdCl_2$, MeOH) to provide compound **17** in quantitative yield. Reduction of **17** with $LiAlH_4$ in refluxing THF gave *gem*-difluoromethylenated dihydroxypyrrolizidine **20** in 72% yield. The results are summarized in Scheme 8.

The synthetic utilities of our method were also extended to the preparation of 1-alkyl-*gem*-difluoromethylenated dihydroxypyrrolizidines. Treatment of **18** with ethylmagnesium chloride in THF at 0 °C for 30 min followed by sequential acidification with 4 M HCl and reduction using $NaBH_3CN$ provided 1-alkyl-*gem*-difluoromethylenated dihydroxypyrrolizidine **21a** in 56% yield as a single isomer. *n*-Butylmagnesium chloride also worked well, providing product **21b** in 58% yield. However, the reaction using a mixture of *n*-BuLi/$CeCl_3$ in THF gave **21b** and compound **22b** in 15 and 43% yields, respectively. A sterically hindered *i*PrMgCl afforded the expected adduct **21c** in 51% yield accompanied with compound **22c** in 12% yield. The results are summarized in Scheme 9 and Table 2. The relative stereochemistry of **21** was established on the basis of the NOE experiments (see the Supporting Information).

Scheme 9. Preparation of 1-Alkyl *gem*-Difluoromethylenated Dihydroxypyrrolizidines 21

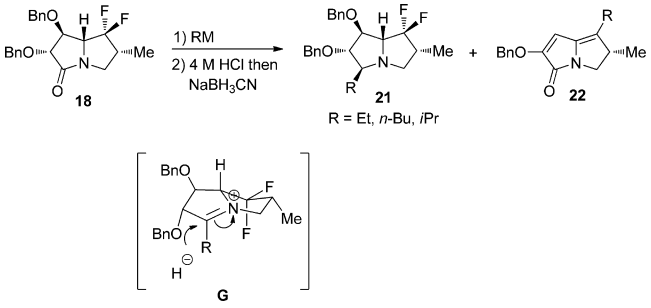


Table 2. Results Obtained for the Preparation of 1-Alkyl *gem*-Difluoromethylenated Dihydroxypyrrolizidines 21

		products (% yield)[a]		
entry	RM	R	**21**	**22**
1	EtMgCl	Et	**21a** (56)	**22a** (−)
2	*n*-BuMgCl	*n*-Bu	**21b** (58)	**22b** (trace)
3	*n*-BuLi/$CeCl_3$	*n*-Bu	**21b** (15)	**22b** (43)
4	*i*PrMgCl	*i*Pr	**21c** (51)	**22c** (12)

[a]Isolated yields.

The resulting stereochemical outcomes of the reaction can be explained by the addition of the organometallic reagents to the carbonyl carbon of the amide moiety. Subsequent acidification afforded iminium ions **G**, which were reduced by the attack of the hydride from the stereoelectronically pseudoaxial face, leading to the favorable *cis*-ring junction adducts **21**.[15]

The competitive formation of compounds **22** was observed when more bulky organometallic reagents, e.g., *i*PrMgCl and BuLi/$CeCl_3$, were employed as nucleophiles. The mechanistic pathways (A and B) for their formation was depicted in Scheme 10. First, a more rapid α-deprotonation of **18** occurs to give an enolate anion **18A**, which leads to the elimination of the β-benzyloxy group, affording **18B**. It is worth mentioning base promoted elimination of β-Boc, β-OAc and β-OBn substituted γ-lactams has been previously reported.[16] Subsequent γ-deprotonation of **18B** followed by elimination of a fluorine atom through dienolate **18C** leads to **18D**, which undergoes conjugate addition−elimination via an intermediate **18E** to furnish compounds **22**. An alternative mechanism for the formation of compounds **22** includes base-induced HF elimination followed by SN2′ displacement of the β-benzyloxy group, affording **18G**. Subsequent α-deprotonation of **18G** gave **18E**, which can undego elimination of a second fluorine atom, leading to compounds **22**.[17]

The synthesis of 1-alkyl-substituted *gem*-difluoromethylenated dihydroxyindolizidines also proceeded smoothly, starting from *trans*-**13**. Reduction of *trans*-**13** with Et_3SiH and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 24 h gave a mixture of *cis*-**23** and *trans*-**23** in 40 and 22% yields, respectively (Scheme 11). The relative stereochemistry of *trans*-**23** was confirmed by the NOE experiments (see the Supporting Information). Subsequent reductive alkylation of *cis*-**23** by reacting with EtMgCl in THF followed by acidification with 4 M HCl in dioxane/MeOH and reduction with $NaBH_3CN$ afforded a mixture of **24a** and **25a** in 50 and 22% yields, respectively. The results are summarized in Scheme 12 and Table 3. Under the similar reaction conditions, the reaction of *cis*-**23** with *n*-BuMgCl gave a mixture of **24b** (43%), **25b** (16%) together with **26b** (14%). When *i*PrMgCl in THF was employed under the same conditions, compound **26c** was obtained in 48% yield along with the starting compound *cis*-**23** in 24% yield: no trace of the expected products **24c** and **25c** was detected. The formation of **26b,c** can be explained as for compounds **22** from **18** as shown in Scheme 10. The relative stereochemistries of compounds **24** were established by the NOE experiments (see the Supporting Information).

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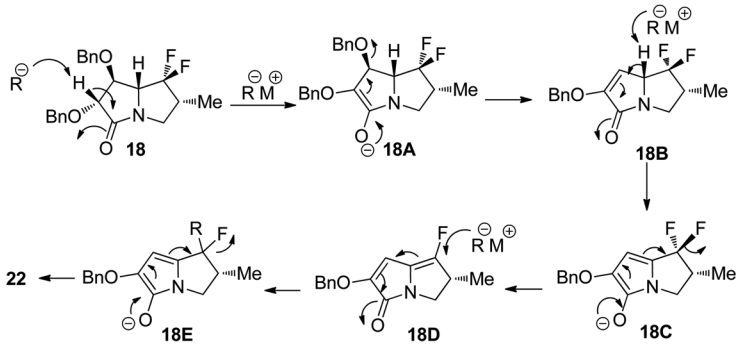
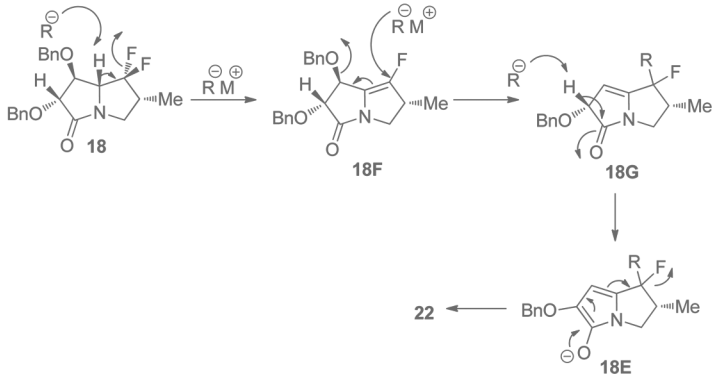
Scheme 10. Proposed mechanistic Pathways (A and B) for the Formation of Compounds 22

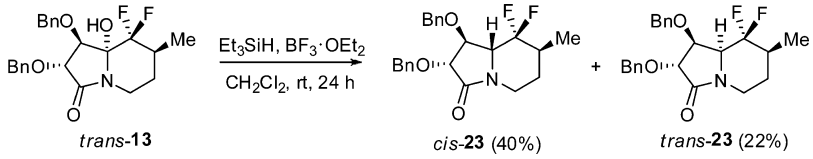
Pathway A



Pathway B



Scheme 11. Reductive Cleavage of the Hydroxyl Group of *trans*-13



Scheme 12. Preparation of 1-Alkyl *gem*-Difluoromethylenated Dihydroxyindolizidines

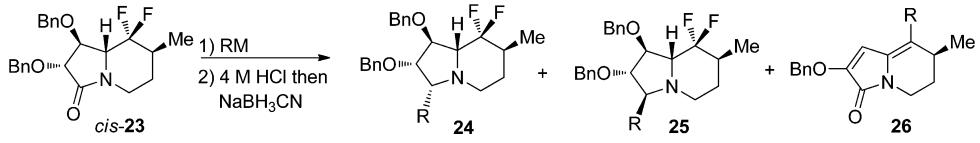


Table 3. Results Obtained for the Preparation of 1-Alkyl *gem*-Difluoromethylenated Dihydroxyindolizidines

		products (% yield)[a]			
entry	RM	R	**24**	**25**	**26**
1	EtMgCl	Et	**24a** (50)	**25a** (22)	**26a** (–)
2	*n*-BuMgCl	*n*-Bu	**24b** (43)	**25b** (16)	**26b** (14)
3	*i*PrMgCl	*i*Pr	**24c** (–)	**25c** (–)	**26c** (48)

[a]Isolated yields.

Finally, the conversions of dibenzyl protected compounds **21a–c** and **24a,b** to the corresponding dihydroxy derivatives **27a–c** and **28a,b** were straightforward and successfully performed by treatment with $H_2/PdCl_2$ in methanol at room temperature. The results are summarized in Scheme 13. The relative stereochemistry of compound **28b** was confirmed by X-ray crystallography (see the Supporting Information).

CONCLUSION

In conclusion, we have demonstrated the synthetic utilities of $PhSCF_2SiMe_3$ as a useful *gem*-difluoromethylene building block for an asymmetric synthesis of *gem*-difluoromethylenated dihydroxypyrrolizidine and indolizidine derivatives. The present work started from readily available chiral starting imides and involved sequential stereoselective fluoride-catalyzed addition of $PhSCF_2SiMe_3$ to chiral imide, intramolecular radical cyclization, reduction of the hydroxy functionality and organometallic addition followed by hydrogenolysis. The method provides a

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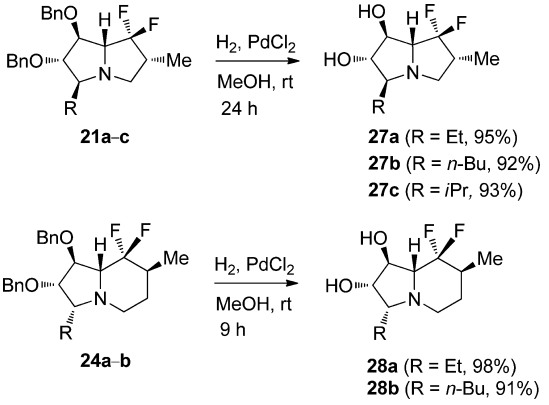
Scheme 13. Preparation of *gem*-Difluoromethylenated Pyrrolizidines 27 and Indolizidines 28



general access to chiral *gem*-difluoromethylenated dihydroxypyrrolizidines and indolizidines and may be applied for synthesis of analogues of some pyrrolizidine and indolizidine natural products.

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR spectra were recorded on 300 and 500 MHz spectrometers and are reported in ppm. NMR data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets; coupling constant(s) in Hz; integration; assignment. Proton decoupled ^{13}C NMR spectra were recorded on 75 and 125 MHz spectrometers and are reported in ppm. ^{19}F NMR spectra were recorded on a 470 MHz spectrometer and are reported in ppm.

Reactions were monitored by thin layer chromatography and visualized by UV and solution of $KMnO_4$. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene and *N*,*N*-dimethylformamide (DMF) were distilled over calcium hydride and were stored over activated molecular sieves (4 Å). All glass wares and syringes were oven-dried and kept in a desiccator before use. Purification of reaction products were carried out by preparative TLC plates, column chromatography or flash column chromatography.

(3*R*,4*R*)-1-Allyl-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidine-2,5-dione (2).[7a−c] A mixture of L-tartaric acid (4.51 g, 30 mmol) and allylamine (2.3 mL, 30.7 mmol) in xylene (30 mL) was heated at reflux by using a Dean−Stark apparatus for 15 h. The resulting solution was cooled to room temperature and concentrated in vacuo. The obtained solid material was coevaporated with ethanol to remove traces of xylene. The suspension was cooled to room temperature, and the resulting precipitates were filtered and washed with cold CH_2Cl_2 to give a pale yellow crystal of (3*R*,4*R*)-1-allyl-3,4-dihydroxypyrrolidine-2,5-dione (2.57 g, 50% yield): mp 154−155 °C; $[\alpha]^{26}_D$ +134.6° (*c* 1, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 5.81−5.74 (m, 1H), 5.63−5.52 (br s, 2H), 5.15−5.04 (m, 2H), 4.49 (s, 2H), 4.02 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.6 (2 × CO), 132.3 (CH), 117.5 (CH_2), 75.9 (2 × CH), 40.9 (CH_2); IR (KBr) ν_{max} 3387*br*, 1707*s*, 1333*s*, 1089*s*, 993*m* cm^{-1}; MS *m*/*z* (%) relative intensity 172 (M^+ + 1, 58), 171 (M^+, 6), 153 (18), 142 (25), 128 (10), 125 (41), 114 (20), 96 (39), 83 (12), 69 (45), 58 (100); HRMS (ESI-TOF) calcd for $C_7H_{10}NO_4$ [M + H]$^+$ 172.0610, found 172.0642. A mixture of (3*R*,4*R*)-1-allyl-3,4-dihydroxypyrrolidine-2,5-dione (1.30 g, 7.6 mmol), TBSCl (2.98 g, 19.8 mmol) and imidazole (1.55 g, 22.8 mmol) in dry DMF (15 mL) was allowed to stir at room temperature for 1 h, quenched with ice water, and extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was washed successively with water (25 mL), brine (25 mL), and dried over anhydrous Na_2SO_4. After solvent removal, a crude product was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to give a colorless oil of **2** (2.99 g, 99% yield): $[\alpha]^{26}_D$ +102.2° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 6.1, 10.1, 16.7 Hz, 1H), 5.29−5.18 (m, 2H), 4.50 (s, 2H), 4.14−4.06 (m, 2H), 0.96 (s, 18H), 0.24 (s, 6H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9 (2 × CO), 130.3 (CH), 119.0 (CH_2), 76.9 (2 × CH), 40.8 (CH_2), 25.6 (6 × CH_3), 18.2 (2 × C), −4.5 (2 × CH_3), −5.0 (2 × CH_3); IR (neat) ν_{max} 1727*s*, 1371*m*, 1254*s*, 1112*s*, 838*s* cm^{-1}; MS *m*/*z* (%) relative intensity 399 (M^+, 2), 342 (100), 314 (58), 231 (13), 155 (55), 149 (16), 133 (14), 111 (5), 73 (37); HRMS (ESI-TOF) calcd for $C_{19}H_{38}NO_4Si_2$ [M + H]$^+$ 400.2339, found 400.2322.

(3*R*,4*R*)-1-(But-3-enyl)-3,4-bis(*tert*-butyldimethylsilyloxy)-pyrrolidine-2,5-dione (3). The reaction of L-tartaric acid (4.51 g, 30 mmol) with *p*-methoxybenzylamine (3.9 mL, 30.6 mmol) in xylene (30 mL) gave a white solid of (3*R*,4*R*)-3,4-dihydroxy-1-(4-methoxybenzyl) pyrrolidine-2,5-dione[7a,b] (7.02 g, 93% yield): mp 193−194 °C; $[\alpha]^{26}_D$ +89.0° (*c* 1, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.43−5.41 (br s, 2H), 4.57 (s, 2H), 4.48 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 174.6 (2 × CO), 160.2 (C), 130.5 (2 × CH), 129.2 (C), 114.6 (2 × CH), 76.0 (2 × CH), 55.5 (OCH_3) 41.9 (CH_2); IR (KBr) ν_{max} 3285*br*, 1710*s*, 1615*m*, 1513*s*, 1352*s*, 813*w* cm^{-1}; MS *m*/*z* (%) relative intensity 251 (M^+, 2), 136 (100), 121 (83), 109 (18), 91 (23), 77 (20), 65 (5). The reaction of (3*R*,4*R*)-3,4-dihydroxy-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (5.05 g, 20.1 mmol) with TBSCl (7.88 g, 52.3 mmol) and imidazole (4.11 g, 60.4 mmol) in dry DMF (40 mL) gave a colorless oil of (3*R*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione[7d,e] (9.52 g, 99% yield) after column chromatography (SiO_2, 10% EtOAc in hexanes): $[\alpha]^{26}_D$ +102.9° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 4.45 (s, 2H), 3.78 (s, 3H), 0.93 (s, 18H), 0.21 (s, 6H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (2 × CO), 159.3 (C), 130.5 (2 × CH), 127.6 (C), 114.0 (2 × CH), 76.9 (2 × CH), 55.2 (OCH_3), 41.8 (CH_2), 25.6 (6 × CH_3), 18.2 (2 × C), −4.5 (2 × CH_3), −5.0 (2 × CH_3); IR (neat) ν_{max} 1724*s*, 1612*m*, 1514*s*, 1250*s*, 1135*s*, 838*s* cm^{-1}; MS *m*/*z* (%) relative intensity 479 (M^+, trace), 421 (6), 121 (100), 91 (9), 77 (7); HRMS (ESI-TOF) calcd for $C_{24}H_{42}NO_5Si_2$ [M + H]$^+$ 480.2602, found 480.2607. A solution of (3*R*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyl) pyrrolidine-2,5-dione (2.40 g, 5 mmol) in CH_3CN (20 mL) cooled at 0 °C was treated with a solution of ceric ammonium nitrate (10.96 g, 20 mmol) in water (30 mL) over 20 min. The mixture was stirred at 0 °C for 5 h, diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. After solvent removal, a crude product was purified by gradient column chromatography (SiO_2, 3−5% EtOAc in hexanes) to give a colorless oil of (3*R*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidine-2,5-dione[7d,e] (0.94 g, 52% yield): $[\alpha]^{26}_D$ +196.1° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63−8.61 (br s, 1H), 4.54 (s, 2H), 0.96 (s, 18H), 0.23 (s, 6H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (2 × CO), 77.5 (2 × CH), 25.6 (6 × CH_3), 18.2 (2 × C), −4.5 (2 × CH_3), −5.0 (2 × CH_3); IR (neat) ν_{max} 3263*br*, 2930*s*, 1732*s*, 1135*s*, 839*s* cm^{-1}; MS *m*/*z* (%) relative intensity 359 (M^+, trace), 344 (21), 274 (100), 147 (6), 117 (8), 73 (36). A mixture of (3*R*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidine-2,5-dione (0.32 g, 0.9 mmol), 4-bromobut-1-ene (0.1 mL, 1 mmol) and anhydrous potassium carbonate (0.15 g, 1.1 mmol) in acetone (3 mL) was heated at reflux for 6 h. After cooling to 20 °C, the mixture was filtered and the solvent was evaporated to give a yellow oil, which was purified by column chromatography (SiO_2, 3% EtOAc in hexanes) to provide a colorless oil of **3** (0.33 g, 89% yield): $[\alpha]^{26}_D$ +503° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 7.4, 10.2, 17.0 Hz, 1H), 5.09−5.04 (m, 2H), 4.45 (s, 2H), 3.61−3.49 (m, 2H), 2.39−2.33 (m, 2H), 0.95 (s, 18H), 0.23 (s, 6H), 0.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (2 × CO), 134.0 (CH), 117.6 (CH_2), 76.8 (2 × CH), 37.7 (CH_2), 31.8 (CH_2), 25.6 (6 × CH_3), 18.2 (2 × C), −4.5 (2 × CH_3), −5.1 (2 × CH_3); IR (neat) ν_{max} 1727*s*, 1361*m*, 1109*s* cm^{-1}; MS *m*/*z* (%) relative intensity 414 (M^+ + 1, 4), 398 (28), 356 (100), 340 (15), 328 (75), 231 (41), 129 (11), 73 (52); HRMS (ESI-TOF) calcd for $C_{20}H_{40}NO_4Si_2$ [M + H]$^+$ 414.2496, found 414.2471.

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(3*R*,4*R*)-1-Allyl-3,4-bis(benzyloxy)pyrrolidine-2,5-dione (4). Ethanol (35.2 mL, 0.6 mol) and DOWEX 50 WX8 ($H^{\oplus}$-form (30 g) were added to a solution of L-tartaric acid (15.1 g, 0.1 mol) in benzene (63 mL). The reaction mixture was heated at reflux by using a Dean−Stark apparatus to remove water. After stirring for 24 h, the reaction mixture was allowed to cool to room temperature, filtered and evaporated in vacuo to give a colorless oil of (2*R*,3*R*)-diethyl 2,3-dihydroxysuccinate[7f] (19.76 g, 95% yield) after distillation under reduced pressure (0.4 Torr, bp 110 °C): $[\alpha]^{25}_{D}$ +7.4° (*c* 1.6, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (s, 2H), 4.29 (dq, *J* = 1.8, 7.2 Hz, 4H), 1.31 (dd, *J* = 7.2, 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (2 × CO), 72.1 (2 × CH), 62.2 (2 × CH_2), 14.0 (2 × CH_3); IR (neat) ν_{max} 3445*s*, 1732*s*, 1280*m*, 1131*m*, 1093*m*, 1019*w* cm^{-1}; MS *m*/*z* (%) relative intensity 207 (M^+ + 1, 5), 206 (M^+, 5), 201(25), 178 (100), 167 (39), 149 (85), 99 (23), 97 (26); HRMS (ESI-TOF) calcd for $C_8H_{14}O_6Na$ [M + Na]$^+$ 229.0688, found 229.0705. A suspension of NaH (60% in mineral oil, 0.8 g, 20 mmol) in dry DMF (40 mL) was added dropwise to a solution of (2*R*,3*R*)-diethyl 2,3-dihydroxysuccinate (2.06 g, 10 mmol) in dry DMF (30 mL) at −20 °C. The reaction mixture was allowed to stir for 30 min and was added BnBr (3.6 mL, 30.3 mmol) in DMF (10 mL). After stirring at this temperature for 40 min, the mixture was allowed to warm to 0 °C and stir for 1 h. The reaction mixture was cautiously quenched by adding water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5% EtOAC in hexanes) to give (2*R*,3*R*)-diethyl 2,3-bis(benzyloxy)succinate[7g,h] (3.28 g, 85% yield) as a colorless liquid: $[\alpha]^{25}_{D}$ +122.9° (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 10H), 4.91 (d, *J* = 12.0 Hz, 2H), 4.49 (d, *J* = 12.0 Hz, 2H), 4.43 (s, 2H), 4.23 (dq, *J* = 7.3, 10.7 Hz, 2H), 4.10 (dq, *J* = 7.3, 10.7 Hz, 2H), 1.21 (dd, *J* = 7.2, 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (2 × CO), 136.9 (2 × C), 128.2 (8 × CH), 127.8 (2 × CH), 78.4 (2 × CH), 73.1 (2 × CH_2), 61.2 (2 × CH_2), 14.0 (2 × CH_3); IR (neat) ν_{max} 1755*s*, 1623*m*, 1455*m*, 1271*m*, 1193*s*, 1152*s*, 1105*s*, 740*m*, 699*s* cm^{-1}; MS *m*/*z* (%) relative intensity 386 (M^+, trace), 278 (27), 250 (30), 207 (25), 205 (38), 197 (38), 189 (38), 105 (16), 91 (100), 65 (4); HRMS (ESI-TOF) calcd for $C_{22}H_{26}O_6Na$ [M + Na]$^+$ 409.1627, found 409.1605. A mixture of (2*R*,3*R*)-diethyl 2,3-bis(benzyloxy)succinate (3.86 g, 10 mmol) and LiOH·H_2O (1.68 g, 40 mmol) in a mixture of EtOH−H_2O (3:1, 20 mL) was stirred at 0 °C for 24 h. After removal of ethanol under reduced pressure, the residue was acidified with HCl to reach pH 2, and the resultant mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give (2*R*,3*R*)-2,3-bis(benzyloxy)succinic acid[7g,h] (3.29 g, 100% yield) as a colorless oil, which was used in the next step without further purification: $[\alpha]^{24}_{D}$ +29.8° (*c* 1.0, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 10H), 4.84 (d, *J* = 11.6 Hz, 2H), 4.56 (d, *J* = 11.6 Hz, 2H), 4.52 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0 (2 × CO), 135.8 (2 × C), 128.6 (5 × CH), 128.5 (5 × CH), 78.0 (2 × CH), 74.1 (2 × CH_2); IR (neat) ν_{max} 3472*s*, 3131*br*, 1715*s*, 1634*m*, 1463*s*, 1377*m*, 1219*m*, 950*m*, 892*s*, 821*m* cm^{-1}; MS *m*/*z* (%) relative intensity 330 (M^+, 1), 205 (43), 188 (21), 181 (20), 150 (12), 116 (5), 92 (9), 91 (100), 65 (24); HRMS (ESI-TOF) calcd for $C_{18}H_{18}O_6Na$ [M + Na]$^+$ 353.1001, found 353.1019. A mixture of (2*R*,3*R*)-2,3-bis(benzyloxy)succinic acid (4.95 g, 15 mmol) and acetyl chloride (15 mL) was heated at reflux for 4 h. After concentrating under reduced pressure, the residue was dissolved in CH_2Cl_2 (15 mL), to which was added a solution of *p*-methoxybenzylamine (2.4 mL, 18.4 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The resulting mixture was heated at reflux for 5 h and then concentrated in vacuo. The residue was dissolved in acetyl chloride (15 mL) and refluxed for 5 h. After concentration of the reaction mixture in vacuo, the residue was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to give (3*R*,4*R*)-3,4-bis(benzyloxy)-1-(4-methoxybenzyl)-pyrrolidine-2,5-dione[7g,h] (5.82 g, 90% yield) as a white crystal: mp 127−128 °C; $[\alpha]^{25}_{D}$ +200.3° (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.35 (m, 12H), 6.88−6.86 (m, 2H), 5.02 (d, *J* = 11.6 Hz, 2H), 4.78 (d, *J* = 11.6 Hz, 2H), 4.65 (d, *J* = 14.0 Hz, 1H), 4.61 (d, *J* = 14.0 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (2 × CO), 159.4 (C), 136.5 (2 × C), 130.4 (2 × CH), 128.5 (4 × CH), 128.2 (5 × CH), 127.2 (C), 114.0 (3 × CH), 78.8 (2 × CH), 73.4 (2 × CH_2), 55.2 (OCH_3), 41.7 (CH_2); IR (KBr) ν_{max} 1728*s*, 1717*s*, 1514*m*, 1385*w*, 1251*w*, 1106*m*, 750*w*, 700*w* cm^{-1}; MS *m*/*z* (%) relative intensity 432 (M^+ + 1, trace), 325 (3), 220 (12), 219 (86), 162 (16), 121 (100), 91 (12), 65 (1); HRMS (ESI-TOF) calcd for $C_{26}H_{25}NO_5Na$ [M + Na]$^+$ 454.1630, found 454.1644. A mixture of (3*R*,4*R*)-3,4-bis(benzyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (4.31 g, 10 mmol) and ceric ammonium nitrate (27.41 g, 50 mmol) in a mixture of MeCN−H_2O (9:1, 100 mL) was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h to give (3*R*,4*R*)-3,4-bis(benzyloxy)pyrrolidine-2,5-dione[7i] (2.64 g, 85% yield) as a white solid after column chromatography (SiO_2, 15% EtOAc in hexanes): mp 58 °C; $[\alpha]^{25}_{D}$ +144.8° (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49−8.47 (br s, 1H), 7.41−7.35 (m, 10H), 5.00 (d, *J* = 11.6 Hz, 2H), 4.77 (d, *J* = 11.6 Hz, 2H), 4.67 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (2 × CO), 136.4 (2 × C), 128.5 (4 × CH), 128.3 (2 × CH), 128.2 (4 × CH), 79.4 (2 × CH), 73.5 (2 × CH_2); IR (KBr) ν_{max} 3508*w*, 3243*br*, 1800*m*, 1732*s*, 1455*m*, 1322*s*, 1266*m*, 1176*m*, 1114*s*, 740*m*, 699*s* cm^{-1}; MS *m*/*z* (%) relative intensity 311 (M^+, 1), 144 (56), 107 (94), 99 (60), 92 (24), 91 (100), 77 (8), 65 (9); HRMS (ESI-TOF) calcd for $C_{18}H_{17}NO_4Na$ [M + Na]$^+$ 334.1055, found 334.1039. A mixture of (3*R*,4*R*)-3,4-bis(benzyloxy)-pyrrolidine-2,5-dione (1.55 g, 5 mmol), triphenylphosphine (1.31 g, 5 mmol) and allyl alcohol (0.3 mL, 4.5 mmol) in dry THF (20 mL) was treated with diisopropyl azodicarboxylate (1.1 mL, 5.6 mmol) at 0 °C. The resulting yellow solution was allowed to stir at room temperature for 16 h, and then it was quenched with a saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by gradient column chromatography (SiO_2, 2−5% EtOAc in hexanes) to give a white solid of **4** (1.29 g, 82% yield): mp 60−62 °C; $[\alpha]^{26}_{D}$ +139.7° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.36 (m, 10H), 5.82 (ddt, 6.0, 10.2, 17.1 Hz, 1H), 5.29 (dd, *J* = 1.1, 17.1 Hz, 1H), 5.25 (dd, *J* = 1.1, 10.2 Hz, 1H), 5.04 (d, *J* = 11.6 Hz, 2H), 4.81 (d, *J* = 11.6 Hz, 2H), 4.44 (s, 2H), 4.19−4.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (2 × CO), 136.5 (2 × C), 130.0 (CH), 128.5 (4 × CH), 128.2 (6 × CH), 119.0 (CH_2), 78.8 (2 × CH), 73.4 (2 × CH_2), 40.6 (CH_2); IR (KBr) ν_{max} 1715*s*, 1643*w*, 1350*m*, 1194*m*, 1139*w*, 1104*s*, 738*m*, 698*s* cm^{-1}; MS *m*/*z* (%) relative intensity 352 (M^+ + 1, trace), 140 (9), 139 (100), 111 (30), 107 (8), 96 (29), 91 (33), 77 (2), 65 (3); HRMS (ESI-TOF) calcd for $C_{21}H_{21}NO_4Na$ [M + Na]$^+$ 374.1368, found 374.1341.

(3*R*,4*R*)-3,4-Bis(benzyloxy)-1-(but-3-enyl)pyrrolidine-2,5-dione (5).[7i] The reaction of (3*R*,4*R*)-3,4-bis(benzyloxy)pyrrolidine-2,5-dione (3.11 g, 10 mmol) with triphenylphosphine (2.62 g, 10 mmol), 3-buten-1-ol (0.78 mL, 9 mmol) and diisopropyl azodicarboxylate (2.2 mL, 11.2 mmol) in dry THF (40 mL) gave **5** (2.83 g, 86% yield) as a colorless oil after column chromatography (SiO_2, 2−5% EtOAc in hexanes): $[\alpha]^{24}_{D}$ +129.7° (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.35 (m, 10H), 5.74 (ddt, *J* = 7.0, 10.2, 17.0 Hz, 1H), 5.12−5.04 (m, 2H), 5.02 (d, *J* = 11.6 Hz, 2H), 4.79 (d, *J* = 11.6 Hz, 2H), 4.40 (s, 2H), 3.68−3.57 (m, 2H), 2.44−2.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (2 × CO), 136.6 (2 × C), 133.9 (CH), 128.5 (5 × CH), 128.2 (5 × CH), 117.9 (CH_2), 78.7 (2 × CH), 73.4 (2 × CH_2), 37.7 (CH_2), 31.7 (CH_2); IR (neat) ν_{max} 1715*s*, 1644*w*, 1455*m*, 1398*m*, 1348*m*, 1100*s*, 921*m*, 739*s*, 699*s* cm^{-1}; MS *m*/*z* (%) relative intensity 365 (M^+, trace), 153 (86), 111 (15), 105 (28), 99 (29), 91 (100), 77 (11), 65 (21); HRMS (ESI-TOF) calcd for $C_{22}H_{23}NO_4Na$ [M + Na]$^+$ 388.1525, found 388.1520.

(3*R*,4*R*,5*R*)- and (3*R*,4*R*,5*S*)-1-Allyl-3,4-bis(*tert*-butyldimethylsilyloxy)-5-(difluoro(phenylthio)methyl)-5-hydroxypyrrolidin-2-one (*syn*-6 and *anti*-6). *General Procedure A.* A mixture of $PhSCF_2TMS$ (**1**) (3.71 g, 16 mmol) and **2** (3.20 g, 8 mmol) in dry DMF (25 mL) was treated with a solution of 10 mol % TBAT (0.86 g, 1.6 mmol) in dry DMF (15 mL) at 0 °C for 2 h. The reaction mixture

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was quenched with water (25 mL) and the resulting mixture was stirred at room temperature for 30 min and then extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was washed successively with brine (25 mL) and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by gradient column chromatography (SiO_2, 5−10% EtOAc in hexanes) to give a white solid of *syn*-**6** (3.22 g, 72% yield) and a pale yellow liquid of *anti*-**6** (0.35 g, 8% yield). *syn*-**6**: mp 122−123 °C; $[\alpha]^{26}_D$ +74.0° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64−7.59 (m, 2H), 7.49−7.44 (m, 1H), 7.43−7.38 (m, 2H), 5.89 (ddt, *J* = 5.9, 10.2, 17.1 Hz, 1H), 5.23 (dd, *J* = 1.3, 17.1 Hz, 1H), 5.14 (dd, *J* = 1.3, 10.2 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.25 (d, *J* = 6.8 Hz, 1H), 4.16 (dd, *J* = 5.9, 15.7 Hz, 1H), 3.84−3.81 (br s, 1H), 3.81 (dd, *J* = 5.9, 15.7 Hz, 1H), 0.99 (s, 9H), 0.97 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1 (CO), 136.8 (2 × CH), 133.6 (CH), 130.1 (CH), 129.1 (2 × CH), 128.3 (dd, *J* = 287.6, 287.6 Hz, CF_2), 125.3 (C), 117.3 (CH_2), 90.9 (t, *J* = 24.2 Hz, C), 82.9 (CH), 75.2 (CH), 43.0 (CH_2), 26.0 (3 × CH_3), 25.9 (3 × CH_3), 18.2 (C), 17.9 (C), −4.0 (CH_3), −4.1 (CH_3), −4.5 (CH_3), −4.6 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −79.76 (d, *J* = 216.2 Hz, 1F), −78.85 (d, *J* = 216.2 Hz, 1F); IR (KBr) ν_{max} 3375*br*, 2931*m*, 1697*s*, 1474*m*, 1397*m*, 1361*m*, 1253*m*, 1158*m*, 1057*m*, 981*m*, 842*s*, 750*m* cm^{-1}; MS *m*/*z* (%) relative intensity 559 (M^+, 2), 518 (43), 502 (100), 482 (17), 314 (43), 277 (14), 239 (12), 170 (13), 143 (17), 73 (55); HRMS (ESI-TOF) calcd for $C_{26}H_{43}F_2NO_4SSi_2Na$ $[M + Na]^+$ 582.2317, found 582.2314. *anti*-**6**: $[\alpha]^{24}_D$ −1.0° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.4 Hz, 2H), 7.51−7.45 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 5.90 (ddt, *J* = 5.9, 10.3, 17.2 Hz, 1H), 5.25 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.16 (dd, *J* = 1.4, 10.3 Hz, 1H), 4.57 (s, 1H), 4.51 (d, *J* = 2.6 Hz, 1H), 4.19 (dd, *J* = 5.9, 15.8 Hz, 1H), 4.13 (d, *J* = 2.6 Hz, 1H), 3.99 (dd, *J* = 5.9, 15.8 Hz, 1H), 0.97 (s, 9H), 0.93 (s, 9H), 0.27 (s, 6H), 0.23 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (CO), 136.8 (2 × CH), 133.1 (CH), 130.1 (CH), 129.1 (2 × CH), 128.7 (dd, *J* = 287.7, 287.7 Hz, CF_2), 125.1 (C), 117.0 (CH_2), 89.4 (t, *J* = 26.0 Hz, C), 76.7 (CH), 75.9 (CH), 43.8 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C) 18.0 (C), −3.8 (CH_3), −4.2 (CH_3), −5.0 (CH_3), −5.1 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −83.90 (d, *J* = 211.0 Hz, 1F), −81.87 (d, *J* = 211.0 Hz, 1F); IR (neat) ν_{max} 3372*br*, 2931*s*, 1695*s*, 1473*m*, 1391*m*, 1361*m*, 1252*s*, 1150*s*, 1098*s*, 981*w*, 842*s*, 749*m*, 691*m* cm^{-1}; MS *m*/*z* (%) relative intensity 560 (M^+ + 1, 0.8), 516 (100), 502 (98), 482 (23), 155 (19), 151 (28), 73 (83); HRMS (ESI-TOF) calcd for $C_{26}H_{43}F_2NO_4SSi_2Na$ $[M + Na]^+$ 582.2317, found 582.2312.

(3*R*,4*R*,5*R*)- and (3*R*,4*R*,5*S*)-1-(But-3-enyl)-3,4-bis(*tert*-butyldimethylsilyloxy)-5-(difluoro(phenylthio)methyl)-5-hydroxypyrrolidin-2-one (*syn*-7 and *anti*-7). According to the *general procedure A*, the reaction of **1** (2.32 g, 10 mmol) with **3** (2.07 g, 5 mmol) in the presence of 10 mol % TBAT (0.54 g, 1 mmol) followed by gradient column chromatography (SiO_2, 2−10% EtOAc in hexanes) gave a white solid of *syn*-**7** (2.18 g, 76% yield) and a pale yellow liquid of *anti*-**7** (0.12 g, 4% yield). *syn*-**7**: mp 132−134 °C; $[\alpha]^{26}_D$ +54.3° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.59 (m, 2H), 7.50−7.44 (m, 1H), 7.43−7.38 (m, 2H), 5.79 (ddt, *J* = 6.9, 10.2, 17.2 Hz, 1H), 5.13−5.03 (m, 2H), 4.43 (d, *J* = 6.3 Hz, 1H), 4.17 (d, *J* = 6.3 Hz, 1H), 3.68 (s, 1H), 3.54 (ddd, *J* = 6.2, 9.5, 14.7 Hz, 1H), 3.27 (ddd, *J* = 6.2, 9.5, 14.7 Hz, 1H), 2.53−2.44 (m, 1H), 2.43−2.34 (m, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (CO), 136.7 (2 × CH), 135.6 (CH), 130.1 (CH), 129.1 (2 × CH), 128.3 (t, *J* = 288.5 Hz, CF_2), 125.4 (C), 116.9 (CH_2), 90.9 (t, *J* = 24.9 Hz, C), 82.7 (CH), 75.2 (CH), 40.2 (CH_2), 32.5 (CH_2), 25.9 (3 × CH_3), 25.8 (3 × CH_3), 18.2 (C), 17.9 (C), −4.1 (CH_3), −4.2 (CH_3), −4.5 (2 × CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.14 (d, *J* = 215.5 Hz, 1F), −79.48 (d, *J* = 215.5 Hz, 1F); IR (KBr) ν_{max} 3370*br*, 1686*s*, 1642*w*, 1473*m*, 1390*w*, 1361*w*, 1251*m*, 1150*s*, 1105*s*, 842*s*, 748*w* cm^{-1}; MS *m*/*z* (%) relative intensity 573 (M^+, 1), 517 (37), 516 (100), 496 (15), 277 (9), 255 (13), 185 (11), 151 (11), 147 (10), 73 (38); HRMS (ESI-TOF) calcd for $C_{27}H_{45}F_2NO_4SSi_2Na$ $[M + Na]^+$ 596.2474, found 596.2480. *anti*-**7**: $[\alpha]^{24}_D$ +2.8° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.62 (m, 2H), 7.50−7.45 (m, 1H), 7.43−7.40 (m, 2H), 5.80 (ddt, *J* = 6.4, 10.2, 17.2 Hz, 1H), 5.12−5.08 (m, 1H), 5.05−5.03 (m, 1H), 4.52 (s, 1H), 4.47 (d, *J* = 2.8 Hz, 1H), 4.11 (d, *J* = 2.8 Hz, 1H), 3.66 (ddd, *J* = 6.4, 9.3, 15.0 Hz, 1H), 3.39 (ddd, *J* = 6.4, 9.3, 15.0 Hz, 1H), 2.56−2.49 (m, 1H), 2.45−2.38 (m, 1H), 0.97 (s, 9H), 0.93 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (CO), 136.8 (2 × CH), 135.4 (CH), 130.1 (CH), 129.1 (2 × CH), 128.8 (t, *J* = 287.8 Hz, CF_2), 125.1 (C), 116.6 (CH_2), 89.4 (t, *J* = 25.9 Hz, C), 76.7 (CH), 75.9 (CH), 41.0 (CH_2), 32.4 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C), 17.9 (C), −3.8 (CH_3), −4.2 (CH_3), −4.9 (CH_3), −5.2 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −84.00 (d, *J* = 211.0 Hz, 1F), −81.89 (d, *J* = 211.0 Hz, 1F); IR (neat) ν_{max} 3296*br*, 2960*m*, 1686*s*, 1642*w*, 1472*m*, 1391*m*, 1362*m*, 1250*m*, 1150*s*, 910*m*, 842*s* cm^{-1}; MS *m*/*z* (%) relative intensity 574 (M^+ + 1, 3), 516 (100), 496 (24), 386 (8), 310 (10), 277 (11), 255 (15), 184 (12), 155 (12), 151 (15), 77 (14), 73 (63); HRMS (ESI-TOF) calcd for $C_{27}H_{45}F_2NO_4SSi_2Na$ $[M + Na]^+$ 596.2474, found 596.2450.

(3*R*,4*R*,5*R*)- and (3*R*,4*R*,5*S*)-1-Allyl-3,4-bis(benzyloxy)-5-(difluoro(phenylthio)methyl)-5-hydroxypyrrolidin-2-one (*syn*-8 and *anti*-8). According to the *general procedure A*, the reaction of **1** (1.39 g, 6 mmol) with **4** (1.06 g, 3 mmol) in dry THF (10 mL) in the presence of 10 mol % TBAT (0.32 g, 0.6 mmol) in dry THF (5 mL) at −78 °C for 8 h followed by gradient chromatography (SiO_2, 5−10% EtOAc in hexanes) gave *syn*-**8** (0.73 g, 48% yield) and *anti*-**8** (0.47 g, 31% yield) as pale yellow oils. *syn*-**8**: $[\alpha]^{25}_D$ +90.1° (*c* 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.42−7.33 (m, 13H), 5.85 (ddt, *J* = 6.2, 10.2, 17.0, 1H), 5.24 (dd, *J* = 1.4, 17.0 Hz, 1H), 5.14 (dd, *J* = 1.4, 10.2 Hz, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.71−4.65 (br s, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.27 (dd, *J* = 1.8, 7.8 Hz, 1H), 4.15−4.10 (m, 1H), 3.85 (dd, *J* = 6.6, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (CO), 137.4 (C), 137.2 (C), 136.8 (2 × CH), 133.1 (CH), 130.1 (CH), 129.0 (2 × CH), 128.4 (4 × CH), 128.3 (dd, *J* = 288.7, 288.7 Hz, CF_2), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.8 (CH), 125.3 (C), 117.7 (CH_2), 90.5 (dd, *J* = 23.0, 27.9 Hz, C), 87.5 (CH), 78.7 (d, *J* = 3.0 Hz, CH), 74.2 (CH_2), 73.3 (CH_2), 42.9 (CH_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −81.13. (d, *J* = 217.1 Hz, 1F), −80.24 (d, *J* = 217.1 Hz, 1F); IR (neat) ν_{max} 3307*br*, 1694*s*, 1455*m*, 1442*m*, 1330*w*, 1138*m*, 1094*m*, 750*m*, 699*m* cm^{-1}; MS *m*/*z* (%) relative intensity 512 (M^+ + 1, 1), 314 (14), 296 (24), 294 (14), 224 (17), 217 (32), 216 (100), 181 (28), 172 (29), 161 (52), 91 (91), 65 (5); HRMS (ESI-TOF) calcd for $C_{28}H_{27}F_2NO_4SNa$ $[M + Na]^+$ 534.1527, found 534.1531. *anti*-**8**: $[\alpha]^{25}_D$ +68.8° (*c* 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.51−7.47 (m, 1H), 7.46−7.36 (m, 10H), 7.33−7.30 (m, 2H), 5.93 (ddt, *J* = 6.7, 10.3, 17.1, 1H), 5.30 (dd, *J* = 1.3, 17.1 Hz, 1H), 5.20 (dd, *J* = 1.3, 10.3 Hz, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 4.7 Hz, 1H), 4.41 (s, 1H), 4.27 (dd, *J* = 6.1, 15.6 Hz, 1H), 4.18 (d, *J* = 4.7 Hz, 1H), 4.02 (dd, *J* = 6.1, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (CO), 137.1 (C), 136.8 (2 × CH), 136.0 (C), 133.0 (CH), 130.2 (CH), 129.1 (2 × CH), 128.6 (3 × CH), 128.5 (6 × CH), 128.2 (dd, *J* = 254.6, 254.6 Hz, CF_2), 128.1 (CH), 124.7 (C), 117.6 (CH_2), 88.6 (t, *J* = 25.8 Hz, C), 78.3 (CH), 78.0 (CH), 73.6 (CH_2), 72.6 (CH_2), 44.0 (CH_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −84.78 (d, *J* = 210.4 Hz, 1F), −82.10 (d, *J* = 210.4 Hz, 1F); IR (neat) ν_{max} 3390*br*, 1732*s*, 1606*w*, 1455*s*, 1359*m*, 1328*m*, 1206*m*, 1155*m*, 924*m*, 741*m*, 699*s* cm^{-1}; MS *m*/*z* (%) relative intensity 511 (M^+, trace), 314 (3), 299 (11), 246 (4), 217 (32), 216 (100), 181 (12), 131 (10), 91 (33), 65 (2); HRMS (ESI-TOF) calcd for $C_{28}H_{27}F_2NO_4SNa$ $[M + Na]^+$ 534.1527, found 534.1526.

(3*R*,4*R*,5*R*)- and (3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-1-(but-3-enyl)-5-(difluoro(phenylthio)methyl)-5-hydroxypyrrolidin-2-one (*syn*-9 and *anti*-9). According to the *general procedure A*, the reaction of **1** (1.86 g, 8 mmol) with **5** (1.47 g, 4 mmol) in dry THF (15 mL) in the presence of 10 mol % TBAT (0.44 g, 0.8 mmol) in dry THF (5 mL) at −78 °C for 10 h, followed by gradient chromatography (SiO_2, 5−10% EtOAc in hexanes) gave a pale yellow oil of *syn*-**9** (0.84 g, 40% yield) and a pale yellow solid of *anti*-**9** (0.65 g, 31% yield). *syn*-**9**: $[\alpha]^{24}_D$ +107.7° (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$)

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δ 7.69−7.58 (m, 2H), 7.48−7.31 (m, 13H), 5.78 (ddt, *J* = 7.0, 10.3, 17.2 Hz, 1H), 5.12 (d, *J* = 11.3 Hz, 1H), 5.09 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.06 (dd, *J* = 1.3, 10.3 Hz, 1H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 7.9 Hz, 1H), 4.37−4.26 (br s, 1H), 4.19 (dd, *J* = 2.1, 7.9 Hz, 1H), 3.53 (ddd, *J* = 5.0, 9.3, 14.1 Hz, 1H), 3.30−3.24 (m, 1H), 2.51−2.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (CO), 137.5 (C), 137.1 (C), 136.8 (2 × CH), 135.6 (CH), 130.1 (CH), 129.0 (2 × CH), 128.5 (t, *J* = 288.8 Hz, CF_2), 128.4 (4 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.8 (CH), 125.4 (d, *J* = 3.4 Hz, C), 117.1 (CH_2), 90.2 (dd, *J* = 22.7, 28.4 Hz, C), 87.6 (CH), 78.7 (d, *J* = 3.1 Hz, CH), 74.2 (CH_2), 73.3 (CH_2), 40.2 (CH_2), 32.3 (CH_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −81.57 (d, *J* = 216.7 Hz, 1F), −80.43 (d, *J* = 216.7 Hz, 1F); IR (neat) ν_{max} 3272*br*, 1694*s*, 1683*s*, 1456*s*, 1360*m*, 1148*m*, 1097*m*, 1069*s*, 749*m*, 693*s* cm^{-1}; MS *m*/*z* (%) relative intensity 525 (M^+, trace), 290 (6), 230 (21), 181 (11), 91 (100), 77 (6), 65 (14); HRMS (ESI-TOF) calcd for $C_{29}H_{29}F_2NO_4SNa$ $[M + Na]^+$ 548.1683, found 548.1697. *anti*-**9**: mp 57−58 °C; $[\alpha]^{24}_D$ +60.9° (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.52−7.48 (m, 1H), 7.46−7.35 (m, 10H), 7.33−7.31 (m, 2H), 5.82 (ddt, *J* = 6.9, 10.2, 17.1 Hz, 1H), 5.15−5.05 (m, 2H), 5.10 (d, *J* = 11.8 Hz, 1H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 4.9 Hz, 1H), 4.39 (s, 1H), 4.17 (d, *J* = 4.9 Hz, 1H), 3.76 (ddd, *J* = 5.7, 9.5, 14.2 Hz, 1H), 3.42 (ddd, *J* = 5.7, 9.5, 14.2 Hz, 1H), 2.59−2.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (CO), 137.2 (C), 136.7 (3 × CH), 136.0 (C), 135.2 (CH), 130.2 (CH), 129.2 (3 × CH), 128.7 (t, *J* = 287.9 Hz, CF_2), 128.6 (3 × CH), 128.5 (4 × CH), 128.1 (CH), 124.7 (C), 116.7 (CH_2), 88.7 (t, *J* = 26.0 Hz, C), 78.3 (CH), 78.0 (CH), 73.6 (CH_2), 72.6 (CH_2), 40.9 (CH_2), 32.6 (CH_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −84.91 (d, *J* = 209.9 Hz, 1F), −82.08 (d, *J* = 209.9 Hz, 1F); IR (KBr) ν_{max} 3441*br*, 1715*s*, 1641*w*, 1455*m*, 1410*m*, 1353*m*, 1000*s*, 1018*m*, 749*s*, 698*s* cm^{-1}; MS *m*/*z* (%) relative intensity 525 (M^+, trace), 400 (28), 385 (11), 302 (31), 181 (45), 91 (100), 77 (6), 65 (12); HRMS(ESI-TOF) calcd for $C_{29}H_{29}F_2NO_4SNa$ $[M + Na]^+$ 548.1683, found 548.1697.

(1*R*,2*R*,6*R*,7*aR*)- and (1*R*,2*R*,6*S*,7*aR*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7,7-difluoro-7*a*-hydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (*cis*-10 and *trans*-10). *General Procedure B.* An argon gas was bubbled through a solution of *syn*-**6** (2.24 g, 4 mmol) in dry toluene (25 mL) for 30 min, and then a mixture of Bu_3SnH (1.9 mL, 7.1 mmol) and AIBN (0.10 g, 0.6 mmol) in dry toluene (15 mL) was added dropwise at reflux over a 1 h period. After the completion of the reaction, volatiles were evaporated and the tin byproduct were removed by column chromatography (SiO_2, hexanes (300 mL) then EtOAc) to give a crude product, which was then purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes) to afford *cis*-**10** (0.67 g, 37% yield) as a white solid and *trans*-**10** (0.27 g, 15% yield) as a pale yellow solid. *cis*-**10**: mp 211−212 °C; $[\alpha]^{25}_D$ +2.8° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, *J* = 2.1 Hz, 1H), 4.03 (d, *J* = 2.1 Hz, 1H), 3.97 (dd, *J* = 8.1, 11.5 Hz, 1H), 3.96 (s, 1H), 2.95 (t, *J* = 11.5 Hz, 1H), 2.54−2.45 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (CO), 125.0 (t, *J* = 258.4 Hz, CF_2), 95.1 (dd, *J* = 32.1, 20.9 Hz, C), 79.1 (CH), 78.9 (CH), 45.7 (d, *J* = 5.9 Hz, CH_2), 41.5 (t, *J* = 23.4 Hz, CH), 25.6 (3 × CH_3), 25.5 (3 × CH_3), 17.9 (C), 17.8 (C), 9.5 (d, *J* = 7.1 Hz, CH_3), −4.7 (CH_3), −4.9 (CH_3), −5.1 (d, *J* = 1.8, CH_3), −5.2 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −121.59 (dd, *J* = 19.3, 241.6 Hz, 1F), −119.13 (dd, *J* = 12.7, 241.6 Hz, 1F); IR (KBr) ν_{max} 3354*br*, 2930*s*, 1694*s*, 1464*m*, 1261*s*, 1123*s*, 1059*s*, 844*s* cm^{-1}; MS *m*/*z* (%) relative intensity 452 (M^+ + 1, 1), 451 (M^+, trace), 394 (100), 346 (21), 234 (83), 212 (14), 206 (25), 73 (29); HRMS (ESI-TOF) calcd for $C_{20}H_{39}F_2NO_4Si_2Na$ $[M + Na]^+$ 474.2283, found 474.2253. *trans*-**10**: mp 176−177 °C; $[\alpha]^{24}_D$ +97.4° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, *J* = 4.6 Hz, 1H), 4.14 (dd, *J* = 1.9, 4.6 Hz, 1H), 3.56 (dd, *J* = 9.2, 11.5 Hz, 1H), 3.41−3.33 (br s, 1H), 3.24 (dd, *J* = 8.5, 11.5 Hz, 1H), 3.04−2.93 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 18H), 0.22 (s, 3H), 0.18 (s, 6H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (CO), 123.6 (dd, *J* = 252.4, 266.6 Hz, CF_2), 91.8 (dd, *J* = 24.8, 32.2 Hz, C), 80.9 (CH), 79.7 (CH), 46.1 (d, *J* = 7.3 Hz, CH_2), 38.0 (t, *J* = 22.9 Hz, CH), 25.7 (3 × CH_3), 25.6 (3 × CH_3), 18.1 (C), 17.9 (C), 9.5 (d, *J* = 8.9 Hz, CH_3), −4.2 (CH_3), −4.7 (CH_3), −5.0 (2 × CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −129.38 (dd, *J* = 23.0, 230.8 Hz, 1F), −125.89 (d, *J* = 230.8 Hz, 1F); IR (KBr) ν_{max} 3375*br*, 2930*m*, 1693*s*, 1473*m*, 1252*m*, 1110*s*, 838*s* cm^{-1}; MS *m*/*z* (%) relative intensity 451 (M^+, trace), 394 (100), 346 (31), 234 (37), 212 (26), 206 (14), 73 (19); HRMS (ESI-TOF) calcd for $C_{20}H_{39}F_2NO_4Si_2Na$ $[M + Na]^+$ 474.2283, found 474.2256.

(1*R*,2*R*,7*S*,8*aR*)- and (1*R*,2*R*,7*R*,8*aR*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-8,8-difluoro-8*a*-hydroxy-7-methylhexahydroindolizin-3(5*H*)-one (*trans*-11, *cis*-11). According to the *general procedure B*, radical cyclization of *syn*-**7** (3.44 g, 6 mmol) followed by the removal of tin byproduct and flash column chromatography (SiO_2, 10% EtOAc in hexanes) gave *trans*-**11** (0.95 g, 34% yield) and *cis*-**11** (0.33 g, 12% yield) as white solids. *trans*-**11**: mp 211−212 °C; $[\alpha]^{24}_D$ +28.5° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 2.7, 7.0 Hz, 1H), 4.19 (dd, *J* = 1.1, 7.0 Hz, 1H), 3.95 (dd, *J* = 5.1, 13.3 Hz, 1H), 3.00 (dt, *J* = 3.4, 13.3 Hz, 1H), 2.83 (s, 1H), 2.46−2.38 (m, 1H), 1.66−1.59 (m, 1H), 1.53 (dq, *J* = 5.1, 13.3 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.94 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (CO), 120.5 (dd, *J* = 247.5, 258.9 Hz, CF_2), 85.5 (dd, *J* = 26.4, 35.1 Hz, C), 84.2 (CH), 76.8 (d, *J* = 4.3 Hz, CH), 34.9 (CH_2), 33.9 (t, *J* = 22.3 Hz, CH), 30.2 (d, *J* = 6.3 Hz, CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C), 17.8 (C), 11.9 (t, *J* = 3.8 Hz, CH_3), −4.1 (CH_3), −4.3 (CH_3), −4.6 (CH_3), −4.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −130.04 (dd, *J* = 26.8, 251.3 Hz, 1F), −117.89 (d, *J* = 251.3 Hz, 1F); IR (KBr) ν_{max} 3411*br*, 2930*m*, 1686*s*, 1463*w*, 1361*w*, 1252*m*, 1137*m*, 1094*m*, 838*s* cm^{-1}; MS *m*/*z* (%) relative intensity 465 (M^+, trace), 408 (100), 360 (26), 248 (22), 226 (11), 198 (11), 151 (10), 73 (15); HRMS (ESI-TOF) calcd for $C_{21}H_{41}F_2NO_4Si_2Na$ $[M + Na]^+$ 488.2440, found 488.2455. *cis*-**11**: mp 248−249 °C; $[\alpha]^{25}_D$ +1.9° (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (dd, *J* = 2.7, 6.3 Hz, 1H), 4.11 (dd, *J* = 1.0, 6.3 Hz, 1H), 3.94−3.90 (m, 1H), 3.17 (dt, *J* = 3.7, 12.9 Hz, 1H), 2.82 (s, 1H), 2.42−2.35 (m, 1H), 2.05−1.97 (m, 1H), 1.54−1.51 (m, 1H), 1.29 (d, *J* = 7.4 Hz, 3H), 0.94 (s, 18H), 0.23 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (CO), 120.0 (dd, *J* = 244.4, 261.1 Hz, CF_2), 87.1 (dd, *J* = 26.4, 36.4 Hz, C), 84.3 (CH), 76.8 (d, *J* = 3.6 Hz, CH), 35.8 (t, *J* = 23.1 Hz, CH), 31.3 (CH_2), 28.2 (d, *J* = 5.6 Hz, CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C), 17.8 (C), 13.3 (dd, *J* = 3.9, 7.9 Hz, CH_3), −4.1 (CH_3), −4.3 (CH_3), −4.6 (CH_3), −4.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.14 (dd, *J* = 6.6, 256.2 Hz, 1F), −109.25 (dd, *J* = 14.1, 256.2 Hz, 1F); IR (KBr) ν_{max} 3387*br*, 2961*s*, 1709*s*, 1453*m*, 1388*m*, 1260*s*, 1156*s*, 1067*s*, 844*s* cm^{-1}; MS *m*/*z* (%) relative intensity 466 (M^+ + 1, 2), 448 (12), 408 (100), 360 (24), 248 (23), 200 (24), 73 (25); HRMS (ESI-TOF) calcd for $C_{21}H_{41}F_2NO_4Si_2Na$ $[M + Na]^+$ 488.2440, found 488.2424.

(1*R*,2*R*,6*R*,7*aR*)- and (1*R*,2*R*,6*S*,7*aR*)-1,2-Bis(benzyloxy)-7,7-difluoro-7*a*-hydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (*cis*-12 and *trans*-12). According to the *general procedure B*, radical cyclization of *syn*-**8** (2.05 g, 4 mmol) followed by the removal of tin byproduct and preparative thin-layer chromatography (SiO_2, 10% EtOAc in hexanes ×6) gave *cis*-**12** (0.63 g, 39% yield) as a colorless crystal and *trans*-**12** (0.21 g, 13% yield) as a colorless oil. *cis*-**12**: mp 145−146 °C; $[\alpha]^{23}_D$ +33.4° (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.31 (m, 10H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.19−4.16 (m, 2H), 4.10 (dd, *J* = 9.0, 11.9 Hz, 1H), 4.01 (s, 1H), 2.97 (dd, *J* = 6.3, 11.9 Hz, 1H), 2.66−2.50 (m, 1H), 1.28−1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (CO), 137.1 (C), 136.7 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.2 (3 × CH), 128.0 (CH), 127.9 (2 × CH), 125.1 (dd, *J* = 248.9, 269.8 Hz, CF_2), 92.1 (dd, *J* = 24.6, 34.7 Hz, C), 84.7 (CH), 81.6 (CH), 73.2 (CH_2), 73.0 (CH_2), 46.8 (CH_2), 40.5 (t, *J* = 23.7 Hz, CH), 13.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.59 (d, *J* = 236.9 Hz, 1F), −107.72 (dd, *J* = 23.0, 236.9 Hz, 1F); IR (KBr) ν_{max} 3262*br*, 1728*s*, 1702*m*, 1457*m*, 1338*m*, 1203*s*, 1095*s*, 1062*s*, 756*s*, 701*s* cm^{-1}; MS *m*/*z* (%) relative intensity 404 (M^+ + 1, trace), 191 (93), 171 (23), 151 (14), 136 (18), 111 (17), 91 (100), 77 (5), 65 (24); HRMS (ESI-TOF) calcd for $C_{22}H_{23}F_2NO_4Na$ $[M + Na]^+$ 426.1493, found 426.1495.

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trans-**12**: $[\alpha]^{23}_{D}$ +63.0° (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.29 (m, 10H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.29−4.23 (br s, 1H), 4.22 (s, 2H), 3.54 (t, *J* = 10.5 Hz, 1H), 3.28 (dd, *J* = 8.1, 10.5 Hz, 1H), 3.15−2.99 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (CO), 137.4 (C), 136.9 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 127.9 (3 × CH), 124.0 (dd, *J* = 250.0, 268.9 Hz, CF_2), 91.3 (dd, *J* = 25.2, 33.6 Hz, C), 85.0 (CH), 82.0 (CH), 73.3 (CH_2), 73.2 (CH_2), 47.0 (d, *J* = 7.4 Hz, CH_2), 37.5 (t, *J* = 22.9 Hz, CH), 9.6 (d, *J* = 9.4 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −129.70 (dd, *J* = 23.5, 229.4 Hz, 1F), −127.95 (dd, *J* = 7.1, 229.4 Hz, 1F); IR (neat) ν_{max} 3230*br*, 1708*s*, 1692*s*, 1455*m*, 1416*m*, 1234*s*, 1148*s*, 1026*m*, 1003*m*, 801*m*, 731*s*, 694*s* cm^{-1}; MS *m*/*z* (%) relative intensity 403 (M^+, trace), 191 (100), 174 (10), 171 (25), 151 (17), 136 (15), 111 (24), 91 (99), 77 (10), 65 (30); HRMS (ESI-TOF) calcd for $C_{22}H_{23}F_2NO_4Na$ $[M + Na]^+$ 426.1493, found 426.1490.

(1*R*,2*R*,7*S*,8*aR*)- and (1*R*,2*R*,7*R*,8*aR*)-1,2-Bis(benzyloxy)-8,8-difluoro-8*a*-hydroxy-7-methylhexahydroindolizin-3(5*H*)-one (*trans*-13 and *cis*-13). According to the *general procedure B*, radical cyclization of *syn*-**9** (3.15 g, 6 mmol) followed by the removal of tin byproduct and preparative thin-layer chromatography (SiO_2, 15% EtOAc in hexanes ×5) gave *trans*-**13** (1.08 g, 43% yield) as a colorless oil and *cis*-**13** (0.38 g, 15% yield) as a colorless crystal. *trans*-**13**: $[\alpha]^{25}_{D}$ +16.3° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.26 (m, 10H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.45−4.35 (br s, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.35 (dd, *J* = 2.5, 7.6 Hz, 1H), 4.19 (dd, *J* = 0.9, 7.6 Hz, 1H), 3.86 (dd, *J* = 4.2, 13.3 Hz, 1H), 3.08 (dt, *J* = 4.2, 13.3 Hz, 1H), 2.61−2.44 (m, 1H), 1.67−1.62 (m, 1H), 1.49 (ddt, *J* = 5.0, 13.2, 13.2 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3 (CO), 137.7 (C), 137.0 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 127.8 (2 × CH), 127.7 (CH), 120.6 (dd, *J* = 244.1, 261.1 Hz, CF_2), 87.9 (CH), 85.9 (dd, *J* = 26.7, 35.7 Hz, C), 80.4 (d, *J* = 3.6 Hz, CH), 73.7 (CH_2), 73.6 (d, *J* = 3.3 Hz, CH_2), 34.9 (CH_2), 33.4 (t, *J* = 22.2 Hz, CH), 30.2 (d, *J* = 6.5 Hz, CH_2), 11.8 (t, *J* = 3.7 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −130.0 (dd, *J* = 27.7, 249.4 Hz, 1F), −119.7 (d, *J* = 249.4 Hz, 1F); IR (neat) ν_{max} 3297*br*, 1673*s*, 1456*s*, 1358*s*, 1136*s*, 1006*m*, 742*s*, 730*s*, 696*s* cm^{-1}; MS *m*/*z* (%) relative intensity 418 (M^+ + 1, trace), 417 (M^+, trace), 205 (100), 188 (26), 150 (39), 105 (6), 91 (79), 77 (6), 65 (18); HRMS (ESI-TOF) calcd for $C_{23}H_{25}F_2O_4NNa$ $[M + Na]^+$ 440.1649, found 440.1675. *cis*-**13**: mp 180−182 °C; $[\alpha]^{25}_{D}$ +27.8° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (m, 10H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.32 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.26−4.21 (br s, 1H), 4.09 (d, *J* = 7.6 Hz, 1H), 3.83−3.79 (m, 1H), 3.22 (dt, *J* = 3.8, 13.7 Hz, 1H), 2.44−2.40 (m, 1H), 2.02−1.91 (m, 1H), 1.51 (d, *J* = 13.7 Hz, 1H), 1.35 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (CO), 137.6 (C), 137.1 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 127.7 (CH), 120.0 (dd, *J* = 239.9, 264.8 Hz, CF_2), 88.7 (CH), 87.0 (dd, *J* = 27.3, 36.8 Hz, C), 80.3 (d, *J* = 4.5 Hz, CH), 73.6 (CH_2), 73.5 (d, *J* = 3.1 Hz, CH_2), 36.0 (t, *J* = 33.7 Hz, CH), 31.4 (CH_2), 28.6 (d, *J* = 6.0 Hz, CH_2), 13.5 (t, *J* = 4.4 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.7 (d, *J* = 254.3 Hz, 1F), −108.7 (dd, *J* = 15.0, 254.3 Hz, 1F); IR (KBr) ν_{max} 3304*br*, 1672*s*, 1455*m*, 1173*s*, 1097*s*, 1068*s*, 917*s*, 697*s* cm^{-1}; MS *m*/*z* (%) relative intensity 418 (M^+ + 1, 1), 206 (10), 205 (100), 188 (27), 177 (12), 150 (46), 91 (79), 77 (3), 65 (18); HRMS (ESI-TOF) calcd for $C_{23}H_{25}F_2O_4NNa$ $[M + Na]^+$ 440.1649, found 440.1661.

(1*R*,2*R*,6*R*,7*aS*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7,7-difluoro-7*a*-hydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (*trans*-15). To a cooled solution of *cis*-**10** (226 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C was added dropwise Et_3SiH (0.80 mL, 5 mmol) and $BF_3{\cdot}OEt_2$ (0.19 mL, 1.5 mmol) under an argon atmosphere. The mixture was slowly warmed up to room temperature, stirred for 24 h, quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to give *trans*-**15** (160 mg, 71% yield) as a white solid: mp 153−155 °C; $[\alpha]^{25}_{D}$ +55.3° (*c* 0.7, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (d, *J* = 7.6 Hz, 1H), 4.39 (d, *J* = 7.6 Hz, 1H), 4.17 (s, 1H), 3.52 (t, *J* = 10.2 Hz, 1H), 3.10 (t, *J* = 10.2 Hz, 1H), 3.02−2.84 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 9H), 0.96 (s, 9H), 0.22 (s, 6H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (CO), 122.4 (dd, *J* = 251.0, 262.5 Hz, CF_2), 88.3 (dd, *J* = 27.5, 34.0 Hz, C), 77.9 (CH), 73.4 (d, *J* = 4.5 Hz, CH), 44.4 (d, *J* = 7.0 Hz, CH_2), 36.6 (t, *J* = 22.5 Hz, CH), 25.8 (3 × CH_3), 25.6 (3 × CH_3), 18.3 (C), 17.7 (C), 8.5 (d, *J* = 7.0 Hz, CH_3), −4.2 (CH_3), −4.3 (CH_3), −4.7 (CH_3), −5.3 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −127.96 (dd, *J* = 26.3, 221.7 Hz, 1F), −125.96 (dd, *J* = 4.7, 221.7 Hz, 1F); IR (KBr) ν_{max} 3391*br*, 1721*s*, 1704*s*, 1473*m*, 1385*m*, 1256*s*, 1166*m*, 1145*s*, 1001*s*, 897*m*, 869*m*, 839*s*, 783*s* cm^{-1}; MS *m*/*z* (%) relative intensity 451 (M^+, 1), 436 (4), 396 (17), 395 (33), 394 (100), 234 (26), 212 (13), 206 (57), 186 (11), 75 (6), 73 (13); HRMS (ESI-TOF) calcd for $C_{20}H_{39}F_2NO_4Si_2Na$ $[M + Na]^+$ 474.2283, found 474.2261.

Preparation of (1*S*,2*R*,6*R*,7*aR*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7,7-difluoro-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (14), (1*S*,2*R*,6*R*,7*aR*)-1-(*tert*-Butyldimethylsilyloxy)-7,7-difluoro-2-hydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (16) and (1*S*,2*R*,6*R*,7*aR*)-7,7-Difluoro-1,2-dihydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (17). The reaction of *cis*-**10** (451.4 mg, 1 mmol) with Et_3SiH (1.6 mL, 10 mmol) and $BF_3{\cdot}OEt_2$ (0.38 mL, 3 mmol) in dry CH_2Cl_2 (10 mL) at reflux for 24 h gave **14** (87 mg, 20% yield), **16** (39 mg, 12% yield) and **17** (27 mg, 13% yield) after gradient chromatography (SiO_2, 10−30% EtOAc in hexanes). **14**: a white solid; mp 170−172 °C; $[\alpha]^{25}_{D}$ +37.2° (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, *J* = 8.1 Hz, 1H), 4.39 (dd, *J* = 6.5, 8.1 Hz, 1H), 3.78 (ddd, *J* = 3.9, 6.5, 18.3 Hz, 1H), 3.46 (t, *J* = 10.5 Hz, 1H), 3.23 (t, *J* = 10.5 Hz, 1H), 2.77−2.62 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 6H), 0.96 (s, 3H), 0.93 (s, 6H), 0.92 (s, 3H), 0.22 (s, 3H), 0.15 (s, 6H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8 (CO), 123.8 (t, *J* = 253.8 Hz, CF_2), 79.6 (CH), 75.4 (d, *J* = 7.4 Hz, CH), 66.4 (dd, *J* = 26.3, 32.5 Hz, CH), 46.1 (d, *J* = 6.8 Hz, CH_2), 40.2 (t, *J* = 23.8 Hz, CH), 25.8 (s, 3 × CH_3), 25.6 (s, 3 × CH_3), 18.3 (C), 17.8 (C), 9.1 (d, *J* = 7.6 Hz, CH_3), −4.3 (2 × CH_3), −4.7 (CH_3), −5.2 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.13 (td, *J* = 21.6, 225.5 Hz, 1F), −115.64 (dd, *J* = 4.9, 225.5 Hz, 1F); IR (KBr) ν_{max} 1731*s*, 1713*s*, 1391*m*, 1345*m*, 1261*s*, 1238*m*, 1177*m*, 1130*s*, 919*m*, 867*m*, 835*s*, 781*s* cm^{-1}; MS *m*/*z* (%) relative intensity 435 (M^+, trace), 380 (12), 379 (32), 378 (100), 216 (8), 128 (13), 73 (12); HRMS (ESI-TOF) calcd for $C_{20}H_{40}F_2NO_3Si_2$ $[M + H]^+$ 436.2515, found 436.2498. **16**: a white solid; mp 193−195 °C; $[\alpha]^{24}_{D}$ +30.8° (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44−4.37 (m, 2H), 3.86−3.80 (m, 1H), 3.49 (dd, *J* = 9.1, 11.0 Hz, 1H), 3.42−3.35 (br s, 1H), 3.23 (t, *J* = 11.0 Hz, 1H), 2.80−2.61 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9 (CO), 123.5 (t, *J* = 253.8 Hz, CF_2), 78.5 (CH), 75.3 (d, *J* = 7.8 Hz, CH), 66.8 (dd, *J* = 26.3, 32.1 Hz, CH), 46.3 (d, *J* = 6.5 Hz, CH_2), 40.3 (t, *J* = 23.8 Hz, CH), 25.5 (3 × CH_3), 17.9 (C), 9.1 (d, *J* = 7.5 Hz, CH_3), −4.7 (CH_3), −5.4 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.56 (ddd, *J* = 9.4, 21.2, 225.6 HZ, 1F), −116.44 (ddd, *J* = 4.4, 9.4, 225.6 Hz, 1F); IR (KBr) ν_{max} 3325*br*, 1710*s*, 1687*m*, 1385*m*, 1259*m*, 1238*m*, 1120*s*, 917*m*, 842*s*, 783*m* cm^{-1}; MS *m*/*z* (%) relative intensity 321 (M^+, 1), 265 (14), 264 (100), 204 (17), 188 (19), 170 (11), 128 (85), 100 (19), 80 (18), 73 (31); HRMS (ESI-TOF) calcd for $C_{14}H_{25}F_2NO_3SiNa$ $[M + Na]^+$ 344.1469, found 344.1481. **17**: a colorless oil; $[\alpha]^{24}_{D}$ +17.3° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28−5.06 (br s, 1H), 4.99−4.80 (br s, 1H), 4.52 (d, *J* = 7.7 Hz, 1H), 4.38 (t, *J* = 7.7 Hz, 1H), 3.85 (ddd, *J* = 5.4, 5.4, 17.2 Hz, 1H), 3.42 (t, *J* = 10.4 Hz, 1H), 3.20 (t, *J* = 10.4 Hz, 1H), 2.76−2.56 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8 (CO), 123.5 (t, *J* = 253.6 Hz, CF_2), 78.2 (CH), 74.1 (CH), 65.7 (dd, *J* = 26.0, 32.6 Hz, CH), 46.3 (d, *J* = 6.0 Hz, CH_2), 40.2 (t, *J* = 23.3 Hz, CH), 9.3 (d, *J* = 7.0 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.98 (td, *J* = 19.3, 225.4 Hz, 1F), −116.60 (d, *J* = 225.4 Hz, 1F); IR ($CHCl_3$) ν_{max} 3382*br*, 1708*s*, 1459*m*, 1234*s*, 1119*s*, 981*s* cm^{-1}; MS *m*/*z* (%) relative intensity 207 (M^+, 12), 206 (100), 174 (17),

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134 (24), 94 (5); HRMS (ESI-TOF) calcd for $C_8H_{11}F_2NO_3Na$ $[M + Na]^+$ 230.0605, found 230.0624.

(1*S*,2*R*,6*R*,7*aR*)-1,2-Bis(benzyloxy)-7,7-difluoro-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (18). The reaction of *cis*-**12** (1.21 g, 3 mmol) with Et_3SiH (2.4 mL, 15 mmol) and $BF_3{\cdot}OEt_2$ (1.1 mL, 9 mmol) in dry CH_2Cl_2 (30 mL) at room temperature for 48 h gave **18** (0.85 g, 73% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 5% EtOAc, 15% hexanes in CH_2Cl_2): $[\alpha]^{23}_D$ +69.3° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−6.34 (m, 10H), 5.05 (d, *J* = 11.8 Hz, 1H), 4.81 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.43 (dd, *J* = 5.9, 8.0 Hz, 1H), 3.92 (ddd, *J* = 5.9, 5.9, 18.1 Hz, 1H), 3.53 (t, *J* = 10.5 Hz, 1H), 3.32 (t, *J* = 10.5 Hz, 1H), 2.84−2.68 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1 (CO), 137.4 (C), 137.0 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 128.0 (CH), 127.9 (CH), 127.8 (2 × CH), 123.4 (t, *J* = 253.9 Hz, CF_2), 82.4 (CH), 79.1 (d, *J* = 6.9 Hz, CH), 72.7 (CH_2), 72.3 (CH_2), 65.9 (dd, *J* = 25.8, 33.6 Hz, CH), 46.6 (d, *J* = 6.3 Hz, CH), 40.0 (t, *J* = 23.4 Hz, CH_2), 9.4 (d, *J* = 7.6 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.96 (td, *J* = 20.1, 225.6 Hz, 1F), −116.56 (dd, *J* = 9.4, 225.6 Hz, 1F); IR ($CHCl_3$) ν_{max} 1715*s*, 1456*m*, 1360*m*, 1278*m*, 1215*s*, 1121*s*, 997*m*, 699*m* cm^{-1}; MS *m*/*z* (%) relative intensity 387 (M^+, trace), 175 (100), 174 (34), 120 (11), 96 (43), 91 (64), 68 (23), 65 (25); HRMS (ESI-TOF) calcd for $C_{22}H_{23}F_2NO_3Na$ $[M + Na]^+$ 410.1544, found 410.1522.

(1*R*,2*R*,6*S*,7*aS*)- and (1*R*,2*R*,6*R*,7*aS*)-1,2-Bis(benzyloxy)-7,7-difluoro-7*a*-hydroxy-6-methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (*cis*-19 and *trans*-19). Radical cyclization of *anti*-**8** (1.02 g, 2 mmol), followed by the removal of tin byproduct and preparative thin-layer chromatography (SiO_2, 10% EtOAc in hexanes ×6) gave *cis*-**19** (0.31 g, 38% yield) as a colorless crystal and *trans*-**19** (0.12 g, 15% yield) as a colorless oil. *cis*-**19**: mp 154−155 °C; $[\alpha]^{23}_D$ +108.0° (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.33 (m, 10H), 5.04 (d, *J* = 11.8 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 7.7 Hz, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 4.24 (s, 1H), 3.96 (dd, *J* = 8.4, 11.7 Hz, 1H), 3.08 (ddd, *J* = 1.3, 3.4, 11.7 Hz, 1H), 2.76−2.64 (m, 1H), 1.35 (dd, *J* = 1.3, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (CO), 137.2 (C), 136.1 (C), 128.5 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 123.6 (dd, *J* = 248.2, 265.8 Hz, CF_2), 88.6 (dd, *J* = 28.6, 34.1 Hz, C), 80.8 (CH), 77.8 (d, *J* = 5.1 Hz, CH), 73.1 (CH_2), 72.9 (CH_2), 45.7 (d, *J* = 2.8 HZ, CH_2), 38.9 (dd, *J* = 22.5, 25.1 Hz, CH), 14.6 (t, *J* = 6.1 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.55 (d, *J* = 228.0 Hz, 1F), −103.78 (dd, *J* = 22.1, 228.0 Hz, 1F); IR (KBr) ν_{max} 3228*br*, 1708*s*, 1692*s*, 1455*m*, 1416*m*, 1234*m*, 1148*s*, 1035*m*, 1026*m*, 731*s*, 694*m* cm^{-1}; MS *m*/*z* (%) relative intensity 404 (M^+ + 1, trace), 192 (8), 191 (100), 171 (22), 151 (16), 136 (38), 111 (23), 92 (8), 91 (83), 73 (10), 65 (25); HRMS (ESI-TOF) calcd for $C_{22}H_{23}F_2NO_4Na$ $[M + Na]^+$ 426.1493, found 426.1463. *trans*-**19**: $[\alpha]^{23}_D$ +61.2.0° (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.34 (m, 10H), 5.04 (d, *J* = 11.8 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 7.9 Hz, 1H), 4.39 (d, *J* = 7.9 Hz, 1H), 4.17 (s, 1H), 3.58 (t, *J* = 10.7 Hz, 1H), 3.15 (t, *J* = 10.7 Hz, 1H), 3.09−2.90 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (CO), 137.2 (C), 136.1 (C), 128.6 (2 × CH), 128.5 (CH), 128.4 (3 × CH), 128.2 (CH), 128.1 (2 × CH), 127.9 (CH), 122.1 (t, *J* = 259 Hz, CF_2), 88.3 (t, *J* = 30.8 Hz, C), 80.7 (CH), 77.0 (CH), 73.2 (CH_2), 72.9 (CH_2), 44.8 (CH_2), 36.5 (t, *J* = 22.9 Hz, CH), 8.6 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −127.26 (s, 1F), −127.22 (d, *J* = 6.1 Hz, 1F); IR (neat) ν_{max} 3231*br*, 1708*s*, 1692*s*, 1455*m*, 1362*m*, 1234*m*, 1148*s*, 1035*m*, 1003*m*, 731*s*, 694*s* cm^{-1}; MS *m*/*z* (%) relative intensity 404 (M^+ + 1, trace), 191 (21), 167 (32), 149 (100), 91 (22), 77 (5), 65 (9); HRMS (ESI-TOF) calcd for $C_{22}H_{23}F_2NO_4Na$ $[M + Na]^+$ 426.1493, found 426.1494.

(1*S*,2*S*,6*R*,7*aR*)-7,7-Difluoro-6-methylhexahydro-1*H*-pyrrolizine-1,2-diol (20). A mixture of **14** (87 mg, 0.2 mmol) or **16** (64 mg, 0.2 mmol) with a cation exchange resin, DOWEX 50 WX8 ($H^{\oplus}$-form) (600 mg) in MeOH (5 mL) was stirred at room temperature for 24 h. The resin was filtered off and washed with 10% NH_4OH (20 mL). The filtrate was evaporated to dryness followed by lyophilization to give **17** (28 mg, 68% yield) and (32 mg, 77% yield), respectively.

To a suspension of $LiAlH_4$ (455 mg, 12 mmol) in dry THF (2 mL) was added a solution of **17** (83 mg, 0.4 mmol) in dry THF (2 mL). The mixture was heated at reflux overnight and quenched at 0 °C by careful addition of water (1 mL) followed by 1 M NaOH (1 mL). The resulting mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. Purification by column chromatography (SiO_2, a mixture of 1% NH_3 and 5% MeOH in CH_2Cl_2) gave **20** (55 mg, 72% yield) as a white solid: mp 215−216 °C; $[\alpha]^{24}_D$ +13.4° (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 4.78−4.52 (br s, 2H), 4.23 (t, *J* = 6.1 Hz, 1H), 4.18−4.14 (m, 1H), 3.47 (ddd, *J* = 6.6, 6.6, 21.8 Hz, 1H), 3.35−3.32 (m, 1H), 3.26−3.23 (m, 1H), 2.71−2.47 (m, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 127.4 (t, *J* = 252.7 Hz, CF_2), 79.6 (CH), 75.4 (d, *J* = 9.1 Hz, CH), 74.4 (dd, *J* = 22.9, 28.8 Hz, CH), 60.4 (d, *J* = 8.1 Hz, CH_2), 59.9 (CH_2), 42.6 (dd, *J* = 22.1, 23.6 Hz, CH), 8.4 (d, *J* = 6.1 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −120.96 (td, *J* = 22.1, 225.4 Hz, 1F), −115.04 (d, *J* = 225.4 Hz, 1F); IR (KBr) ν_{max} 3372*br*, 1396*m*, 1384*m*, 1145*s*, 1117*s*, 1024*s*, 976*m*, 605*m* cm^{-1}; MS *m*/*z* (%) relative intensity 194 (M^+ + 1, 47), 167 (30), 151 (35), 129 (35), 105 (47), 104 (55), 91 (100), 81 (39), 67 (53); HRMS (ESI-TOF) calcd for $C_8H_{14}F_2NO_2$ $[M + H]^+$ 194.0993, found 194.1007.

(2*R*,5*S*,6*S*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-ethyl-1,1-difluoro-2-methylhexahydro-1*H*-pyrrolizine (21a). EtMgCl (2 M in THF, 0.5 mL, 1 mmol) was slowly added to a solution of **18** (77 mg, 0.2 mmol) in dry THF (5 mL) at 0 °C for 30 min. To the reaction mixture was added 4 M HCl-dioxane in MeOH (4 M HCl-dioxane/MeOH, 1:29, 5 mL), followed by the addition of excess $NaBH_3CN$ for an additional 1 h. To the mixture was added 10% aqueous NaOH solution (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by chromatography (SiO_2, 5% EtOAc in hexanes) to afford **21a** (45 mg, 56% yield) as a colorless oil: $[\alpha]^{25}_D$ +17.9° (*c* 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.29 (m, 10H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.34 (t, *J* = 7.3 Hz, 1H), 3.94 (t, *J* = 7.3 Hz, 1H), 3.66 (ddd, *J* = 5.7, 5.7, 24.4 Hz, 1H), 3.40 (t, *J* = 9.5 Hz, 1H), 2.67−2.61 (m, 2H), 2.37 (t, *J* = 9.5 Hz, 1H), 1.67−1.61 (m, 1H), 1.54−1.48 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.4 (C), 137.9 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.6 (CH), 126.0 (dd, *J* = 256.4, 266.1 Hz, CF_2), 87.7 (CH), 80.6 (d, *J* = 8.1 Hz, CH), 72.7 (CH_2), 72.3 (d, *J* = 1.8 Hz, CH_2), 71.5 (dd, *J* = 22.3, 28.4 Hz, CH), 69.9 (CH), 59.5 (d, *J* = 8.3 Hz, CH_2), 41.3 (t, *J* = 22.9 Hz, CH), 26.0 (CH_2), 10.2 (CH_3), 8.3 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.12 (td, *J* = 24.2, 220.9 Hz, 1F), −116.48 (d, *J* = 220.9 Hz, 1F); IR ($CHCl_3$) ν_{max} 1604*m*, 1497*m*, 1455*s*, 1360*m*, 1185*s*, 1150*s*, 1093*s*, 1074*s*, 700*s* cm^{-1}; MS *m*/*z* (%) relative intensity 372 (M^+−Et, 9), 310 (17), 164 (11), 161 (25), 146 (56) 91 (100), 77 (12), 65 (22); HRMS (ESI-TOF) calcd for $C_{24}H_{29}F_2O_2NNa$ $[M + Na]^+$ 424.2064, found 424.2071.

(2*R*,5*S*,6*S*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-butyl-1,1-difluoro-2-methylhexahydro-1*H*-pyrrolizine (21b). The reaction of **18** (155 mg, 0.4 mmol) with *n*-BuMgCl (2 M in THF, 1.0 mL, 2 mmol) gave **21b** (100 mg, 58% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes): $[\alpha]^{25}_D$ +20.0° (*c* 0.7, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.29 (m, 10H), 4.83 (d, *J* = 11.5, 1H), 4.68 (d, *J* = 11.6, 1H), 4.64 (d, *J* = 11.5, 1H), 4.49 (d, *J* = 11.6, 1H), 4.33 (t, *J* = 7.1 Hz, 1H), 3.92 (t, *J* = 7.1 Hz, 1H), 3.67 (ddd, *J* = 5.7, 5.7, 24.2 Hz, 1H), 3.39 (t, *J* = 8.4 Hz, 1H), 2.69−2.54 (m, 2H), 2.36 (t, *J* = 10.6 Hz, 1H), 1.61−1.55 (m, 1H), 1.50−1.43 (m, 1H), 1.37−1.25 (m, 4H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.3 (C), 137.8 (C), 128.4 (2 × CH), 128.3, (2 × CH), 127.9 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.6 (CH), 125.9 (t, *J* = 246.8 Hz, CF_2), 88.2 (CH), 80.5 (d, *J* = 8.0 Hz, CH), 72.7 (CH_2), 72.2 (d, *J* = 1.8 Hz, CH_2), 71.5 (dd, *J* = 22.1, 28.4 Hz, CH), 68.8 (CH), 59.7 (d, *J* = 8.6 Hz, CH_2), 41.2 (t, *J* = 23.0 Hz, CH), 33.5 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 14.0 (CH_3),

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8.5 (d, J = 6.0 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.12 (ddd, J = 18.8, 21.9, 225.3 Hz, 1F), −115.67 (dd, J = 4.7, 225.3 Hz, 1F); IR (neat) ν_{max} 1605*s*, 1497*s*, 1455*s*, 1363*s*, 1309*s*, 1157*s*, 1124*s*, 1100*s*, 737*s*, 698*s* cm^{-1}; MS m/z (%) relative intensity 430 (M^+ + 1, 2), 338 (23), 266 (12), 188 (16), 160 (34), 147 (25), 134 (15), 91 (100), 77 (9), 65 (24); HRMS (ESI-TOF) calcd for $C_{26}H_{34}F_2NO_2$ $[M + H]^+$ 430.2558, found 430.2565.

Mixture of (2*R*,5*S*,6*S*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-butyl-1,1-difluoro-2-methylhexahydro-1*H*-pyrrolizine (21b) and (*S*)-6-(Benzyloxy)-1-butyl-2-methyl-2*H*-pyrrolizin-5(3*H*)-one (22b). To a solution of $CeCl_3$ (745 mg, 2 mmol) in THF (5 mL) was added *n*-BuLi (1.5 mL, 2 mmol, 1.35 M solution in hexane) at −78 °C. After stirring at −78 °C for 1 h, a solution of **18** (155 mg, 0.4 mmol) in THF (5 mL) was added. The mixture was stirred at −78 °C for 1 h and then gradually warmed to −20 °C, and quenched by the addition of 4 M HCl-dioxane in MeOH (6 mL) followed by the addition of an excess amount of $NaBH_3CN$. The resulting reaction mixture was stirred at 0 °C for 1 h, and 10% aqueous NaOH solution (6 mL) was then added. The mixture was diluted and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by preparative thin-layer chromatography (SiO_2, 5% EtOAc in hexanes × 2) to afford colorless oils of **21b** (26 mg, 15% yield) and **22b** (51 mg, 43% yield): $[\alpha]^{25}_D$ +8.9° (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.34 (m, 5H), 6.39 (s, 1H), 5.01 (s, 2H), 4.39 (dd, J = 7.7, 11.4 Hz, 1H), 3.72 (dd, J = 4.2, 11.4 Hz, 1H), 3.06−3.03 (m, 1H), 2.67 (t, J = 7.5 Hz, 2H), 1.61 (quint., J = 7.5 Hz, 2H), 1.40−1.34 (m, 5H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2 (CO), 149.9 (C), 137.3 (C), 128.5 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 125.5 (C), 124.9 (C), 93.7 (CH), 72.8 (CH_2), 49.0 (CH_2), 43.4 (CH), 30.5 (CH_2), 23.3 (CH_2), 22.4 (CH_2), 15.9 (CH_3), 13.8 (CH_3); IR (neat) ν_{max} 1682*s*, 1548*w*, 1455*m*, 1373*m*, 1171*m*, 1079*m*, 1024*m*, 770*w*, 738*s*, 699*m* cm^{-1}; MS m/z (%) relative intensity 298, (M^+ + 1, 9), 232 (43), 219 (80), 203 (57), 189 (100), 149 (60), 147 (90), 91 (27), 65 (8); HRMS (ESI-TOF) calcd for $C_{19}H_{23}O_2NNa$ $[M + Na]^+$ 320.1626, found 320.1640.

Mixture of (2*R*,5*S*,6*S*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-1,1-difluoro-5-isopropyl-2-methyl-hexahydro-1*H*-pyrrolizine (21c) and (*S*)-6-(Benzyloxy)-1-isopropyl-2-methyl-2*H*-pyrrolizin-5(3*H*)-one (22c). The reaction of **18** (77 mg, 0.2 mmol) with *i*PrMgCl (2 M in THF, 0.5 mL, 1 mmol) gave **21c** (42 mg, 51% yield) as a colorless oil and **22c** (7 mg, 12% yield) as a yellow oil after preparative thin-layer chromatography (SiO_2, 5% EtOAc in hexanes × 2). **21c**: $[\alpha]^{23}_D$ +48.2° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.29 (m, 10H), 4.81 (d, J = 11.4 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.5 Hz, 1H), 4.36 (t, J = 6.5 Hz, 1H), 4.04 (t, J = 8.1 Hz, 1H), 3.65 (ddd, J = 6.2, 6.2, 23.1 Hz, 1H), 3.33 (t, J = 8.2 Hz, 1H), 2.70−2.50 (m, 2H), 2.38 (t, J = 10.5 Hz, 1H), 1.83−1.77 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.3 (C), 137.9 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.6 (CH), 126.1 (t, J = 253.7 Hz, CF_2), 86.2 (CH), 81.2 (d, J = 8.6 Hz, CH), 73.9 (CH), 72.4 (CH_2), 72.3 (d, J = 1.6 Hz, CH_2), 71.9 (dd, J = 22.5, 28.6 Hz, CH), 60.6 (d, J = 8.5 Hz, CH_2), 41.4 (t, J = 22.8 Hz, CH), 30.4 (CH), 19.6 (CH_3), 18.3 (CH_3), 8.4 (d, J = 6.3 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.30 (d, J = 220.9 Hz, 1F), −115.29 (d, J = 220.9 Hz, 1F); IR ($CHCl_3$) ν_{max} 1603*w*, 1497*m*, 1456*s*, 1362*m*, 1150*s*, 1093*s*, 700*s* cm^{-1}; MS m/z (%) relative intensity 416 (M^+ + 1, 21), 415 (2), 372 (35), 160 (14), 91 (100), 77 (6), 65 (18); HRMS (ESI-TOF) calcd for $C_{25}H_{32}F_2NO_2$ $[M + H]^+$ 416.2401, found 416.2385. **22c**: $[\alpha]^{23}_D$ +16.7° (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.32 (m, 5H), 6.40 (s, 1H), 5.01 (s, 2H), 4.44 (dd, J = 7.7, 11.4 Hz, 1H), 3.77 (dd, J = 4.2, 11.4 Hz, 1H), 3.15 (quint., J = 7.1 Hz, 1H), 3.08−3.01 (m, 1H), 1.38 (d, J = 7.4 Hz, 3H), 1.36 (d, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2 (CO), 149.3 (C), 137.3 (C), 130.0 (C), 128.5 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 124.7 (C), 93.9 (CH), 72.7 (CH_2), 49.8 (CH_2), 43.4 (CH), 25.4 (CH), 20.9 (CH_3), 20.8 (CH_3), 15.8 (CH_3); IR (neat) ν_{max} 1694*s*, 1682*s*, 1485*m*, 1456*s*, 1408*m*, 1361*m*, 1180*m*, 1149*m*, 800*m*, 738*s*, 699*s* cm^{-1}; MS m/z (%) relative intensity 283 (M^+, trace), 267 (10), 251 (6), 239 (13), 237 (6), 193 (6), 191 (7), 155 (21), 125 (43), 111 (64), 97 (75), 91 (22), 71 (73), 65 (12), 57 (100), 55 (80); HRMS (ESI-TOF) calcd for $C_{18}H_{21}O_2NNa$ $[M + Na]^+$ 306.1470, found 306.1495.

(1*S*,2*R*,7*S*,8*aR*)- and (1*S*,2*R*,7*S*,8*aS*)-1,2-Bis(benzyloxy)-8,8-difluoro-7-methylhexahydro-indolizin-3(5*H*)-one (*cis*-23 and *trans*-23). The reaction of *trans*-**13** (417 mg, 1 mmol) with Et_3SiH (0.8 mL, 5 mmol) and $BF_3{\cdot}OEt_2$ (0.38 mL, 3 mmol) in refluxing CH_2Cl_2 (10 mL) for 24 h gave *cis*-**23** (160 mg, 40% yield) as a colorless oil and *trans*-**23** (88 mg, 22% yield) as a white solid after preparative thin-layer chromatography (SiO_2, 5% EtOAc, 25% hexanes in CH_2Cl_2 × 2). *cis*-**23**: $[\alpha]^{24}_D$ +101.0° (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.31 (m, 10H), 5.06 (d, J = 11.7 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.44 (t, J = 5.0 Hz, 1H), 4.28 (dd, J = 1.1, 5.0 Hz, 1H), 4.11−4.07 (m, 1H), 3.74 (ddd, J = 1.1, 4.0, 23.0 Hz, 1H), 2.93 (dt, J = 4.3, 13.6 Hz, 1H), 2.52−2.47 (m, 1H), 2.06−1.96 (m, 1H), 1.67−1.58 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (CO), 137.4 (C), 137.2 (C), 128.4 (4 × CH), 128.3 (2 × CH), 128.0 (CH), 127.9 (3 × CH), 119.9 (t, J = 246.9 Hz, CF_2), 80.8 (CH), 76.8 (d, J = 6.4 Hz, CH), 72.4 (CH_2), 72.2 (d, J = 1.8 Hz, CH_2), 59.2 (dd, J = 24.6, 35.8 Hz, CH), 34.7 (dd, J = 20.1, 24.3 Hz, CH), 33.2 (CH_2), 27.1 (d, J = 6.4 Hz, CH_2), 12.2 (dd, J = 2.3, 8.0 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −112.80 (d, J = 242.0 Hz, 1F), −110.58 (ddd, J = 11.3, 23.4, 242.0 Hz, 1F); IR ($CHCl_3$) ν_{max} 1716*s*, 1456*m*, 1293*m*, 1278*m*, 1121*s*, 997*w*, 699*m* cm^{-1}; MS m/z (%) relative intensity 402 (M^+ + 1, trace), 189 (100), 188 (74), 174 (18), 168 (14), 91 (47), 77 (6), 65 (15); HRMS (ESI-TOF) calcd for $C_{23}H_{25}F_2NO_3Na$ $[M + Na]^+$ 424.1700, found 424.1704. *trans*-**23**: mp 75−76 °C; $[\alpha]^{24}_D$ +63.7° (*c* 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.30 (m, 10H), 5.11 (d, J = 11.8 Hz, 1H), 4.82 (d, J = 11.8 Hz, 2H), 4.62 (d, J = 11.8 Hz, 1H), 4.44 (dd, J = 3.5, 7.6 Hz, 1H), 4.40 (t, J = 7.6 Hz, 1H), 4.28−4.20 (m, 1H), 3.78 (dd, J = 7.6, 27.4 Hz, 1H), 2.70 (dt, J = 3.0, 13.3 Hz, 1H), 2.10−1.99 (m, 1H), 1.68−1.63 (m, 1H), 1.56 (ddt, J = 5.0, 5.0, 13.3 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (CO), 137.8 (C), 137.5 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 127.7 (3 × CH), 120.5 (t, J = 251.5 Hz, CF_2), 79.8 (d, J = 1.9 Hz, CH), 78.7 (CH), 72.9 (CH_2), 72.8 (CH_2), 58.8 (dd, J = 25.8, 30.2 Hz, CH), 39.1 (CH_2), 38.2 (t, J = 22.6 Hz, CH), 30.1 (d, J = 6.9 Hz, CH_2), 11.9 (t, J = 3.9 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −130.21 (td, J = 26.7, 244.2 Hz, 1F), −112.69 (d, J = 244.2 Hz, 1F); IR ($CHCl_3$) ν_{max} 1716*s*, 1456*m*, 1278*m*, 1153*m*, 1121*s*, 996*s*, 699*m* cm^{-1}; MS m/z (%) relative intensity 401 (M^+, 1), 205 (52), 189 (100), 188 (74), 179 (23), 165 (24), 105 (28), 91 (74), 77 (20), 65 (18); HRMS (ESI-TOF) calcd for $C_{23}H_{25}F_2NO_3Na$ $[M + Na]^+$ 424.1700, found 424.1678.

Mixture of (1*S*,2*S*,3*R*,7*S*,8*aR*)- and (1*S*,2*S*,3*S*,7*S*,8*aR*)-1,2-Bis(benzyloxy)-3-ethyl-8,8-difluoro-7-methyloctahydroindolizine (24a and 25a). The reaction of *cis*-**23** (161 mg, 0.4 mmol) with EtMgCl (2 M in THF, 0.4 mL, 0.8 mmol) gave **24a** (83 mg, 50% yield) and **25a** (37 mg, 22% yield) as colorless oils after preparative thin-layer chromatography (SiO_2, 5% EtOAc in hexanes × 2). **24a**: $[\alpha]^{25}_D$ −55.0° (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (m, 10H), 4.68 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.16 (d, J = 6.1 Hz, 1H), 3.82 (d, J = 5.0 Hz, 1H), 2.98−2.88 (m, 1H), 2.59 (ddd, J = 6.1, 8.3, 16.4 Hz, 1H), 2.44−2.38 (m, 2H), 2.21−2.13 (m, 2H), 1.78−1.69 (m, 1H), 1.63−1.52 (m, 2H), 1.14 (d, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (C), 138.0 (C), 128.4 (2 × CH), 128.2 (4 × CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (CH), 121.9 (t, J = 244.6 Hz, CF_2), 82.7 (CH), 81.2 (CH), 72.2 (CH_2), 71.2 (CH_2), 69.1 (CH), 69.0 (dd, J = 25.0, 27.1 Hz, CH), 44.1 (CH_2), 35.2 (t, J = 22.4 Hz, CH), 29.2 (d, J = 4.1 Hz, CH_2), 18.9 (CH_2), 13.6 (t, J = 6.2 Hz, CH_3), 10.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −108.95−(−108.89) (m, 2F); IR (neat) ν_{max} 1606*w*, 1497*m*, 1455*s*, 1360*m*, 1340*m*, 1186*s*, 1120*s*, 1074*m*, 737*s*, 698*s* cm^{-1}; MS m/z (%) relative intensity 416 (M^+ + 1, 3), 386 (17), 203 (25), 181 (24), 174 (22), 160 (29), 134 (15), 91 (100), 77 (3), 65 (14); HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_2F_2N$ $[M + H]^+$ 416.2401, found

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416.2423. **25a**: $[\alpha]^{25}_{D}$ +35.0° (*c* 0.7, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.29 (m, 10H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.26 (d, *J* = 2.0 Hz, 1H), 3.75 (d, *J* = 2.0 Hz, 1H), 3.39−3.31 (m, 1H), 3.13−3.09 (m, 1H), 2.97 (t, *J* = 10.3 Hz, 1H), 2.86−2.63 (m, 1H), 2.47−2.25 (m, 1H), 2.18−2.11 (m, 1H), 1.78−1.70 (m, 1H), 1.47−1.36 (m, 2H), 1.16 (d, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5 (C), 138.1 (C), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (CH), 121.9 (t, *J* = 244.2 Hz, CF_2), 82.7 (CH), 81.3 (CH) 72.2 (d, *J* = 1.6 Hz, CH_2), 71.2 (CH_2), 69.1 (CH), 69.0 (dd, *J* = 25.0, 27.1 Hz, CH), 44.7 (CH_2), 40.2 (d, *J* = 22.4 Hz, CH), 29.2 (d, *J* = 4.3 Hz, CH_2), 23.6 (t, *J* = 5.8 Hz, CH_3), 18.9 (CH_2), 10.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −107.00 (d, *J* = 246.8 Hz, 1F), −104.54 (d, *J* = 246.8 Hz, 1F); IR (neat) ν_{max} 1497*m*, 1455*s*, 1360*m*, 1340*m*, 1186*s*, 1148*s*, 1120*s*, 831*m*, 737*s*, 698*s* cm^{-1}; MS *m*/*z* (%) relative intensity 416 (M^+ + 1, 17), 415 (1), 386 (15), 203 (26), 181 (18), 174 (23), 91 (100), 77 (3), 65 (13); HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_2F_2N$ [M + H^+] 416.2401, found 416.2414.

Mixture of (1*S*,2*S*,3*R*,7*S*,8*aR*)- and (1*S*,2*S*,3*S*,7*S*,8*aR*)-1,2-Bis(benzyloxy)-3-butyl-8,8-difluoro-7-methyloctahydroindolizine (24b and 25b) and (*S*)-2-(Benzyloxy)-8-butyl-7-methyl-6,7-dihydroindolizin-3(5*H*)-one (26b). The reaction of *cis*-**23** (80 mg, 0.2 mmol) with *n*-BuMgCl (2 M in THF, 0.5 mL, 1 mmol) gave **24b** (38 mg, 43% yield), **25b** (14 mg, 16% yield) and **26b** (9 mg, 14% yield) after preparative thin-layer chromatography (SiO_2, 5% EtOAc in hexanes ×3). **24b**: a colorless oil; $[\alpha]^{25}_{D}$ −38.9° (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.29 (m, 10H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 5.4 Hz, 1H), 3.79 (d, *J* = 5.4 Hz, 1H), 2.86−2.87 (m, 1H), 2.58 (ddd, *J* = 5.8, 9.5, 15.2 Hz, 1H), 2.47−2.36 (m, 2H), 2.24−2.11 (m, 2H) 1.78−1.68 (m, 1H), 1.60−1.55 (m, 1H), 1.54−1.46 (m, 1H), 1.40−1.26 (m, 3H), 1.20−1.16 (m, 1H), 1.14 (d, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (2 × CO), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (CH), 121.9 (t, *J* = 244.6 Hz, CF_2), 82.7 (CH), 81.3 (CH), 72.1 (CH_2), 71.1 (CH_2), 69.1 (t, *J* = 25.9 Hz, CH), 67.6 (CH), 44.1 (CH_2), 35.2 (t, *J* = 22.3 Hz, CH), 29.2 (d, *J* = 2.9 Hz, CH_2), 28.4 (CH_2), 25.7 (CH_2), 23.1 (CH_2), 13.9 (CH_3), 13.6 (t, *J* = 6.2 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.44−(−108.39) (m, 2F); IR (neat) ν_{max} 1497*m*, 1455*s*, 1364*m*, 1184*m*, 1122*s*, 736*s*, 698*s* cm^{-1}; MS *m*/*z* (%) relative intensity 444 (M^+ + 1, 5), 280 (24), 202 (10), 181 (51), 174 (43), 91 (100), 77 (5), 65 (10); HRMS (ESI-TOF) calcd for $C_{27}H_{36}O_2F_2N$ [M + H^+] 444.2714, found 444.2703. **25b**: a colorless oil; $[\alpha]^{24}_{D}$ +29.2° (*c* 0.2, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.12 (m, 10H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 12.9 Hz, 1H), 4.40 (d, *J* = 12.9 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.15−4.14 (m, 1H), 3.64−3.62 (m, 1H), 3.25−3.19 (m, 1H), 3.08−3.04 (m, 1H), 2.83 (t, *J* = 11.3 Hz, 1H), 2.65−2.63 (m, 1H), 2.36−2.18 (m, 1H), 2.12−2.04 (m, 1H), 1.78−1.66 (m, 1H), 1.56−1.41 (m, 2H), 1.38−1.28 (m, 2H), 1.25−1.09 (m, 5H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1 (2 × C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (CH), 122.6 (t, *J* = 244.8 Hz, CF_2), 82.7 (CH), 81.4 (CH), 72.5 (CH_2), 71.0 (CH_2), 68.6 (CH_2), 65.1 (t, *J* = 26.5 Hz, CH), 42.1 (CH), 35.2 (t, *J* = 22.1 Hz, CH), 29.2 (d, *J* = 2.9 Hz, CH_2), 28.4 (CH_2), 25.7 (CH_2), 23.1 (CH_2), 13.9 (CH_3), 13.6 (t, *J* = 6.3 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −107.06 (d, *J* = 241.0 Hz, 1F), −104.81 (ddd, *J* = 14.6, 27.5, 241.0 Hz, 1F); IR (neat) ν_{max}, 1497*m*, 1455*s*, 1364*m*, 1183*m*, 1122*s*, 736*s*, 698*s*; MS *m*/*z* (%) relative intensity 444 (M^+ + 1, 8), 352 (12), 280 (28), 181 (72), 174 (49), 165 (22), 91 (100), 77 (7), 65 (12); HRMS (ESI-TOF) calcd for $C_{27}H_{36}O_2F_2N$ [M + H^+] 444.2714, found 444.2713. **26b**: a yellow oil; $[\alpha]^{23}_{D}$ −28.6° (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.31 (m, 5H), 6.68 (s, 1H), 4.99 (s, 2H), 4.07 (ddd, *J* = 4.2, 4.2, 12.6 Hz, 1H), 3.88 (ddd, *J* = 4.2, 10.4, 12.6 Hz, 1H), 2.70−2.51 (m, 2H), 2.32 (ddd, *J* = 4.6, 8.8, 13.5 Hz, 1H), 2.09−2.01 (m, 1H), 1.59−1.52 (m, 2H), 1.42−1.34 (m, 3H), 1.29 (d, *J* = 9.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1 (CO), 145.7 (C), 137.5 (C), 128.3 (2 × CH), 127.8 (CH), 127.4 (2 × CH), 126.0 (C), 125.4 (C), 99.1 (CH), 72.7 (CH_2), 41.1 (CH_2), 39.3 (CH), 31.2 (CH_2), 30.9 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 15.3 (CH_3), 13.8 (CH_3); IR (neat) ν_{max} 1728*m*, 1651*m*, 1644*s*, 1463*s*, 1455*s*, 1381*s*, 1162*s*, 1017*s*, 792*m*, 722*m*, 698*s* cm^{-1}; MS *m*/*z* (%) relative intensity 312 (M^+ + 1, 36), 311 (20), 220 (45), 179 (21), 178 (100), 91 (87), 77 (5), 65 (17); HRMS (ESI-TOF) calcd for $C_{20}H_{25}O_2NNa$ [M + Na^+] 334.1783, found 334.1780.

(*S*)-2-(Benzyloxy)-8-isopropyl-7-methyl-6,7-dihydroindolizin-3(5*H*)-one (26c). The reaction of *cis*-**23** (161 mg, 0.4 mmol) with *i*PrMgCl (2 M in THF, 0.4 mL, 0.8 mmol) gave **26c** (57 mg, 48% yield) as a yellow oil after column chromatography (SiO_2, 5% EtOAc in hexanes): $[\alpha]^{23}_{D}$ −22.4° (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.31 (m, 5H), 6.71 (s, 1H), 4.99 (s, 2H), 4.11 (ddd, *J* = 4.2, 4.2, 12.6 Hz, 1H), 3.89 (ddd, *J* = 4.2, 10.5, 12.6 Hz, 1H), 3.06 (quint., *J* = 7.1 Hz, 1H), 2.60−2.51 (m, 1H), 2.33 (ddd, *J* = 4.7, 8.7, 13.5 Hz, 1H), 2.10−2.02 (m, 1H), 1.38 (d, *J* = 3.9 Hz, 3H), 1.36 (d, *J* = 3.9 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2 (CO), 145.6 (C), 137.6 (C). 129.9 (C), 128.4 (2 × CH), 127.7 (CH), 127.3 (2 × CH), 125.1 (C), 99.6 (CH), 72.5 (CH_2), 41.3 (CH_2), 39.0 (CH), 31.2 (CH_2), 25.3 (CH), 20.9 (2 × CH_3), 15.2 (CH_3); IR (neat) ν_{max} 1712*m*, 1651*s*, 1645*s*, 1471*s*, 1455*s*, 1417*s*, 1372*s*, 1185*s*, 738*m*, 698*m* cm^{-1}; MS *m*/*z* (%) relative intensity 298 (M^+ + 1, 6), 297 (29), 207 (30), 206 (100), 194 (34), 178 (55), 164 (26), 91 (89), 77 (6), 65 (21); HRMS (ESI-TOF) calcd for $C_{19}H_{23}O_2NNa$ [M + Na^+] 320.1626, found 320.1595.

(1*S*,2*S*,3*S*,6*R*,7*aR*)-3-Ethyl-7,7-difluoro-6-methylhexahydro-1*H*-pyrrolizine-1,2-diol (27a). To a solution of **21a** (40 mg, 0.1 mmol) in dry MeOH (2 mL) was added $PdCl_2$ (36 mg, 0.2 mmol). The reaction mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 24 h. The mixture was filtered through a Celite pad, and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo, and the residue was purified by column chromatography (SiO_2, a mixture of 1% NH_3 and 3% MeOH in CH_2Cl_2) to give **27a** (21 mg, 95% yield) as a pale yellow solid: mp 211−212 °C; $[\alpha]^{25}_{D}$ +11.4° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 4.74−4.48 (br s, 2H), 4.15 (t, *J* = 7.8 Hz, 1H), 3.66 (t, *J* = 8.3 Hz, 1H), 3.38 (ddd, *J* = 6.9, 6.9, 21.5 Hz, 1H), 3.35 (t, *J* = 8.2 Hz, 1H), 2.62−2.46 (m, 1H), 2.42−2.35 (m, 1H), 2.32 (t, *J* = 10.8 Hz, 1H), 1.70−1.62 (m, 1H), 1.51−1.42 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.0 (t, *J* = 253.6 Hz, CF_2), 82.3 (CH), 73.8 (d, *J* = 10.3 Hz, CH), 70.9 (CH), 70.5 (dd, *J* = 22.5, 27.9 Hz, CH), 59.6 (d, *J* = 8.5 Hz, CH_2), 41.4 (t, *J* = 22.8 Hz, CH), 26.1 (CH_2), 10.5 (CH_3), 8.3 (d, *J* = 5.8 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −121.96 (d, *J* = 224.2 Hz, 1F), −117.21 (d, *J* = 224.2 Hz, 1F); IR (Nujol-mull) ν_{max} 3502*br*, 1463*s*, 1456*s*, 1377*m*, 1134*m*, 1062*m* cm^{-1}; MS *m*/*z* (%) relative intensity 222 (M^+ + 1, 7), 221 (M^+, 14), 207 (29), 192 (17), 191 (43), 178 (100), 161 (72), 149 (95), 133 (27), 95 (62), 67 (57); HRMS (ESI-TOF) calcd for $C_{10}H_{18}F_2NO_2$ [M + H^+] 222.1306, found 222.1296.

(1*S*,2*S*,3*S*,6*R*,7*aR*)-3-Butyl-7,7-difluoro-6-methylhexahydro-1*H*-pyrrolizine-1,2-diol (27b). The reaction of **21b** (129 mg, 0.3 mmol) with $PdCl_2$ gave **27b** (69 mg, 92% yield) as a white solid after column chromatography (SiO_2, a mixture of 1% NH_3 and 2% MeOH in CH_2Cl_2): mp 217−218 °C; $[\alpha]^{25}_{D}$ +12.9° (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 4.74−4.52 (br s, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.68 (t, *J* = 8.7 Hz, 1H), 3.42 (ddd, *J* = 7.0, 7.0, 21.1 Hz, 1H), 3.38 (t, *J* = 8.1 Hz, 1H), 2.65−2.51 (m, 1H), 2.51−2.44 (m, 1H), 2.38−2.34 (m, 1H), 1.69−1.63 (m, 1H), 1.51−1.34 (m, 5H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (500 MHz, CD_3OD) δ 127.3 (t, *J* = 253.1 Hz, CF_2), 83.8 (CH), 74.2 (d, *J* = 10.0 Hz, CH), 72.1 (t, *J* = 25.6 Hz, CH), 71.5 (CH), 60.9 (d, *J* = 8.5 Hz, CH_2), 42.6 (t, *J* = 22.9 Hz, CH), 34.4 (CH_2), 29.7 (CH_2), 24.1 (CH_2), 14.3 (CH_3), 8.5 (d, *J* = 6.3 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −123.02 (td, *J* = 23.0, 224.0 Hz, 1F), −117.74 (d, *J* = 224.0 Hz, 1F); IR (KBr) ν_{max} 3390*br*, 1462*m*, 1394*m*, 1382*m*, 1223*s*, 1139*s*, 1044*m*, 981*m*, 806*m* cm^{-1}; MS *m*/*z* (%) relative intensity 250 (M^+ + 1, 3), 249, (M^+, 12), 192 (100), 174 (20), 160 (66), 147 (77), 132 (53), 120 (86), 80 (15); HRMS (ESI-TOF) calcd for $C_{12}H_{22}F_2NO_2$ [M + H^+] 250.1619, found 250.1620.

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(1*S*,2*S*,3*S*,6*R*,7*aR*)-7,7-Difluoro-3-isopropyl-6-methylhexahydro-1*H*-pyrrolizine-1,2-diol (27c). The reaction of **21c** (42 mg, 0.1 mmol) with $PdCl_2$ gave **27c** (22 mg, 93% yield) as a pale yellow solid after column chromatography (SiO_2, a mixture of 1% NH_3 and 1% MeOH in CH_2Cl_2): mp 193−195 °C; $[\alpha]^{25}_D$ +18.9° (*c* 0.7, EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 4.74−4.52 (br s, 2H), 4.12 (t, *J* = 8.1 Hz, 1H), 3.80 (t, *J* = 8.7 Hz, 1H), 3.36 (ddd, *J* = 7.7, 7.7, 20.6 Hz, 1H), 3.31−3.28 (m, 1H), 2.63−2.46 (m, 1H), 2.35−2.30 (m, 2H), 1.83−1.72 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, CD_3OD) δ 127.7 (t, *J* = 252.3 Hz, CF_2), 81.5 (CH), 76.4 (CH), 74.8 (d, *J* = 10.8 Hz, CH), 72.3 (dd, *J* = 23.3, 28.0 Hz, CH), 62.0 (d, *J* = 8.3 Hz, CH_2) 42.8 (t, *J* = 23.0, CH), 31.5 (CH), 20.0 (CH_3), 18.7 (CH_3), 8.5 (d, *J* = 6.6 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −122.48 (td, *J* = 21.6, 225.1 Hz, 1F), −115.46 (d, *J* = 225.1 Hz, 1F); IR ($CHCl_3$) ν_{max} 3401*br*, 1473*s*, 1462*s*, 1391*s*, 1230*s*, 1122*s*, 1078*s*, 1045*s*, 983*m* cm^{-1}; MS *m*/*z* (%) relative intensity 236 (M^+ + 1, 6), 235 (M^+, 1), 192 (100), 164 (12), 160 (15), 146 (20), 44 (11), 126 (13), 120 (69), 80 (10); HRMS (ESI-TOF) calcd for $C_{11}H_{20}F_2NO_2$ $[M + H]^+$ 236.1462, found 236.1437.

(1*S*,2*S*,3*R*,7*S*,8*aR*)-3-Ethyl-8,8-difluoro-7-methyloctahydroindolizine-1,2-diol (28a). The reaction of **24a** (42 mg, 0.1 mmol) with $PdCl_2$ gave **28a** (23 mg, 98% yield) as a pale yellow solid after column chromatography (SiO_2, a mixture of 1% NH_3 and 2% MeOH in CH_2Cl_2): mp 222−223 °C; $[\alpha]^{25}_D$ −35.7° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.60−4.63 (br s, 2H), 4.10 (dd, *J* = 1.6, 6.9 Hz, 1H), 3.83 (dd, *J* = 1.6, 5.4 Hz, 1H), 2.86−2.82 (m, 1H), 2.39 (ddd, *J* = 1.3, 6.8, 23.8 Hz, 1H), 2.34−2.23 (m, 2H), 2.20−2.15 (m, 1H), 2.03−1.95 (m, 1H), 1.61−1.51 (m, 3H), 1.09 (d, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 123.4 (t, *J* = 243.8 Hz, CF_2), 79.0 (CH), 77.8 (d, *J* = 2.1 Hz, CH), 70.5 (CH), 70.0 (dd, *J* = 22.9, 28.4 Hz, CH), 45.1 (CH_2), 36.5 (dd, *J* = 20.3, 24.3 Hz, CH), 30.2 (d, *J* = 6.6 Hz, CH_2), 19.9 (CH_2), 13.6 (dd, *J* = 4.3, 8.1 Hz, CH_3), 10.9 (CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −113.04 (d, *J* = 240.2 Hz, 1F), −111.36 (ddd, *J* = 13.3, 23.1, 240.2 Hz, 1F); IR (KBr) ν_{max} 3504*s*, 1472*m*, 1385*s*, 1218*m*, 1134*m*, 1062*s*, 1040*m* cm^{-1}; MS *m*/*z* (%) relative intensity 236 (M^+ + 1, trace), 207 (3), 167 (40), 150 (11), 149 (100), 104 (5), 146 (20), 44 (11), 126 (13), 120 (69), 80 (10); HRMS (ESI-TOF) calcd for $C_{11}H_{20}F_2NO_2$ $[M + H]^+$ 236.1462, found 236.1451.

(1*S*,2*S*,3*R*,7*S*,8*aR*)-3-Butyl-8,8-difluoro-7-methyloctahydroindolizine-1,2-diol (28b). The reaction of **24b** (89 mg, 0.2 mmol) with $PdCl_2$ gave **28b** (48 mg, in 91% yield) as a yellow crystal after column chromatography (SiO_2, a mixture of 1% NH_3 and 2% MeOH in CH_2Cl_2): mp 205−207 °C; $[\alpha]^{25}_D$ −70.4° (*c* 0.5, CD_3OD); ^{1}H NMR (500 MHz, CD_3OD) δ 4.70−4.52 (s, 2H), 4.09 (d, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 5.1 Hz, 1H), 2.89−2.80 (m, 1H), 2.41−2.31 (m, 2H), 2.31−2.22 (m, 1H), 2.19−2.14 (m, 1H), 2.05−1.93 (m, 1H), 1.63−1.53 (m, 2H), 1.53−1.41 (m, 2H), 1.41−1.31 (m, 2H), 1.31−1.21 (m, 1H), 1.09 (d, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 123.5 (t, *J* = 243.7 Hz, CF_2), 79.2 (CH), 77.8 (d, *J* = 1.8 Hz, CH), 70.0 (dd, *J* = 22.7, 28.4 Hz, CH), 69.0 (CH), 45.1 (CH_2), 36.5 (dd, *J* = 20.2, 24.4 Hz, CH), 30.2 (d, *J* = 6.6 Hz, CH_2), 29.6 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 14.4 (CH_3), 13.6 (dd, *J* = 4.0, 8.3 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ −113.03 (d, *J* = 240.5 Hz, 1F), −111.32 (ddd, *J* = 13.3, 22.9, 240.5 Hz, 1F); IR ($CHCl_3$) ν_{max} 3403*br*, 1458*m*, 1386*m*, 1186*m*, 1159*m*, 1121*s*, 1088*s*, 1067*s* cm^{-1}; MS *m*/*z* (%) relative intensity 264 (M^+ + 1, 3), 207 (12), 206 (100), 174 (25), 160 (14), 134 (40), 57 (1); HRMS (ESI-TOF) calcd for $C_{13}H_{24}F_2NO_2$ $[M + H]^+$ 264.1775, found 264.1775.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all compounds and CIF data for single crystal X-ray analyses of *cis*-**10**, *trans*-**11**, *cis*-**13**, *cis*-**19**, and **28b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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