



cis -Dihydroxylated α -Trifluoromethylated N , O -Acetal from l -Tartaric Acid: Synthesis of Tetrasubstituted Stereocenter via Diastereoselective Pictet-Spengler Cyclization of N -Acyliminium Ions

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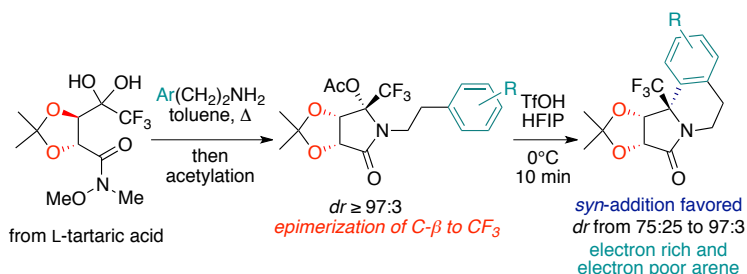
cis-Dihydroxylated α -Trifluoromethylated *N,O*-Acetal from L-Tartaric Acid: Synthesis of Tetrasubstituted Stereocenter *via* Diastereoselective Pictet-Spengler cyclization of *N*-Acyliminium Ions.

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The synthesis of cyclic, chiral α -trifluoromethylated *N,O*-acetals having a protected *cis*-diol moiety has been readily achieved in two steps from a known bis-Weinreb amide derived from L-tartaric acid. Reaction of *O*-acetyl analogues of these *N,O*-acetals with triflic acid in HFIP at 0°C generated *in situ* the corresponding electrophilic α -trifluoromethyl *N*-acyliminium ions which undergo Pictet-Spengler-type cyclizations. After only 10 min of reaction, original enantiopure aza-tricyclic scaffolds bearing a trifluoromethyl substituent at the bridgehead position were obtained with diastereoselectivities ranging from 75:25 to 97:3.

Introduction

N-acyliminium ions are well recognized as highly reactive electrophilic intermediates for C-C and C-heteroatom bond-forming reactions.¹ Cyclization reactions with arenes and hetero-arenes π -nucleophiles in particular have been extensively studied for the construction of fused heterocyclic nitrogen-containing scaffolds as cores of polycyclic alkaloids or as non-natural related systems.^{1b,g} Diastereoselective intramolecular Pictet-Spengler cyclization of five-membered ring *N*-acyliminium ions leading to trisubstituted stereogenic center has been detailed in numerous reports as being under steric control and forming in most cases virtually a single diastereomer.^{1g} In contrast much fewer describe this reaction with fully substituted *N*-acyliminium ions for constructing tetrasubstituted stereocenter. Reading the literature, the sense of diastereocontrol and the diastereoselectivity of the addition depend significantly on the reaction conditions² and the substituents already contained within the pyrrolidin-2-one core.^{3,4,5}

Because of the intrinsic properties of the fluorine atom⁶ the use of α -trifluoromethylated *N*-acyliminium ions for the elaboration of tetrasubstituted carbons on saturated nitrogen heterocycles is challenging and still largely underdeveloped,⁷ even in intramolecular cyclization processes.^{7a,c} Reaction involving these particular intermediates was disclosed for the first time by Eguchi and co-workers to prepare indolizidine derivatives, trifluoromethylated at the bridgehead position (Scheme 1).^{7a} The intramolecular addition of arene and hetero-arene nucleophiles required the treatment of the *N*-acyliminium ion precursor, an *N,O*-acetal, with 2 equiv of triflic acid in dichloromethane at room temperature for at least one day. Years later Anbarasan and his colleague reported a sequential process for the generation of α -trifluoromethylated *N,O*-acetals and the cyclization steps, with the latter being performed in the presence of 5 equiv of methanesulfonic acid under heating in 1,2-dichloroethane for a couple

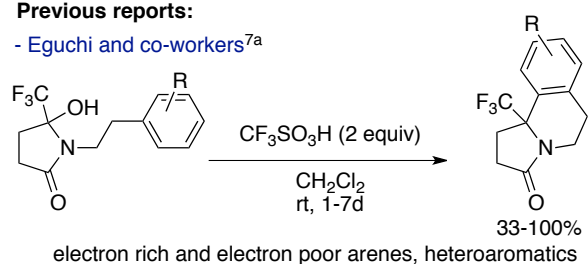
of hours (Scheme 1).^{7c} It is noteworthy that imide derived from cyclohexyl-1,2-dicarboxylic acid afforded the nitrogen-containing tetracyclic product as a 60:40 mixture of stereoisomers whose relative configurations were not determined.^{7c}

As part of our project concerning the study of α -amidoalkylations of chiral α -trifluoromethyl *N*-acyliminium ions we have previously examined the diastereoselective intermolecular addition of nitriles.^{7d} These electrophilic intermediates were generated *in situ* by reaction of the precursors *O*-acetyl *N,O*-acetals derived from L-tartaric acid with 3 equiv of Lewis acid (BF₃.Et₂O) at room temperature. Enantiopure 3a-(trifluoromethyl)-pyrrolo[2,3-d]-oxazolones having *trans*-diol moiety were thus obtained in good yields. The use of enantiopure *N*-acyliminium ions generated from the chiral pool is a popular strategy to study diastereoselective α -amidoalkylation reactions.^{1,4-5,7d} However, the limited number of readily available chiral starting molecules convenient for the synthesis of 5-membered ring α -substituted *N*-acyliminium ions impact the diversity of substituents on aza-heterocycle skeletons. In this article we wish to disclose the straightforward synthesis of chiral α -trifluoromethylated *N,O*-acetals having a protected *cis*-diol moiety. Studies of diastereoselective Pictet-Spengler cyclizations on this new family of *N*-acyliminium ions precursors will lead to original, enantiopure trifluoromethylated fused aza-tricyclic scaffolds (Scheme 1).

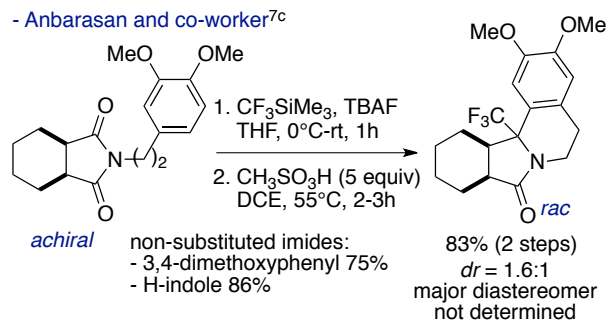
Scheme 1: Pictet-Spengler cyclization with α -CF₃-N-Acyliminium Ions: Previous Reports and Present Work.

Previous reports:

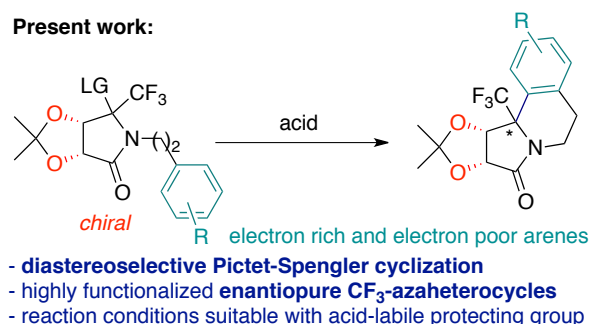
- Eguchi and co-workers^{7a}



- Anbarasan and co-worker^{7c}



Present work:

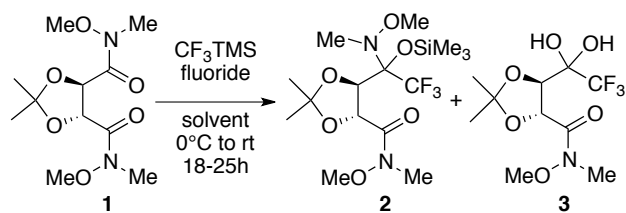


Results and Discussion

A few years ago, in the course of our studies, a control experiment highlighted that trifluoromethyltrimethylsilane in the presence of fluoride ion can undergo nucleophilic trifluoromethylation of bis-Weinreb amide derived from L-tartaric acid to give the corresponding mono trifluoromethylated silylated hemiaminal.^{8,9} As this functional group can be easily transformed into trifluoromethyl ketones,¹⁰ we studied this reaction on bis-Weinreb tartramide **1**, protected with an acetonide group, in order to gain access to the corresponding mono trifluoromethylketone. Our investigations are summarized in Table 1. Attempts to perform the nucleophilic trifluoromethylation of **1** were first realized with 1 equiv of

trifluoromethyltrimethylsilane in the presence of cesium fluoride in THF or toluene.¹⁰ Regardless the solvent, the reaction was not complete and the mono-trifluoromethylated hemiaminal **2** was isolated in moderate yields (51% and 40%, respectively, Table 1, entries 1-2). No traces of the bis-trifluoromethylated derivative were detected in the ¹⁹F NMR spectrum of the crude reaction mixture. All usual ammonium fluorides in THF gave a complex mixture of fluorinated compounds (Table 1, entry 3). The use of tetrabutylammonium difluorotriphenylsilicate (TBAT) led to the silylated hemiaminal **2** and a small amount of hydrated ketone¹¹ **3**, isolated in 62% and 10% yields, respectively (Table 1, entry 4). The use of 2 equiv of CF₃SiMe₃ in the presence of this fluoride source made it possible to increase the overall yield of the desired trifluoromethylated products **2** and **3** to 88% (84% of silylated hemiaminal **2** and 4% of hydrated ketone **3**, respectively, Table 1, entry 5). It is noteworthy that none of these reaction conditions enabled us to perform the nucleophilic trifluoromethylation of *O,O'*-dibenzyl-protected bis-Weinreb amide derived from L-tartaric acid.

Table 1. Attempts for the Nucleophilic Trifluoromethylation of Bis-Weinreb Amide 1.^a

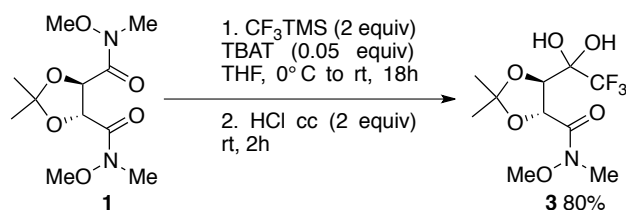


entry	source of fluoride	solvent	yield (%)	
			2	3
1	CsF	THF	51 ^b	5
2	CsF ^c	toluene	40 ^b	traces
3	TBAF or TMAF ^d	THF	- ^e	- ^e
4	TBAT	THF	62 ^b	10
5 ^f	TBAT	THF	84 ^b	4

^aReaction conditions: CF_3TMS (1 equiv), fluoride (0.05 equiv), 0°C to rt ^bDiastereomeric ratio (*dr*) of **2** determined by ^{19}F NMR of the crude reaction mixture: 70:30 (entry 1), 84:16 (entry 2), 99:1 (entries 4 and 5). ^c0.2 equiv. ^d0.05 equiv or 0.2 equiv of anhydrous TBAF in THF solution or TBAF·3H₂O or TMAF. ^eA complex mixture was obtained according to the ^{19}F NMR spectrum of the crude reaction mixture. ^f2 equiv of CF_3TMS were used.

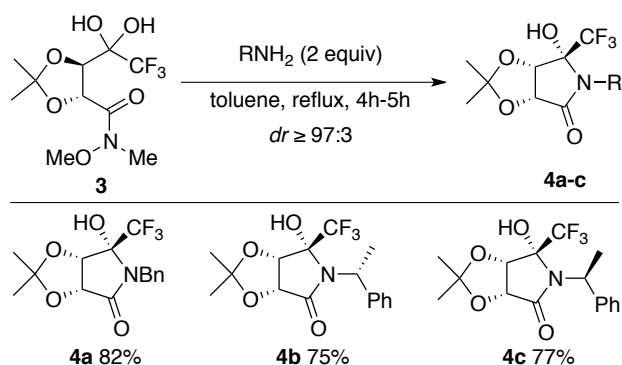
Having found the optimized reaction conditions for the mono trifluoromethylation of bis-Weinreb amide **1**, this reaction step was followed by an *in situ* acidic treatment to cleave the silylated hemiaminal **2** and to give the corresponding ketone by elimination of the amino substituent. The hydrated ketone **3** was thus isolated in 80% yield and its structure was confirmed by single crystal X-ray analysis (Scheme 2). All our attempts to isolate the non-hydrated form of the ketone **3** were unsuccessful.^{11,12}

Scheme 2: Synthesis of Hydrated Ketone **3** from Bis-Weinreb Amide **1**.



We were then pleasantly surprised to observe that the treatment of the hydrated ketone **3** with 2 equiv of benzylamine at reflux of toluene for 4h led only to the chiral cyclic hemiaminal **4a**. X-ray analysis of a single crystal of **4a** highlighted an unexpected *cis* protected diol motif.¹³ Cyclic hemiaminal **4a** was formed with an excellent diastereocontrol ($dr = 97:3$ for the formation of the new stereocenter bearing the trifluoromethyl group according to the ^{19}F NMR spectrum of the crude reaction mixture), and was isolated as a single diastereomer in 82% yield (Table 2). Reaction of hydrated ketone **3** with chiral amines occurred also with an excellent diastereoselectivity ($dr = 99:1$ according to the ^{19}F NMR spectra of the crude reaction mixtures). The enantiopure cyclic hemiaminals **4b-c** were thus isolated in similar good yields (75% and 77% respectively) (Table 2). The epimerisation of the carbon in β -position of the trifluoromethyl substituent was unequivocally supported by X-ray diffraction analysis of cyclic hemiaminal **4b**, *N*-substituted by a chiral auxiliary. Thus we have found an original and straightforward route towards enantiopure α -trifluoromethylated *N,O*-acetals having a protected *cis*-diol moiety which allows to circumvent the “*meso*-imide problem”.¹⁴ Such *N,O*-acetals could not have been conventionally obtained by nucleophilic trifluoromethylation of imides^{7b-d,15} from *meso*-tartaric acid as it is optically inactive.

Table 2. Reaction of Chiral Hydrated Ketone **3 with Benzylamine and its Derivatives.**



The formation of cyclic hemiaminals **4a-c** from hydrated ketone **3** involves at least four successive reactions and an excellent diastereofacial control for two of them. A possible reaction mechanism first requires the dehydration of **3** into the corresponding ketone at reflux of toluene.¹³ The deprotonation of the acidic proton in α -position to the trifluoromethyl ketone¹¹ by amine followed by the reprotonation of the formed enolate from the least hindered upper *re*-face leads to the epimerization of the carbon in β -position from the trifluoromethyl group. Formation of the new stereocenter bearing the trifluoromethyl group would imply the highly diastereoselective addition of aza-nucleophile on the epimerized trifluoromethyl ketone. The aza nucleophile could be the benzyl amine (intermolecular reaction) or the benzyl amide resulting from the transamidation of Weinreb amide¹⁶ (intramolecular reaction).¹⁷ According to the stereochemical outcome of the reaction, regardless the nucleophile, addition to the trifluoromethyl ketone would happen *via* the Felkin-Anh transition state **TS-2**,^{18,19} as shown in Figure 1. Cyclization towards hemiaminals **4a-c** is made possible thanks to the *syn* stereochemical relationship of the acetonide-protected diol.

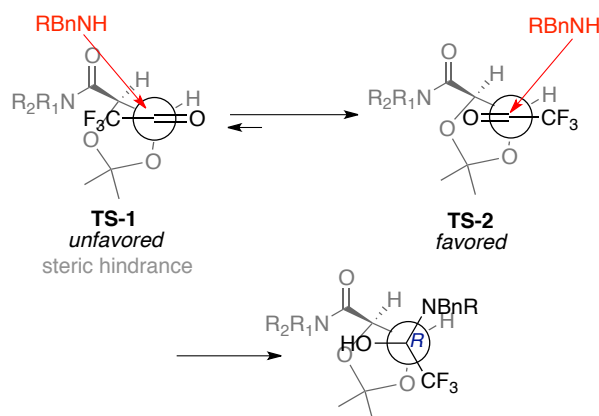
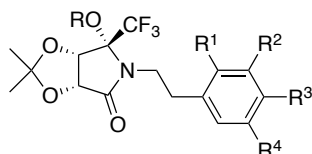
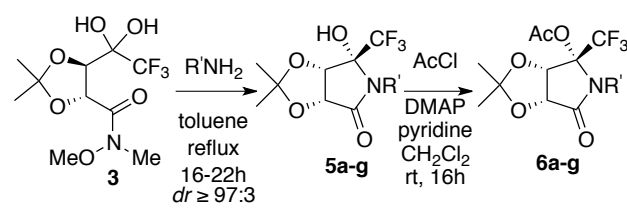


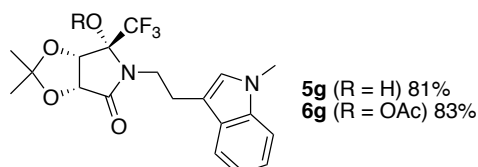
Figure 1. Felkin-Anh Model for the Diastereoselective Nucleophilic Addition of Aza-Nucleophile on the α -Trifluoromethyl Ketone Function.

Having developed a short and highly efficient synthesis of enantiopure α -trifluoromethylated *N,O*-acetals having a *cis*-diol motif, we envisaged to use this reaction sequence to prepare original *N*-acyliminium ions precursors allowing to study diastereoselective Pictet-Spengler cyclization. The required starting *N,O*-acetals **5a-g** were easily prepared by reacting the hydrated ketone **3** with 2 equiv of variously substituted phenethylamines or the 1-methyltryptamine at reflux of toluene (Table 3). As α -trifluoromethyl *N*-acyliminium ions are known to be difficult to generate,⁷ especially under mild reaction conditions suitable with the acetonide protecting group, *O*-acetyl-*N,O*-acetals **6a-g** containing a better leaving group^{7d} were then prepared from the enantiopure **5a-g** using standard reaction conditions (Table 3).

Table 3. Preparation of Enantiopure Cyclic α -Trifluoromethyl *N,O*-Acetals **5a-g and *O*-Acetyl-*N,O*-Acetals **6a-g**.**



$R^1, R^2 = H, R^3, R^4 = OMe$	5a ($R = H$) 82%	6a ($R = OAc$) 96%
$R^1, R^2, R^4 = H, R^3 = OMe$	5b ($R = H$) 82%	6b ($R = OAc$) 83%
$R^1, R^2, R^3, R^4 = H$	5c ($R = H$) 84%	6c ($R = OAc$) 73%
$R^1, R^2, R^4 = H, R^3 = Cl$	5d ($R = H$) 71%	6d ($R = OAc$) 98%
$R^1, R^2, R^4 = H, R^3 = F$	5e ($R = H$) 76%	6e ($R = OAc$) 89%
$R^1, R^3 = Cl, R^2, R^4 = H$	5f ($R = H$) 70%	6f ($R = OAc$) 86%

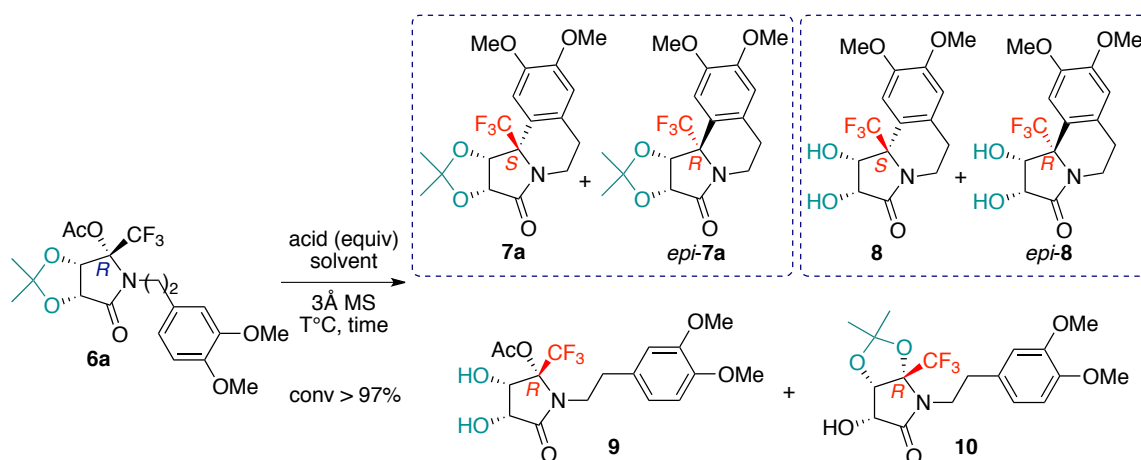


The experimental conditions for the cyclization were optimized on 0.20-0.25 mmol of the *O*-acetyl *N,O*-acetal **6a**, substituted with the electron-rich 3,4-dimethoxyphenyl group. Our results are summarized in Table 4. $BF_3 \cdot Et_2O$ was first evaluated to promote this reaction as it has already been used for the *in situ* generation of α - CF_3 *N*-acyliminium ion derived from L-tartaric acid at room temperature.^{7d} Such reaction conditions have been reported several times to be compatible with the acid-labile acetonide protecting group.¹ The reaction of *O*-acetyl *N,O*-acetal **6a** with 3 equiv of $BF_3 \cdot Et_2O$ in dichloromethane at room temperature was very sluggish, full conversion of **6a** was obtained after 28h (Table 4, entry 1). Examination of the ^{19}F NMR spectrum of the crude reaction mixture showed the presence of the two diastereomers of the Pictet-Spengler product **7a** and *epi*-**7a** in only 21% amount. The structure of **7a** was determined by single crystal X-ray crystallography. Deprotection of the acetonide occurred during the prolonged reaction time leading to the Pictet-Spengler products **8**²⁰ and *epi*-**8**²⁰ (23%) and the

O-acetyl *N,O*-acetal **9** (28%). While both diastereomers of the protected Pictet-Spengler product **7a** and *epi*-**7a** can be easily separated by chromatography on silica gel, deprotected diastereomers **8** and *epi*-**8** are unfortunately unseparable forcing us to find some reaction conditions avoiding the cleavage of the protecting group. In order to reduce the reaction time and thus the amount of deprotected products, the reaction was then performed with 10 equiv of Lewis acid (Table 4, entry 2). Under these conditions, full conversion of **6a** was obtained after only 4h of reaction. Cyclized products **7a** and *epi*-**7a** were the main products (80%), but the diastereoselectivity of the reaction was still very low (51:49 instead of 45:55, Table 4, entries 1-2). Performing the reaction at 0°C led, after 22h, to a complex mixture of compounds according to the ¹⁹F NMR spectrum (Table 4, entry 3). Pictet-Spengler products **7a**, *epi*-**7a**, **8** and *epi*-**8** were formed in only small amounts (20%) and with a similar poor diastereoselectivity. The obtention of the (*R,S,R*) diastereomer of the deprotected *O*-acetyl *N,O*-acetal **9**²¹ as main product suggests that the *N*-acyliminium ion is difficult to form from **6a** with BF₃.Et₂O at this temperature. The π-nucleophile cyclization was then performed with strong Brönsted acids (Table 4, entries 4-10). With 10 equiv of methanesulfonic acid in dichloromethane at room temperature, the cyclization products **7a**, *epi*-**7a**, **8** and *epi*-**8** were formed in good amounts, albeit in favour of the deprotected ones (23% of **7a** and *epi*-**7a**, 49% of **8** and *epi*-**8**), and with a better diastereoselectivity (78:22) after 6h of stirring (Table 4, entry 4). A non-negligeable amount of **10** (18%), for which the acetonide protecting group has migrated, was also formed.²² Performing the reaction at 0°C improved the amount of desired products **7a** and *epi*-**7a** (42%) but also of deprotected *O*-acetyl *N,O*-acetal **9** (34%) (Table 4, entry 5). Despite the good diastereoselectivities observed for the cyclization reaction with methanesulfonic acid (Table 4, entries 4-5), the significant amounts of deprotected products **8** and/or **9** and of alcohol **10** formed during the reaction course led us to evaluate a stronger Brönsted acid, the trifluoromethanesulfonic acid (Table 4, entries 6-10). The reaction of *O*-

acetyl *N,O*-acetal **6a** with 3 equiv of triflic acid in dichloromethane at 0°C was very sluggish (Table 4, entry 6). The long reaction time (29h30) led to the formation of a complex mixture of compounds according to the ¹⁹F NMR spectrum. The Pictet-Spengler cyclized products **7a** and *epi*-**7a** were formed in only 38% amount albeit in good diastereoselectivity (74:26 in favor of **7a**) with only traces of deprotected derivatives **8** and *epi*-**8** (5%). Other products having been identified were the deprotected *O*-acetyl *N,O*-acetal **9** (32%) and the alcohol **10** (23%). Changing dichloromethane for 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),²³ a very suitable solvent to carry out reactions involving short-lived carbocations, considerably shortened the reaction time (Table 4, entry 7). Full conversion of **6a** was achieved in only 1h20 instead of more than 29h (Table 4, entries 6-7). The crude reaction mixture contained almost only the protected products **7a** and *epi*-**7a** (83%) and the deprotected ones **8** and *epi*-**8** (13%) with a global 73:27 facial diastereoselectivity for the cyclization reaction. Using more equivalents of triflic acid (10 equiv) reduced dramatically the reaction time to only 10 min while maintaining the high amount of protected cyclized products **7a** and *epi*-**7a** (86%) and the diastereoselectivity (75:25) (Table 4, entry 8). Finally, performing the reaction at lower temperature (-10°C) in a 1:1 mixture of dichloromethane and HFIP neither increased the amount of **7a** and *epi*-**7a** nor the diastereoselectivity (Table 4, entry 9). The best conditions found for this Pictet-Spengler cyclization, 10 equiv of trifluoromethanesulfonic acid in HFIP at 0°C, were then applied to 1.5 mmol of *O*-acetyl *N,O*-acetal **6a** (Table 4, entry 10). After 10 min of reaction, the diastereomers of the protected cyclized products **7a** and *epi*-**7a** were formed in an amount of 97% as a 77:23 mixture. After purification by chromatography on silica gel, the major **7a** was isolated in 60% yield and the minor *epi*-**7a** in 21% yield (Table 4, entry 10 and Table 5).

Table 4. Screening of Reaction Conditions for the Pictet-Spengler cyclization reaction of the *O*-Acetyl *N,O*-Acetal **6a Substituted with an Electron Rich Phenyl Group.^a**



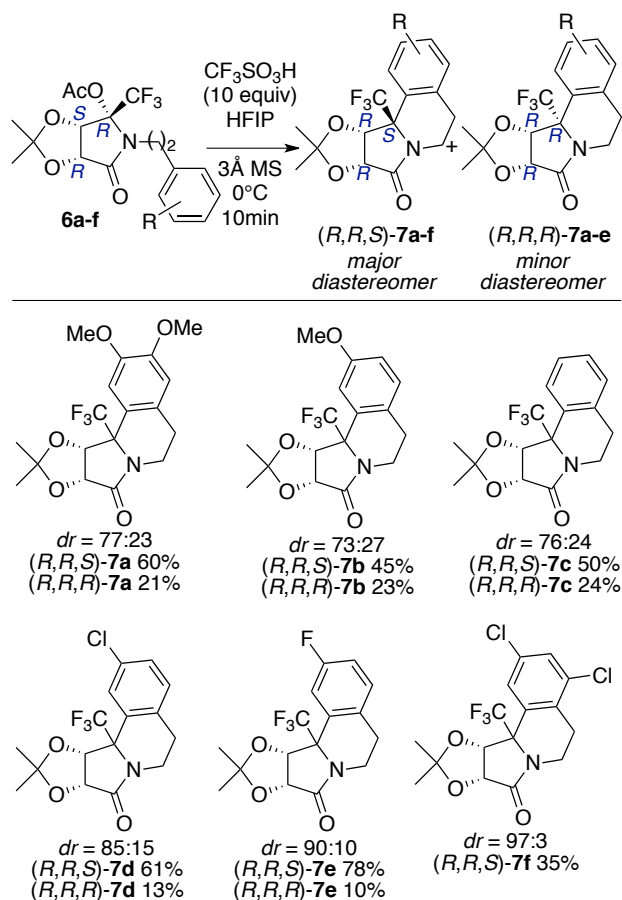
ent.	acid (equiv)	solvent	T(°C)	time	7a + <i>epi</i> - 7a (%) (<i>dr</i>) ^b	8 + <i>epi</i> - 8 (%) (<i>dr</i>) ^b	<i>dr</i> ^b (7a + 8): <i>epi</i> -(7a + 8)	9 (%) ^b	10 (%) ^b
1	BF ₃ .Et ₂ O (3)	CH ₂ Cl ₂	rt	28h	21 (71:29)	23 (22:78)	45:55	28 ^c	-
2	BF ₃ .Et ₂ O (10)	CH ₂ Cl ₂	rt	4h	80 (52:48)	2 (0:100)	51:49	4	-
3	BF ₃ .Et ₂ O (10)	CH ₂ Cl ₂	0°C	22h	6 (100:0)	14 (37:63)	57:43	34 ^c	1
4	MeSO ₃ H (10)	CH ₂ Cl ₂	rt	6h	23 (100:0)	49 (68:32)	78:22	6	18
5	MeSO ₃ H (10)	CH ₂ Cl ₂	0°C	6h30	42 (89:11)	4 (27:73)	83:17	34 ^c	11
6	CF ₃ SO ₃ H (3)	CH ₂ Cl ₂	0°C	29h30	38 (74:26)	5 (18:82)	67:33	32 ^c	23
7	CF ₃ SO ₃ H (3)	HFIP	0°C	1h20	83 (79:21)	13 (32:68)	73:27	3	-
8	CF ₃ SO ₃ H (10)	HFIP	0°C	10 min	86 (75:25)	8 (26:74)	71:29	1	2
9	CF ₃ SO ₃ H (10)	HFIP:CH ₂ Cl ₂ (1:1)	-10°C	18 min	82 (74:26)	2 (18:82)	73:27	3	4
10 ^d	CF ₃ SO ₃ H (10)	HFIP	0°C	10 min	97 (77:23)	1 (0:100)	76:24	<1	1

^aReaction performed on 0.20-0.25 mmol scale, except for entry 10. ^bPercentage of products and diastereomeric ratios (*dr*) determined by ¹⁹F NMR (470MHz, CDCl₃) of the crude reaction mixture: δ (ppm) -67.0 (br s) *epi*-**7a**, -68.7 (s) *epi*-**8**, -71.9 (s) **8**, -74.1 (s) **7a**, -77.8 (s) **10**, -78.4 (s) **6a**, -80.2 (s) **9** major, -80.6 (s) **9** minor. ^cDiastereomeric ratios (*dr* *R*:*S*) for **9**: 95:5 (entry 1), 93:7 (entry 3), 89:11 (entry 5), 91:9 (entry 6). ^dReaction performed on 1.5 mmol scale (100% conversion), both diastereomers were separated by chromatography on silica gel (major **7a**: 60% yield, minor *epi*-**7a**: 21% yield, see Table 5).

Having identified the optimized reaction conditions for the intramolecular Pictet-Spengler cyclization (10 equiv of triflic acid in HFIP, 0°C for 10 min), an overview of the scope and limitations of the substituted aryl group was investigated. As shown in Table 5, electron-enriched as well as electron-poor phenyl group are tolerated. In all cases, both diastereomers were separated by chromatography on silica gel. Electron-enriched phenyl ring substituted with *para*-methoxy group led cleanly to the diastereomeric cyclized products **7b** and *epi*-**7b** as a 73:27 mixture. Pictet-Spengler products **7c** and *epi*-**7c**, from the cyclization of the phenyl group, were obtained with a similar diastereoselection.²⁴ Electron-poor *para*-chloro and *para*-fluorophenethylamine were also effective to cyclize leading to the Pictet-Spengler products **7d**/*epi*-**7c** and **7e**/*epi*-**7e** with a better diastereoselectivity (85:15 and 90:10 respectively). 2,4-Dichlorophenyl unfortunately led to a complex mixture containing only 52% of Pictet-Spengler products **7f**/*epi*-**7f** (according to the ¹⁹F NMR spectrum of the crude reaction mixture) albeit in an excellent diastereoselectivity of 97:3. The major diastereomer **7f** was thus isolated in 35% yield. Hemiaminal **11** resulting from the nucleophilic addition of HFIP²³ on the highly reactive α -CF₃ *N*-acyliminium ion was also formed in 17% amount during the reaction course and was isolated in 12% yield (the structure of **11** was confirmed by 2D NOESY and ¹⁹F-¹H-HOESY experiments) (Figure 2). Unfortunately, treatment of the *O*-acetyl *N,O*-acetal **6g** containing an *N*-methylindole ring under this strong acidic conditions led only to a very complex mixture from which Pictet-Spengler products could not be identified.

The major diastereomers **7a** and **7f** obtained for the Pictet-Spengler cyclization of **6a** and **6f** were unambiguously established by X-ray crystallography to have the *S* configuration for the newly formed stereogenic center. Similar trends in the ¹⁹F chemical shifts observed for the major diastereomer **7a-f** (s, -73.6-74.1 ppm) and for the minor diastereomer *epi*-**7a-f** (br s,²⁵ -66.1-67.0 ppm) of all Pictet-Spengler products allowed the assignment of the same stereochemistry.

Table 5. Pictet-Spengler cyclization of *O*-Acetyl *N,O*-Acetals **6a-f with Triflic Acid in HFIP.^{a,b}**



^aReaction performed on 1.54 mmol of **6a** and 0.45-0.53 mmol scale for **6b-f**. ^bDiastereomeric ratios (*dr*) determined by ^{19}F NMR of the crude reaction mixture.

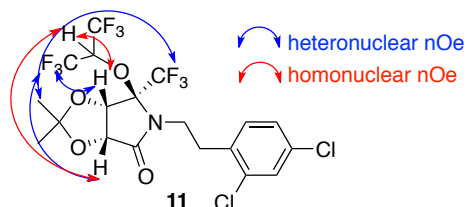


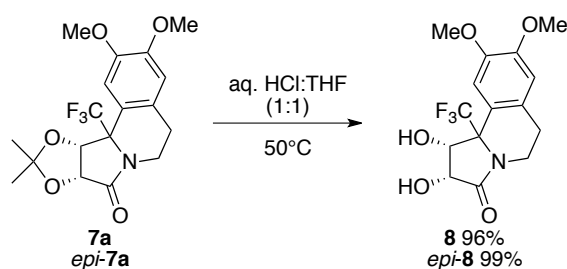
Figure 2. NOE Connectivities on *N,O*-Acetal **11.**

The preferential formation of the *S* stereocenter during the Pictet-Spengler cyclization implies that the favoured approach of the aromatic ring towards the electrophilic carbon of the

α -trifluoromethyl *N*-acyliminium ion is from the same side of the acetonide protecting group, the most hindered face (*syn* selective addition). Surprising at first sight, these results can be rationalized on the basis of the computational studies reported recently by Pyne and co-workers on the intermolecular *syn* addition of indoles on β -methoxy α -cyclopropyl *N*-acyliminium ion derived from L-lactic acid.²⁶ By analogy with their observations, we postulate that transition-state where the bulky²⁷ and highly electronwithdrawing trifluoromethyl group is forced towards the *O*-protected substituent leading to the *anti* intramolecular addition of the aromatic ring is less stable than transition-state where the fluorinated substituent is furthest from the acetonide group leading to the *syn*-addition product.

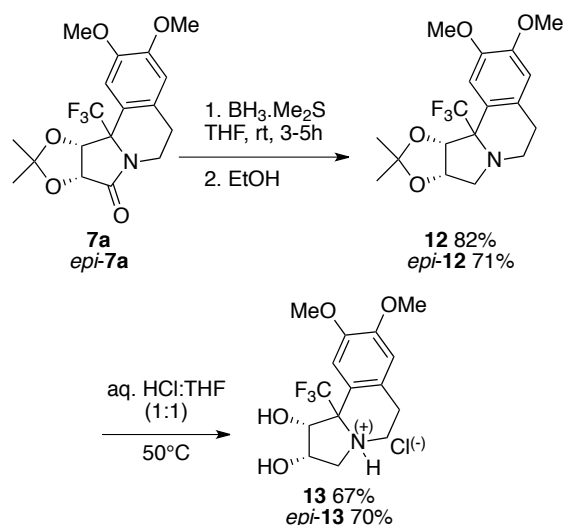
Deprotection of the acetonide protecting group of Pictet-Spengler products **7a** and *epi*-**7a** was performed under treatment with a 1:1 mixture of aq. HCl in THF at 50°C (Scheme 3). Deprotected derivatives **8** and *epi*-**8** were isolated in 96% and 99% yields, respectively.

Scheme 3. Deprotection of Acetonide Protecting Groups of Pictet-Spengler Products **7a** and *epi*-**7a**.



Reduction of the amide function of both diastereomers **7a** and *epi*-**7a** of the protected polycyclic derivative under standard conditions^{7a} gave the amines **12** and *epi*-**12** in 82% and 71% yields, respectively (Scheme 4). The acetonide protecting group of amines **12** and *epi*-**12** is then removed under acidic treatment to give the original, enantiopure alkaloid-like trifluoromethyl derivatives **13** and *epi*-**13** having a *cis*-diol moiety.

Scheme 4. Towards Alkaloid-Like Trifluoromethyl Aza-Derivatives **13** and *epi*-**13**.



Conclusion

We have shown that the nucleophilic trifluoromethylation of a well-known bis-Weinreb amide derived from L-tartaric acid, having the natural *trans*-diol motif protected by an acetonide group, followed by an acidic treatment gave the corresponding mono-amide mono-trifluoromethylketone analogue. Treatment of this compound with a primary amine at reflux of toluene led surprisingly to the clean formation of a chiral cyclic α -trifluoromethylated *N,O*-acetal having a *cis*-diol moiety. This reaction sequence enabled to circumvent the “*meso*-imide problem”.

Despite that highly electrophilic α -trifluoromethylated *N*-acyliminium ions are difficult to generate from the corresponding fluorinated *N,O*-acetals,⁷ an excess of triflic acid in HFIP allowed to perform intramolecular Pictet-Spengler cyclizations with α -trifluoromethylated *O*-acetyl *N,O*-acetals *N*-substituted with phenethyl amine derivatives at 0°C in less than 10 min. Formation of the tetrasubstituted stereocenter bearing the trifluoromethyl group occurred in good to very good diastereoselectivities in favor to the *syn*-addition product. As electron-rich

as well as electron-deficient phenyl rings were tolerated, various original, enantiopure trifluoromethylated fused aza-polycyclic scaffolds were thereby obtained.

Experimental section

THF, toluene and CH₂Cl₂ were dried using a Pure Solv solvent drying system over aluminum oxide under an Argon atmosphere. HFIP was dried over molecular sieves 3Å. CF₃SiMe₃ was distilled under Ar and TBAT was recrystallized from EtOAc prior to use. Molecular Sieves were activated by heating at 200°C under vacuum for at least 6 hours and were stored in a vacuum oven at 70°C. Thin-layer chromatography using precoated aluminum backed plates (Merck Kieselgel 60F254) were visualized by UV light and/or by phosphomolybdic acid, potassium permanganate or ninhydrine solutions. Silicagel 40-63 µm (Macherey-Nagel GmbH & Co KG) was used for flash chromatography. NMR spectra were recorded in CDCl₃ with 250, 500, or 600 MHz spectrometers. Chemical shifts (δ) were reported in ppm relative to TMS for ¹H and ¹³C{¹H} NMR spectra and to CFC1₃ for ¹⁹F NMR spectra. In the ¹³C{¹H} NMR data (J-MOD or DEPT-Q), reported signal multiplicities are related to C-F coupling. The following abbreviations were used to indicate the multiplicities: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), hept (heptuplet), m (multiplet). Diastereomeric ratios (*dr*) were determined by ¹⁹F NMR. HRMS were recorded on an ESI-Q-TOF mass spectrometer using an electrospray source in positive mode. Optical rotations were measured at room temperature (c.a. 20 °C).

(4R,5R)-N-methoxy-N,2,2-trimethyl-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)-1,3-dioxolane-4-carboxamide 3. CF₃SiMe₃ (3.25 mL, 21.2 mmol, 2 equiv) was added dropwise, at 0°C and under Ar, to a solution of bis-Weinreb amide **1**²⁸ (3.03 g, 10 mmol) and TBAT (270 mg, 0.5 mmol, 0.05 equiv) in THF (50 mL). After 20 min of stirring at 0°C and 18h at rt, the reaction mixture was hydrolyzed with HCl 12M aq. sol. (450 µL, 5.40 mmol, 2 equiv) for 2h. The

reaction mixture was diluted with EtOAc. The organic layer was washed with a sat. aq. sol. of NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (PE/EtOAc 3:2) afforded hydrated α -trifluoromethyl ketone **3** (2.69 g, 80%) as a white amorphous solid : $[\alpha]_D^{20} = -31$ (*c* 1.01, MeOH); IR (KBr) ν_{\max} 725, 845, 1073, 1259, 1377, 1504, 1641, 2954, 2998, 3218, 3429 cm⁻¹; ¹⁹F NMR (470 MHz, CD₃OCD₃) δ -83.7 (s, 3F) ; ¹H NMR (500 MHz, CD₃OCD₃) δ 6.42 (br s, 1H), 6.03 (s, 1H), 5.12 (br s, 1H), 4.84 (d, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.19 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H); ¹³C {¹H} NMR (125.7 MHz, CD₃OCD₃) δ 170.4, 124.3 (q, *J* = 288.5 Hz), 112.9, 92.9 (q, *J* = 31.0 Hz), 78.4, 73.1, 62.3, 32.4, 26.9, 26.6; HRMS (ESI⁺) *m/z* calcd for C₁₀H₁₆F₃NNaO₆ [M+Na]⁺ 326.0827, found 326.0816. An analytical sample of **3** was crystallized from Et₂O/hexane.

General procedure for the synthesis of cyclic *N,O*-acetal **4a-c and **5a-g** from hydrated ketone **3**.** *General Procedure A.* A solution of hydrated ketone **3** and amine (2 equiv) was heated at reflux of toluene with a heating mantle. After completion of the reaction (monitored by ¹⁹F NMR), the solution was cooled to rt and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel afforded *N,O*-acetals **4a-c** and **5a-g**.

(3*aR*,6*R*,6*aS*)-5-benzyl-6-hydroxy-2,2-dimethyl-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **4a**. According to General Procedure A, hydrated ketone **3** (207 mg, 0.68 mmol) reacted with benzylamine (150 μ L, 1.37 mmol, 2 equiv) at reflux of toluene (5 mL) for 5h. Purification on silica gel (PE/EtOAc 5 :1) afforded *N,O*-acetal **4a** (182 mg, 82%) as a pale yellow amorphous solid : $[\alpha]_D^{20} = -58$ (*c* 1.00, MeOH); IR (KBr) ν_{\max} 608, 707, 937, 1109, 1179, 1409, 1499, 1706, 2939, 2996, 3314 cm⁻¹; ¹⁹F NMR (235.5 MHz, CDCl₃) δ -81.0 (s, 3F) ; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.30-7.21 (m, 3H), 4.81 (d, *J* = 6.0 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 4.44 (d, *J* = 15.0 Hz,

1H), 4.14 (br s, 1H), 1.42 (s, 3H), 1.30 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.5, 136.6, 128.41, 128.39, 127.6, 122.9 (q, J = 286.0 Hz), 114.9, 86.8 (q, J = 32.5 Hz), 76.8, 73.9, 44.1, 26.9, 26.3; HRMS (ESI^+) m/z calcd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 354.0929, found 354.0922. An analytical sample of **4a** was crystallized from $\text{Et}_2\text{O}/\text{PE}$.

(3*aR*,6*R*,6*aS*)-6-hydroxy-2,2-dimethyl-5-((*R*)-1-phenylethyl)-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **4b**. According to General Procedure A, hydrated ketone **3** (252 mg, 0.83 mmol) reacted with (*R*)-(+)- α -methylbenzylamine (211 μL , 1.66 mmol, 2 equiv) at reflux of toluene (8 mL) for 4h. Purification on silica gel (PE/EtOAc 4 :1) afforded *N,O*-acetal **4b** (217 mg, 75%) as a white amorphous solid : $[\alpha]_{\text{D}}^{20}$ = -105 (c 1.01, MeOH); IR (KBr) ν_{max} 510, 704, 931, 1109, 1179, 1418, 1700, 3001, 3377 cm^{-1} ; ^{19}F NMR (235.5 MHz, CDCl_3) δ -81.0 (s, 3F) ; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.0 Hz, 2H), 7.22 (m, 1H), 4.84 (q, J = 6.5 Hz, 1H), 4.73 (d, J = 5.5 Hz, 1H), 4.71 (d, J = 5.5 Hz, 1H), 4.38 (br s, 1H), 1.80 (d, J = 7.0 Hz, 3H), 1.53 (s, 3H), 1.48 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.7, 140.1, 128.3, 127.3, 122.8 (q, J = 285.5 Hz), 114.8, 86.8 (q, J = 32.5 Hz), 76.8, 73.8, 53.1, 27.5, 26.6, 19.8; HRMS (ESI^+) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 368.1086, found 368.1070. An analytical sample of **4b** was crystallized from $\text{CH}_2\text{Cl}_2:\text{PE}$.

(3*aR*,6*R*,6*aS*)-6-hydroxy-2,2-dimethyl-5-((*S*)-1-phenylethyl)-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **4c**. According to General Procedure A, hydrated ketone **3** (206 mg, 0.68 mmol) reacted with (*S*)-(-)- α -methylbenzylamine (171 μL , 1.36 mmol, 2 equiv) at reflux of toluene (5 mL) for 5h. Purification on silica gel (PE/EtOAc 4 :1) afforded *N,O*-acetal **4c** (179 mg, 77%) as a white amorphous solid : $[\alpha]_{\text{D}}^{20}$ = -60 (c 1.01, MeOH); IR (KBr) ν_{max} 700, 989, 1108, 1170, 1420, 1709, 2996, 3398 cm^{-1} ; ^{19}F NMR (235.5 MHz, CDCl_3) δ -81.6 (s, 3F) ; ^1H NMR (500 MHz, CDCl_3) δ 7.56 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.23 (m, 1H), 4.75 (q, J = 7.5 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.21 (br s, 1H), 1.85 (d, J = 7.5 Hz), 1.37 (s, 3H), 1.01 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3)

δ 169.8, 139.9, 128.20, 128.19, 127.7, 123.1 (q, J = 285.5 Hz), 114.6, 86.6 (q, J = 32.5 Hz), 77.0, 73.8 (q, J = 1.0 Hz), 53.0, 26.8, 26.7, 16.3; HRMS (ESI⁺) m/z calcd for C₁₆H₁₈F₃NNaO₄ [M+Na]⁺ 368.1086, found 368.1086.

(3aR,6R,6aS)-5-(3,4-dimethoxyphenethyl)-6-hydroxy-2,2-dimethyl-6-(trifluoromethyl)

dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4(5H)-one 5a. According to General Procedure A, hydrated ketone **3** (5.88 g, 19.4 mmol) reacted with (3,4-dimethoxyphenyl)ethylamine (6.55 mL, 38.8 mmol, 2 equiv) at reflux of toluene (140 mL) for 22h. Purification on silica gel (PE/EtOAc 2 :1) afforded *N,O*-acetal **5a** (6.49 g, 82%) as a white amorphous solid : $[\alpha]_D^{20} = +5$ (c 1.00, CHCl₃); IR (film) ν_{\max} 614, 755, 939, 1107, 1179, 1444, 1698, 2946, 2994, 3414 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F) ; ¹H NMR (600 MHz, CDCl₃) δ 6.80-6.75 (m, 3H), 4.77 (d, J = 6.0 Hz, 1H), 4.70 (d, J = 6.0 Hz), 4.00 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.65 (ddd, J = 14.0 Hz, J = 11.0 Hz, J = 5.0 Hz, 1H), 3.46 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 6.0 Hz, 1H), 2.96 (ddd, J = 13.0 Hz, J = 11.0 Hz, J = 6.0 Hz, 1H), 2.83 (ddd, J = 13.0 Hz, J = 10.5 Hz, J = 5.0 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H); ¹³C {¹H} NMR (150.9 MHz, CDCl₃) δ 170.4, 149.0, 147.8, 130.9, 123.0 (q, J = 285.5 Hz), 120.9, 115.1, 112.0, 111.2, 86.4 (q, J = 32.5 Hz), 76.8, 73.7, 56.00, 55.98, 42.6, 33.7, 27.1, 26.3; HRMS (ESI⁺) m/z calcd for C₁₈H₂₂F₃NNaO₆ [M+Na]⁺ 428.1297, found 428.1284. An analytical sample of **5a** was crystallized from Et₂O/hexane.

(3aR,6R,6aS)-6-hydroxy-5-(4-methoxyphenethyl)-2,2-dimethyl-6-(trifluoromethyl)

dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4(5H)-one 5b. According to General Procedure A, hydrated ketone **3** (1.51 g, 5.0 mmol) reacted with (4-methoxyphenyl)ethylamine (1.45 mL, 9.9 mmol, 2 equiv) at reflux of toluene (30 mL) for 23h. Purification on silica gel (PE/Et₂O 2 :1) afforded *N,O*-acetal **5b** (1.53 g, 82%) as a pale yellow amorphous solid : $[\alpha]_D^{20} = +12$ (c 1.00, CHCl₃); IR (film) ν_{\max} 629, 770, 979, 1105, 1179, 1405, 1701, 2840, 2961, 2994, 3385 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F) ; ¹H NMR (500 MHz, CDCl₃) δ 7.16 (d, J = 8.5

Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 4.76 (d, $J = 6.0$ Hz, 1H), 4.69 (d, $J = 6.0$ Hz, 1H), 3.90 (s, 1H), 3.78 (s, 3H), 3.64 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 5.0$ Hz, 1H), 3.43 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H), 2.97 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H), 2.83 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 5.0$ Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.4, 158.5, 130.5, 130.0, 123.0 (q, $J = 285.5$ Hz), 115.0, 114.1, 86.4 (q, $J = 32.5$ Hz), 76.8, 73.7, 55.4, 42.7, 33.1, 27.1, 26.3; HRMS (ESI^+) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$ 398.1191, found 398.1191.

(3*aR*,6*R*,6*aS*)-6-hydroxy-2,2-dimethyl-5-phenethyl-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **5c**. According to General Procedure A, hydrated ketone **3** (1.01 g, 3.32 mmol) reacted with phenylethylamine (850 μL , 6.65 mmol, 2 equiv) at reflux of toluene (25 mL) for 16h. Purification on silica gel (PE/EtOAc 6 :1) afforded *N,O*-acetal **5c** (969 mg, 84%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = +9$ (c 1.00, CHCl_3); IR (film) ν_{max} 636, 744, 978, 1101, 1187, 1407, 1703, 2994, 3383 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -80.9 (s, 3F) ; ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.19 (m, 5H), 4.77 (d, $J = 6.0$ Hz, 1H), 4.71 (d, $J = 6.0$ Hz), 4.08 (br s, 1H), 3.69 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 5.0$ Hz, 1H), 3.48 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H), 3.05 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H), 2.90 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 5.0$ Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.4, 138.4, 129.0, 128.6, 126.7, 122.9 (q, $J = 285.5$ Hz), 115.0, 86.4 (q, $J = 32.5$ Hz), 76.7, 73.7, 42.5, 33.9, 27.0, 26.2; HRMS (ESI^+) m/z calcd for $\text{C}_{16}\text{H}_{19}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 346.1266, found 346.1265.

(3*aR*,6*R*,6*aS*)-5-(4-chlorophenethyl)-6-hydroxy-2,2-dimethyl-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **5d**. According to General Procedure A, hydrated ketone **3** (1.02 g, 3.36 mmol) reacted with 2-(4-chlorophenyl)ethylamine (934 μL , 6.72 mmol, 2 equiv) at reflux of toluene (30 mL) for 20h. Purification on silica gel (PE/EtOAc 6 :1) afforded *N,O*-acetal **5d** (910 mg, 71%) as a white amorphous solid; $[\alpha]_{\text{D}}^{20} = +8$ (c 1.02,

CHCl₃); IR (film) ν_{\max} 870, 977, 1105, 1186, 1407, 1721, 2989, 3342 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 4.76 (d, J = 6.0 Hz, 1H), 4.70 (d, J = 6.0 Hz, 1H), 4.04 (br s, 1H), 3.63 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 6.0 Hz, 1H), 3.44 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 6.0 Hz, 1H), 3.00 (ddd, J = 13.0 Hz, J = 10.5 Hz, J = 6.0 Hz, 1H), 2.85 (ddd, J = 13.0 Hz, J = 10.5 Hz, J = 5.0 Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 170.4, 136.9, 132.6, 130.4, 128.8, 123.0 (q, J = 285.5 Hz), 115.1, 86.4 (q, J = 32.5 Hz), 76.7, 73.7 (q, J = 1.0 Hz), 42.3, 33.3, 27.0, 26.2; HRMS (ESI⁺) m/z calcd for C₁₆H₁₈ClF₃NO₄ [M+H]⁺ 380.0876, found 380.0876.

(3*aR*,6*R*,6*aS*)-5-(4-fluorophenethyl)-6-hydroxy-2,2-dimethyl-6-(trifluoromethyl) dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4(5*H*)-one **5e**. According to General Procedure A, hydrated ketone **3** (963 mg, 3.18 mmol) reacted with 2-(4-fluorophenyl)ethylamine (833 μ L, 6.35 mmol, 2 equiv) at reflux of toluene (30 mL) for 20h. Purification on silica gel (PE/EtOAc 6 :1) afforded *N,O*-acetal **5e** (878 mg, 76%) as a yellow oil : $[\alpha]_{\text{D}}^{20}$ = +4 (*c* 0.99, CHCl₃); IR (film) ν_{\max} 730, 824, 978, 1109, 1159, 1190, 1511, 1710, 1719, 2940, 2992, 3342 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F), -116.4 (ddd, J = 14.0 Hz, J = 9.0 Hz, J = 5.5 Hz, 1F); ¹H NMR (500 MHz, CDCl₃) δ 7.19 (dd, J = 8.5 Hz, J = 5.5 Hz, 2H), 6.97 (t, J = 8.5 Hz, 1H), 4.76 (d, J = 6.0 Hz, 1H), 4.70 (d, J = 6.0 Hz, 1H), 4.07 (br s, 1H), 3.63 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 5.0 Hz, 1H), 3.44 (m, 1H), 3.00 (ddd, J = 13.0 Hz, J = 10.5 Hz, J = 6.5 Hz, 1H), 2.86 (ddd, J = 13.0 Hz, J = 10.5 Hz, J = 5.0 Hz, 1H), 1.45 (s, 6H); ¹³C NMR {¹H} (125.7 MHz, CDCl₃) δ 170.4, 161.8 (d, J = 244.5 Hz), 134.1 (d, J = 3.0 Hz), 130.5 (d, J = 8.0 Hz), 123.0 (q, J = 285.5 Hz), 115.5 (d, J = 21.0 Hz), 115.1, 86.4 (q, J = 32.5 Hz), 76.7, 73.7 (q, J = 1.0 Hz), 42.5, 33.2, 27.0, 26.2; HRMS (ESI⁺) m/z calcd for C₁₆H₁₈F₄NO₄ [M+H]⁺ 364.1172, found 364.1172.

(3*aR*,6*R*,6*aS*)-5-(2,4-dichlorophenethyl)-6-hydroxy-2,2-dimethyl-6-(trifluoromethyl)

dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4(5H)-one **5f**. According to General Procedure A, hydrated ketone **3** (1.05 g, 3.46 mmol) reacted with 2-(2,4-dichlorophenyl)ethylamine (842 μ L, 6.93 mmol, 2 equiv) at reflux of toluene (30 mL) for 20h. Purification on silica gel (PE/EtOAc 5:1) afforded *N,O*-acetal **5f** (1.00 g, 70%) as a white amorphous solid : $[\alpha]_{\text{D}}^{20} = +8$ (*c* 1.00, CHCl₃); IR (film) ν_{max} 730, 823, 976, 1106, 1167, 1718, 2987, 3355, 3664 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.06 (s, 1H), 3.64 (ddd, *J* = 14.0 Hz, *J* = 10.5 Hz, *J* = 5.5 Hz, 1H), 3.49 (ddd, *J* = 14.0 Hz, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 3.10 (ddd, *J* = 14.0 Hz, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 3.03 (ddd, *J* = 14.0 Hz, *J* = 10.5 Hz, *J* = 5.5 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H); ¹³C NMR {¹H} (125.7 MHz, CDCl₃) δ 170.5, 135.1, 134.8, 133.3, 132.0, 129.5, 127.3, 122.9 (q, *J* = 285.5 Hz), 115.2, 86.4 (q, *J* = 32.5 Hz), 76.7, 73.7 (q, *J* = 1.5 Hz), 40.3, 31.4, 27.1, 26.2; HRMS (ESI⁺) *m/z* calcd for C₁₆H₁₇Cl₂F₃NO₄ [M+H]⁺ 414.0487, found 414.0484.

(3aR,6R,6aS)-6-hydroxy-2,2-dimethyl-5-(2-(1-methyl-1H-indol-3-yl)ethyl)-6-(trifluoromethyl)dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4(5H)-one **5g**. According to General Procedure A, hydrated ketone **3** (1.00 g, 3.30 mmol) reacted with 1-methyltryptamine (1.12 g, 6.43 mmol, 1.95 equiv) at reflux of toluene (25 mL) for 19h. Purification on silica gel (PE/Et₂O 1:1) afforded *N,O*-acetal **5g** (1.06 g, 81%) as a beige amorphous solid : $[\alpha]_{\text{D}}^{20} = -1$ (*c* 0.98, CHCl₃); IR (film) ν_{max} 742, 1097, 1155, 1703, 2940, 3444 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -80.9 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.23 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 7.13 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 6.93 (s, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.09 (s, 1H), 3.74 (s, 3H), 3.73 (m, 1H), 3.56 (ddd, *J* = 14.0 Hz, *J* = 11.0 Hz, *J* = 6.0 Hz, 1H), 3.17-3.05 (m, 2H), 1.48 (s, 3H), 1.45 (s, 3H); ¹³C {¹H} NMR (125.7 MHz, CDCl₃) δ 170.5, 137.1, 127.8, 127.1, 123.0 (q, *J* = 285.5 Hz), 121.8, 119.21, 119.15, 115.1, 111.1, 109.3, 86.5 (q, *J* = 32.5 Hz), 76.9,

73.9, 41.8, 32.7, 27.2, 26.4, 23.9; HRMS (ESI⁺) *m/z* calcd for C₁₉H₂₂F₃N₂O₄ [M+H]⁺ 399.1532, found 399.1532.

General procedure for the preparation of *O*-acetyl-*N,O*-acetals **6a-g from **5a-g**. General**

Procedure B. A solution of α -trifluoromethylated *N,O*-acetal **5a-g**, pyridine, acetic anhydride and DMAP in dichloromethane was stirred at rt under Ar. After the complete conversion of starting *N,O*-acetal **5a-g**, the reaction was quenched with an aq. sol. of hydrochloric acid (10% vol.) and extracted twice with CH₂Cl₂. The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel afforded *N,O*-acetals **6a-g**.

(3*aS*,4*R*,6*aR*)-5-(3,4-dimethoxyphenethyl)-2,2-dimethyl-6-oxo-4-(trifluoromethyl) tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4-yl acetate **6a**. According to General Procedure B, a solution of *N,O*-acetal **5a** (285 mg, 0.70 mmol), pyridine (90 μ L, 1.11 mmol, 1.58 equiv), acetic anhydride (115 μ L, 1.21 mmol, 1.73 equiv) and DMAP (9 mg, 0.07 mmol, 0.1 equiv) in CH₂Cl₂ (5 mL) was stirred 16h. Purification on silica gel (PE/EtOAc 4:1) afforded *O*-acetyl-*N,O*-acetal **6a** (304 mg, 96%) as a colorless oil : [α]_D²⁰ = +16 (*c* 1.00, CHCl₃); IR (film) ν_{max} 1154, 1191, 1236, 1515, 1733, 1778, 2941 cm⁻¹; ¹⁹F NMR (CDCl₃, 470 MHz) δ -78.4 (s, 3F); ¹H NMR (CDCl₃, 500 MHz) δ 6.80-6.73 (m, 3H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.49 (td, *J* = 13.0 Hz, *J* = 5.0 Hz, 1H), 3.42 (ddd, *J* = 14.0 Hz, *J* = 11.5 Hz, *J* = 5.0 Hz, 1H), 2.96 (td, *J* = 12.0 Hz, *J* = 5.5 Hz, 1H), 2.77 (td, *J* = 12.0 Hz, *J* = 5.0 Hz, 1H), 2.14 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H); ¹³C {¹H} NMR (125.7 MHz, CDCl₃) δ 170.8, 166.6, 149.1, 147.9, 130.9, 122.3 (q, *J* = 288.5 Hz), 120.8, 114.9, 112.2, 111.4, 91.0 (q, *J* = 32.5 Hz), 76.3, 73.9, 56.02, 56.00, 44.0, 33.5, 26.2, 25.9, 21.4; HRMS (ESI⁺) *m/z* calcd for C₂₀H₂₄F₃NNaO₇ [M+Na]⁺ 470.1403, found 470.1414.

(3*aS*,4*R*,6*aR*)-5-(4-methoxyphenethyl)-2,2-dimethyl-6-oxo-4-(trifluoromethyl)

tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4-yl acetate **6b**. According to General Procedure B, a solution of *N,O*-acetal **5b** (1.13 g, 3.01 mmol), pyridine (380 μ L, 4.67 mmol, 1.55 equiv), acetic anhydride (500 μ L, 5.28 mmol, 1.75 equiv) and DMAP (37 mg, 0.30 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL) was stirred 23h. Purification on silica gel (PE/EtOAc 5:1) afforded *O*-acetyl-*N,O*-acetal **6b** (1.05 g, 83%) as a yellow oil : $[\alpha]_{\text{D}}^{20} = +46$ (*c* 1.00, CHCl_3); IR (film) ν_{max} 1193, 1513, 1733, 1778, 2942, 2993 cm^{-1} ; ^{19}F NMR (CDCl_3 , 470 MHz) δ -78.2 (s, 3F); ^1H NMR (CDCl_3 , 500 MHz) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.08 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 3.78 (s, 3H), 3.50-3.38 (m, 2H), 2.96 (ddd, *J* = 13.0 Hz, *J* = 10.5 Hz, *J* = 6.5 Hz, 1H), 2.79 (ddd, *J* = 13.0 Hz, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 2.14 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.8, 166.5, 158.5, 130.4, 129.9, 122.4 (q, *J* = 288.0 Hz), 114.8, 114.1, 91.0 (q, *J* = 32.5 Hz), 76.4, 73.9, 55.4, 44.0, 33.0, 26.3, 26.0, 21.4; HRMS (ESI⁺) *m/z* calcd for $\text{C}_{19}\text{H}_{22}\text{F}_3\text{NNaO}_6$ $[\text{M}+\text{Na}]^+$ 440.1297, found 440.1294.

(3*aS*,4*R*,6*aR*)-2,2-dimethyl-6-oxo-5-phenethyl-4-(trifluoromethyl)*tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolidin-4-yl acetate* **6c**. According to General Procedure B, a solution of *N,O*-acetal **5c** (670 mg, 1.94 mmol), pyridine (250 μ L, 3.01 mmol, 1.6 equiv), acetic anhydride (320 μ L, 3.38 mmol, 1.75 equiv) and DMAP (24 mg, 0.19 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL) was stirred 16h. Purification on silica gel (PE/EtOAc 9:1) afforded *O*-acetyl-*N,O*-acetal **6c** (547 mg, 73%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = +48$ (*c* 1.00, CHCl_3); IR (film) ν_{max} 1090, 1192, 1734, 1778, 2943, 2992 cm^{-1} ; ^{19}F NMR (CDCl_3 , 470 MHz) δ -78.2 (s, 3F); ^1H NMR (CDCl_3 , 500 MHz) δ 7.33-7.28 (m, 2H), 7.25-7.20 (m, 3H), 5.09 (d, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 3.55-3.43 (m, 2H), 3.04 (ddd, *J* = 13.0 Hz, *J* = 9.5 Hz, *J* = 7.5 Hz, 1H), 2.86 (ddd, *J* = 13.0 Hz, *J* = 9.5 Hz, *J* = 6.5 Hz, 1H), 2.13 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.8, 166.6, 138.4, 129.0, 128.7, 126.8, 122.5 (q, *J* = 290.0 Hz), 114.8, 91.0

(q, $J = 32.5$ Hz), 76.4, 74.0, 43.9, 33.9, 26.3, 26.0, 21.4; HRMS (ESI⁺) m/z calcd for C₁₈H₂₀F₃NNaO₅ [M+Na]⁺ 410.1191, found 410.1194.

(3*aS*,4*R*,6*aR*)-5-(4-chlorophenethyl)-2,2-dimethyl-6-oxo-4-(trifluoromethyl)tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4-yl acetate **6d**. According to General Procedure B, a solution of *N,O*-acetal **5d** (476 mg, 1.25 mmol), pyridine (156 μ L, 1.94 mmol, 1.55 equiv), acetic anhydride (220 μ L, 2.19 mmol, 1.75 equiv) and DMAP (15 mg, 0.13 mmol, 0.1 equiv) in CH₂Cl₂ (10 mL) was stirred 18h. Purification on silica gel (PE/EtOAc 7:1) afforded *O*-acetyl-*N,O*-acetal **6d** (517 mg, 98%) as a colorless oil; $[\alpha]_{\text{D}}^{20} = +49$ (c 0.99, CHCl₃); IR (film) ν_{max} 1089, 1193, 1736, 1779, 2942, 2991 cm⁻¹; ¹⁹F NMR (CDCl₃, 470 MHz) δ -78.3 (s, 3F); ¹H NMR (CDCl₃, 500 MHz) δ 7.25 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 5.07 (d, $J = 6.0$ Hz, 1H), 4.74 (d, $J = 6.0$ Hz, 1H), 3.50-3.38 (m, 2H), 3.00 (ddd, $J = 13.0$ Hz, $J = 10.0$ Hz, $J = 6.5$ Hz, 1H), 2.80 (ddd, $J = 13.0$ Hz, $J = 10.0$ Hz, $J = 6.0$ Hz, 1H), 2.11 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 170.8, 166.5, 136.8, 132.6, 130.3, 128.8, 122.4 (q, $J = 288.0$ Hz), 114.8, 90.9 (q, $J = 32.5$ Hz), 76.3, 73.9, 43.6, 33.2, 26.2, 25.9, 21.3; HRMS (ESI⁺) m/z calcd for C₁₈H₁₉ClF₃NNaO₅ [M+Na]⁺ 444.0802, found 444.0803.

(3*aS*,4*R*,6*aR*)-5-(4-fluorophenethyl)-2,2-dimethyl-6-oxo-4-(trifluoromethyl)tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4-yl acetate **6e**. According to General Procedure B, a solution of *N,O*-acetal **5e** (741 mg, 2.00 mmol), pyridine (250 μ L, 3.10 mmol, 1.55 equiv), acetic anhydride (357 μ L, 3.57 mmol, 1.75 equiv) and DMAP (24 mg, 0.20 mmol, 0.1 equiv) in CH₂Cl₂ (15 mL) was stirred 18h. Purification on silica gel (PE/EtOAc 7:1) afforded *O*-acetyl-*N,O*-acetal **6e** (717 mg, 89%) as a colorless oil : $[\alpha]_{\text{D}}^{20} +42$ (c 1.02, CHCl₃); IR (film) ν_{max} 1089, 1193, 1736, 1779, 2942, 2991 cm⁻¹; ¹⁹F NMR (CDCl₃, 470 MHz) δ -78.3 (s, 3F), -116.4 (ddd, $J = 14.0$ Hz, $J = 8.5$ Hz, $J = 5.5$ Hz, 1F); ¹H NMR (CDCl₃, 500 MHz) δ 7.18 (dd, $J = 8.5$ Hz, $J = 5.5$ Hz, 2H), 6.96 (t, $J = 8.5$ Hz, 2H), 5.07 (d, $J = 6.0$ Hz, 1H), 4.74 (d, $J = 6.0$ Hz, 1H), 3.50-3.38 (m, 2H), 2.99 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H), 2.80 (ddd, $J = 13.0$

Hz, $J = 10.5$ Hz, $J = 5.5$ Hz, 1H), 2.12 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.8, 166.5, 161.8 (d, $J = 244.5$ Hz), 134.0 (d, $J = 3.0$ Hz), 130.4 (d, $J = 8.0$ Hz), 122.4 (q, $J = 288.0$ Hz), 115.4 (d, $J = 21.5$ Hz), 114.8, 90.9 (q, $J = 32.5$ Hz), 76.3, 73.9, 43.8, 33.0, 26.2, 25.9, 21.3; HRMS (ESI^+) m/z calcd for $\text{C}_{18}\text{H}_{19}\text{F}_4\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$ 428.1097, found 428.1098.

(3*aS*,4*R*,6*aR*)-5-(2,4-dichlorophenethyl)-2,2-dimethyl-6-oxo-4-(trifluoromethyl)tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4-yl acetate **6f**. According to General Procedure B, a solution of *N,O*-acetal **5f** (393 mg, 0.95 mmol), pyridine (119 μL , 1.47 mmol, 1.55 equiv), acetic anhydride (166 μL , 1.66 mmol, 1.75 equiv) and DMAP (12 mg, 0.09 mmol, 0.1 equiv) in CH_2Cl_2 (7 mL) was stirred 18h. Purification on silica gel (PE/EtOAc 7:1) afforded *O*-acetyl-*N,O*-acetal **6f** (371 mg, 86%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = +54$ (c 0.71, CHCl_3); IR (film) ν_{max} 1090, 1194, 1736, 1779, 2941 cm^{-1} ; ^{19}F NMR (CDCl_3 , 470 MHz) δ -78.0 (s, 3F); ^1H NMR (CDCl_3 , 500 MHz) δ 7.36 (d, $J = 2.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.17 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 5.10 (d, $J = 6.0$ Hz, 1H), 4.74 (d, $J = 6.0$ Hz, 1H), 3.53-3.43 (m, 2H), 3.12 (m, 1H), 3.00 (m, 1H), 2.13 (d, $J = 1.0$ Hz, 3H), 1.43 (s, 3H), 1.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.9, 166.5, 134.8, 134.5, 133.4, 132.2, 129.4, 127.5, 122.4 (q, $J = 288.5$ Hz), 114.6, 90.9 (q, $J = 32.5$ Hz), 76.4, 74.0, 41.6, 31.2, 26.4, 26.0, 21.3; HRMS (ESI^+) m/z calcd for $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{F}_3\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$ 478.0412, found 478.0413.

(3*aS*,4*R*,6*aR*)-2,2-dimethyl-5-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-6-oxo-4-(trifluoromethyl)tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrolidin-4-yl acetate **6g**. According to General Procedure B, a solution of *N,O*-acetal **5g** (833 mg, 2.09 mmol), pyridine (260 μL , 3.24 mmol, 1.55 equiv), acetic anhydride (345 μL , 3.65 mmol, 1.75 equiv) and DMAP (25 mg, 0.20 mmol, 0.1 equiv) in CH_2Cl_2 (15 mL) was stirred 23h. Purification on silica gel (PE/EtOAc 4:1) afforded *O*-acetyl-*N,O*-acetal **6g** (766 mg, 83%) as a yellow oil : $[\alpha]_{\text{D}}^{20} = +56$ (c 1.00, CHCl_3); IR (film) ν_{max} 731, 1188, 1207, 1731, 1775, 2934 cm^{-1} ; ^{19}F NMR (CDCl_3 , 470 MHz) δ -78.2 (s,

3F); ^1H NMR (CDCl_3 , 500 MHz) δ 7.69 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.14 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.94 (s, 1H), 5.12 (d, J = 6.0 Hz, 1H), 4.79 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H), 3.63-3.49 (m, 2H), 3.18 (ddd, J = 13.5 Hz, J = 11.5 Hz, J = 6.0 Hz, 1H), 3.04 (ddd, J = 13.5 Hz, J = 11.5 Hz, J = 5.5 Hz, 1H), 2.13 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 171.0, 166.6, 137.2, 127.8, 127.2, 122.6 (q, J = 288.0 Hz), 121.8, 119.1, 119.0, 114.8, 111.0, 109.4, 91.1 (q, J = 32.5 Hz), 76.5, 74.1, 43.2, 32.7, 26.4, 26.1, 23.5, 21.4; HRMS (ESI^+) m/z calcd for $\text{C}_{21}\text{H}_{23}\text{F}_3\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 463.1457, found 463.1457.

General procedure for the Pictet-Spengler cyclization of *O*-acetyl *N,O*-acetal **6a-f.** *General Procedure C.* A solution of *O*-acetyl *N,O*-acetal **6a-f** and trifluoromethanesulfonic acid (10 equiv) in hexafluoroisopropanol (HFIP) containing 3 Å molecular sieves was stirred 10 min at 0°C and under Ar. The reaction mixture was then diluted with CH_2Cl_2 and hydrolyzed with a sat. sol. of NaHCO_3 . The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue (mixture of 2 diastereomers) on silica gel afforded the major diastereomer of Pictet-Spengler product **7a-f** and then the minor diastereomer *epi*-**7a-e**.

(8*aR*, 11*aR*, 11*bS*)-2,3-dimethoxy-10,10-dimethyl-11*b*-(trifluoromethyl)-5,6,11*a*,11*b*-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(8*aH*)-one **7a** and (8*aR*, 11*aR*, 11*bR*)-2,3-dimethoxy-10,10-dimethyl-11*b*-(trifluoromethyl)-5,6,11*a*,11*b*-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(8*aH*)-one *epi*-**7a**. According to General Procedure C, *O*-acetyl *N,O*-acetal **6a** (690 mg, 1.54 mmol) and triflic acid (1.35 mL, 15.4 mmol, 10 equiv) reacted in HFIP (18 mL). Purification of the residue (*dr* **7a**:*epi*-**7a** = 77 :23) on silica gel (PE/Et₂O 1:1) afforded cyclized derivative **7a** (360 mg, 60%) as a pale yellow amorphous solid and cyclized derivative *epi*-**7a** (119 mg, 21%) as a pale yellow moss. **7a** : $[\alpha]_{\text{D}}^{20}$ = +216 (*c* 1.00, CHCl_3); IR (film) ν_{max} 783, 1107, 1256, 1524, 1723 cm^{-1} ; ^{19}F NMR

(470 MHz, CDCl₃) δ -74.1 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 6.85 (s, 1H), 6.62 (s, 1H), 4.99 (d, J = 5.5 Hz, 1H), 4.92 (d, J = 5.5 Hz, 1H), 4.41 (dd, J = 13.0 Hz, J = 6.5 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.26 (td, J = 13.5 Hz, J = 5.0 Hz, 1H), 2.85 (ddd, J = 16.0 Hz, J = 12.0 Hz, J = 6.5 Hz, 1H), 2.74 (dd, J = 16.0 Hz, J = 4.0 Hz, 1H), 1.34 (s, 3H), 1.16 (s, 3H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 171.3, 149.6, 147.7, 128.2, 125.5 (q, J = 288.5 Hz), 117.8, 113.2, 111.5, 110.8 (q, J = 2.5 Hz), 78.1 (q, J = 2.0 Hz), 76.0, 67.6 (q, J = 26.5 Hz), 56.3, 55.9, 36.0, 27.5, 27.2, 26.6; HRMS (ESI⁺) m/z calcd for C₁₈H₂₁F₃NO₅ [M+H]⁺ 388.1372, found 388.1374. An analytical sample of **7a** was crystallized from Et₂O:hexane. *epi-7a* : [α]_D²⁰ = -150 (*c* 1.20, CHCl₃); IR (film) ν_{\max} 781, 1121, 1177, 1519, 1714 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -67.0 (br s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 1H), 6.59 (s, 1H), 5.00 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.42 (dd, J = 13.5 Hz, J = 7.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.36 (td, J = 13.0 Hz, J = 5.5 Hz, 1H), 2.96 (ddd, J = 16.5 Hz, J = 12.0 Hz, J = 7.5 Hz, 1H), 2.67 (dd, J = 16.5 Hz, J = 5.5 Hz, 1H), 1.56 (s, 3H), 1.43 (s, 3H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 170.3, 150.0, 148.2, 127.9, 124.4 (q, J = 287.5 Hz), 121.8, 115.5, 112.0, 109.2 (q, J = 1.5 Hz), 80.4, 77.5, 67.4 (q, J = 27.5 Hz), 56.4, 56.0, 36.3 (d, J = 1.0 Hz), 26.5, 25.9, 25.5; HRMS (ESI⁺) m/z calcd for C₁₈H₂₁F₃NO₅ [M+H]⁺ 388.1372, found 388.1375.

(*8aR,11aR,11bS*)-3-methoxy-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(*8aH*)-one **7b** and (*8aR,11aR,11bR*)-3-methoxy-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(*8aH*)-one *epi-7b*. According to General Procedure C, *N,O*-acetal **6b** (214 mg, 0.51 mmol) and triflic acid (450 μ L, 5.08 mmol, 10 equiv) reacted in HFIP (7 mL). Purification of the residue (*dr 7b:epi-7b* = 73:27) on silica gel (PE/Et₂O 1:1) afforded cyclized derivative **7b** (82 mg, 45%) as a white amorphous solid and cyclized derivative *epi-7b* (42 mg, 23%) as a colorless oil. **7b** : [α]_D²⁰ = +240 (*c* 1.00, CHCl₃); IR (film) ν_{\max} 1151, 1170, 1194, 1408, 1715 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -73.9 (s, 3F);

^1H NMR (500 MHz, CDCl_3) δ 7.10 (d, $J = 8.5$ Hz, 1H), 6.96 (m, 1H), 6.90 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H), 5.00 (d, $J = 5.0$ Hz, 1H), 4.92 (d, $J = 5.0$ Hz, 1H), 4.40 (ddd, $J = 12.5$ Hz, $J = 6.5$ Hz, $J = 2.0$ Hz, 1H), 3.83 (s, 3H), 3.26 (td, $J = 12.5$ Hz, $J = 5.5$ Hz, 1H), 2.84 (m, 1H), 2.77 (ddd, $J = 16.0$ Hz, $J = 5.5$ Hz, $J = 2.5$ Hz, 1H), 1.34 (s, 3H), 1.17 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150.9 MHz, CDCl_3) δ 171.3, 157.9, 130.4, 127.4, 127.0, 125.4 (q, $J = 288.5$ Hz), 114.8, 113.7 (q, $J = 2.5$ Hz), 113.2, 78.0, 76.1, 67.8 (q, $J = 26.5$ Hz), 55.5, 36.2, 27.5, 26.8, 26.5; HRMS (ESI^+) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 358.1266, found 358.1269. *epi-7b*: $[\alpha]_{\text{D}}^{20} = -185$ (c 0.84, CHCl_3); IR (film) ν_{max} 1149, 1180, 1209, 1246, 1715 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -66.9 (br s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.08 (d, $J = 8.5$ Hz), 7.03 (s, 1H), 6.90 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H), 5.03 (d, $J = 5.0$ Hz, 1H), 4.65 (d, $J = 5.0$ Hz, 1H), 4.43 (dd, $J = 13.5$ Hz, $J = 7.5$ Hz, 1H), 3.83 (s, 3H), 3.36 (dddd, $J = 13.5$ Hz, $J = 12.0$ Hz, $J = 5.5$ Hz, $J = 1.5$ Hz, 1H), 2.94 (ddd, $J = 16.5$ Hz, $J = 12.0$ Hz, $J = 7.5$ Hz, 1H), 2.71 (dd, $J = 16.5$ Hz, $J = 5.5$ Hz, 1H), 1.56 (s, 3H), 1.43 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150.9 MHz, CDCl_3) δ 170.3, 158.4, 131.1, 131.0, 127.0, 124.4 (q, $J = 287.5$ Hz), 115.6, 115.5, 112.1, 80.5, 77.4, 67.7 (q, $J = 27.5$ Hz), 55.6, 36.4, 26.0, 25.9, 25.5; HRMS (ESI^+) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 358.1266, found 358.1268.

(*8aR,11aR,11bS*)-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(*8aH*)-one **7c** and (*8aR,11aR,11bR*)-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(*8aH*)-one *epi-7c*. According to General Procedure C, *O*-acetyl *N,O*-acetal **6c** (175 mg, 0.45 mmol) and triflic acid (400 μL , 4.52 mmol, 10 equiv) reacted in HFIP (7 mL). Purification of the residue (*dr 7c:epi-7c* = 76:24) on silica gel (PE/EtOAc 4:1) afforded cyclized derivative **7c** (74 mg, 50%) as a white amorphous solid and cyclized derivative *epi-7c* (35 mg, 24%) as a colorless oil. **7c**: $[\alpha]_{\text{D}}^{20} = +173$ (c 1.00, CHCl_3); IR (film) ν_{max} 1113, 1152, 1183, 1714 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -74.1 (s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.44

(dt, $J = 7.5$ Hz, $J = 2.0$ Hz, 1H), 7.31 (m, 2H), 7.18 (dd, $J = 7.5$ Hz, $J = 2.5$ Hz, 1H), 5.04 (d, $J = 5.0$ Hz, 1H), 4.93 (d, $J = 5.0$ Hz, 1H), 4.42 (ddd, $J = 13.5$ Hz, $J = 6.5$ Hz, $J = 2.0$ Hz, 1H), 3.30 (td, $J = 12.5$ Hz, $J = 5.0$ Hz, 1H), 2.91 (m, 1H), 2.84 (m, 1H), 1.33 (s, 3H), 1.15 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 171.3, 135.4, 129.6, 129.0, 128.9 (q, $J = 2.5$ Hz), 126.7, 126.2, 125.5 (q, $J = 288.5$ Hz), 113.2, 78.0 (q, $J = 2.5$ Hz), 76.1, 67.8 (q, $J = 26.5$ Hz), 35.9, 27.5, 27.4, 26.5; HRMS (ESI^+) m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 328.1161, found 328.1164.

epi-7c : $[\alpha]_{\text{D}}^{20} = -119$ (c 0.58, CHCl_3); IR (film) ν_{max} 1148, 1179, 1257, 1715 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -67.0 (br s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.54 (m, 1H), 7.33 (m, 2H), 7.16 (m, 1H), 5.04 (d, $J = 7.0$ Hz, 1H), 4.65 (d, $J = 7.0$ Hz, 1H), 4.45 (dd, $J = 13.5$ Hz, $J = 7.5$ Hz, 1H), 3.40 (td, $J = 13.5$ Hz, $J = 5.5$ Hz, 1H), 3.03 (m, 1H), 2.79 (dd, $J = 17.0$ Hz, $J = 5.5$ Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150.9 MHz, CDCl_3) δ 170.2, 135.3, 130.3, 130.1, 129.5, 127.2, 126.9 (q, $J = 1.5$ Hz), 124.4 (q, $J = 288.5$ Hz), 115.5, 80.5, 77.4, 67.4 (q, $J = 27.5$ Hz), 36.2, 26.7, 25.9, 25.4; HRMS (ESI^+) m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 328.1161, found 328.1165.

(8aR,11aR,11bS)-2-chloro-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-a]isoquinolin-8(8aH)-one **7d** and (8aR,11aR,11bR)-2-chloro-10,10-dimethyl-11b-(trifluoromethyl)-5,6,11a,11b-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-a]isoquinolin-8(8aH)-one *epi-7d*. According to General Procedure C, *O*-acetyl *N,O*-acetal **6d** (225 mg, 0.53 mmol) and triflic acid (473 μL , 5.34 mmol, 10 equiv) reacted in HFIP (8 mL). Purification of the residue (*dr 7d:epi-7d* = 85:15) on silica gel (PE/Et₂O 3:2) afforded cyclized derivative **7d** (116 mg, 61%) as a white amorphous solid and cyclized derivative *epi-7d* (25 mg, 13%) as a colorless oil. **7d** : $[\alpha]_{\text{D}}^{20} = +214$ (c 0.50, CHCl_3); IR (film) ν_{max} 1109, 1157, 1193, 1257, 1403, 1713, 1732 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -74.0 (s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.43 (t, $J = 2.0$ Hz, 1H), 7.30 (dd, $J = 8.5$ Hz, $J = 2.0$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 5.00 (d, $J = 5.0$ Hz, 1H), 4.93 (d, $J = 5.0$ Hz,

1H), 4.42 (ddd, $J = 13.5$ Hz, $J = 5.5$ Hz, $J = 3.0$ Hz, 1H), 3.26 (m, 1H), 2.90-2.80 (m, 2H), 1.34 (s, 3H), 1.16 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 171.1, 133.9, 132.4, 130.8, 129.4, 128.2 (q, $J = 3.0$ Hz), 127.9, 125.2 (q, $J = 288.5$ Hz), 113.4, 77.9 (q, $J = 2.0$ Hz), 75.9 (q, $J = 1.5$ Hz), 67.5 (q, $J = 26.5$ Hz), 35.7, 27.4, 27.1, 26.5; HRMS (ESI⁺) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{ClF}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 362.0771, found 362.0772. *epi-7d*: $[\alpha]_{\text{D}}^{20} = -174$ (c 0.23, CHCl_3); IR (film) ν_{max} 1109, 1158, 1173, 1257, 1403, 1713, 1732 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -67.0 (br s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.53 (s, 1H), 7.32 (dd, $J = 8.5$ Hz, $J = 2.0$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 5.00 (d, $J = 7.0$ Hz, 1H), 4.67 (d, $J = 7.0$ Hz, 1H), 4.45 (dd, $J = 13.5$ Hz, $J = 7.5$ Hz, 1H), 3.37 (dddd, $J = 13.5$ Hz, $J = 2.0$ Hz, $J = 5.5$ Hz, $J = 1.5$ Hz, 1H), 2.96 (m, 1H), 2.77 (dd, $J = 17.0$ Hz, $J = 5.5$ Hz, 1H), 1.57 (s, 3H), 1.43 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.0, 133.8, 132.9, 132.1, 131.4, 129.9, 127.0 (q, $J = 2.0$ Hz), 124.2 (q, $J = 287.5$ Hz), 115.8, 80.5, 77.4, 67.4 (q, $J = 28.0$ Hz), 35.9 (q, $J = 1.5$ Hz), 26.3, 25.9, 25.4; HRMS (ESI⁺) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{ClF}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 362.0771, found 362.0771.

(8*aR*, 11*aR*, 11*bS*)-2-fluoro-10,10-dimethyl-11*b*-(trifluoromethyl)-5,6,11*a*, 11*b*-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(8*aH*)-one **7e** and (8*aR*, 11*aR*, 11*bR*)-2-fluoro-10,10-dimethyl-11*b*-(trifluoromethyl)-5,6,11*a*, 11*b*-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(8*aH*)-one *epi-7e*. According to General Procedure C, *O*-acetyl *N,O*-acetal **6e** (220 mg, 0.54 mmol) and triflic acid (480 μL , 5.42 mmol, 10 equiv) reacted in HFIP (8 mL). Purification of the residue (*dr 7e:epi-7e* = 90:10) on silica gel (PE/EtOAc 5:1) afforded cyclized derivative **7e** (146 mg, 78%) as a white amorphous solid and cyclized derivative *epi-7e* (18 mg, 10%) as a colorless oil. **7e**: $[\alpha]_{\text{D}}^{20} = +143$ (c 1.01, CHCl_3); IR (film) ν_{max} 1107, 1149, 1188, 1246, 1406, 1713, 1732 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -74.1 (s, 3F), -114.8 (td, $J = 9.0$ Hz, $J = 6.5$ Hz, 1F); ^1H NMR (500 MHz, CDCl_3) δ 7.15 (m, 2H), 7.04 (td, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H), 5.00 (d, $J = 5.0$ Hz, 1H), 4.92 (dt, $J = 5.0$ Hz, $J = 1.5$ Hz, 1H), 4.44 (m, 1H), 3.26 (m, 1H), 2.86-2.81 (m, 2H), 1.33 (s, 3H), 1.15 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$

NMR (125.7 MHz, CDCl₃) δ 171.1, 161.1 (d, J = 245.5 Hz), 131.1 (d, J = 3.0 Hz), 131.0 (d, J = 8.0 Hz), 127.8 (d, J = 7.5 Hz), 125.2 (q, J = 288.5 Hz), 116.6 (d, J = 21.5 Hz), 115.1 (dq, J = 23.5 Hz, J = 2.5 Hz), 113.5, 77.9 (q, J = 2.0 Hz), 76.0 (q, J = 1.5 Hz), 67.7 (qd, J = 26.5 Hz, J = 2.0 Hz), 35.9, 27.4, 26.9, 26.4; HRMS (ESI⁺) m/z calcd for C₁₆H₁₆F₄NO₃ [M+H]⁺ 346.1066, found 346.1066. *epi-7e*: $[\alpha]_D^{20}$ = -108 (*c* 0.24, CHCl₃); IR (film) ν_{\max} 1144, 1187, 1416, 1704, 1724 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -66.9 (br s, 3F), -113.8 (m, 1F); ¹H NMR (600 MHz, CDCl₃) δ 7.26 (m, 2H), 7.15 (dd, J = 8.5 Hz, J = 5.5 Hz, 1H), 7.06 (td, J = 8.5 Hz, J = 2.0 Hz, 1H), 4.99 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.45 (dd, J = 14.0 Hz, J = 7.5 Hz, 1H), 3.37 (m, 1H), 2.96 (m, 1H), 2.77 (dd, J = 17.0 Hz, J = 5.5 Hz, 1H), 1.57 (s, 3H), 1.43 (s, 3H); ¹³C{¹H} NMR (150.9 MHz, CDCl₃) δ 170.1, 161.3 (d, J = 247.0 Hz), 131.9 (d, J = 6.5 Hz), 131.7 (d, J = 7.5 Hz), 130.9 (d, J = 3.5 Hz), 124.2 (q, J = 287.5 Hz), 117.0 (d, J = 21.0 Hz), 115.8, 113.9 (dq, J = 23.0 Hz, J = 1.5 Hz), 80.5, 77.4, 67.5 (qd, J = 28.0 Hz, J = 1.5 Hz), 36.1 (q, J = 1.0 Hz), 26.2, 25.9, 25.4; HRMS (ESI⁺) m/z calcd for C₁₆H₁₆F₄NO₃ [M+H]⁺ 346.1066, found 346.1068.

(*8aR,11aR,11bS*)-2,4-dichloro-10,10-dimethyl-11*b*-(trifluoromethyl)-5,6,11*a*,11*b*-tetrahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinolin-8(*8aH*)-one **7f** and (*3aR,6S,6aS*)-5-(2,4-dichlorophenethyl)-6-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2,2-dimethyl-6-(trifluoromethyl)dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrol-4(*5H*)-one **11**. According to General Procedure C, *O*-acetyl *N,O*-acetal **6f** (223 mg, 0.49 mmol) and triflic acid (433 μ L, 4.89 mmol, 10 equiv) reacted in HFIP (8 mL). Purification of the residue [containing 52% of Friedel-Crafts product (*dr* **7f**:*epi-7f* = 97:3) and 17% of **11**] on silica gel (PE/EtOAc 6:1) afforded *N,O*-acetal **11** (33 mg, 12%) as a colorless oil and cyclized derivative **7f** (68 mg, 35%) as a white amorphous solid. **7f**: $[\alpha]_D^{20}$ = +184 (*c* 0.18, CHCl₃); IR (film) ν_{\max} 1114, 1159, 1181, 1403, 1722 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -73.6 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 7.47 (s, 1H), 7.37 (s, 1H), 5.00 (d, J = 5.0 Hz, 1H), 4.93 (d, J = 5.0 Hz, 1H), 4.50 (dd, J = 13.5 Hz, J =

7.5 Hz, 1H), 3.24 (td, $J = 13.5$ Hz, $J = 5.0$ Hz, 1H), 3.09 (dd, $J = 17.5$ Hz, $J = 5.0$ Hz, 1H), 2.66 (1H), 1.35 (s, 3H), 1.17 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 170.8, 135.5, 132.7, 132.2, 130.1, 129.6, 127.0 (q, $J = 3.0$ Hz), 125.1 (q, $J = 288.5$ Hz), 113.6, 78.0 (q, $J = 2.0$ Hz), 75.9 (q, $J = 1.5$ Hz), 67.3 (d, $J = 27.0$ Hz), 34.9, 27.4, 26.5, 24.8; HRMS (ESI^+) m/z calcd for $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 396.0381, found 396.0384. An analytical sample of **7f** was crystallized from Et_2O :hexane. **11** : $[\alpha]_{\text{D}}^{20} = -56$ (c 0.67, CHCl_3); IR (film) ν_{max} 1103, 1165, 1196, 1284, 1456, 1746 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -71.4 (br s, 3F), -72.6 (m, 3F), -72.8 (m, 3F); ^1H NMR (500 MHz, CDCl_3) δ 7.38 (d, $J = 2.0$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.20 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 4.83 (d, $J = 5.5$ Hz, 1H), 4.78 (d, $J = 5.5$ Hz, 1H), 4.29 (hept, $J = 5.0$ Hz, 1H), 3.65 (td, $J = 13.5$ Hz, $J = 5.0$ Hz, 1H), 3.48 (ddd, $J = 13.5$ Hz, $J = 11.5$ Hz, $J = 5.5$ Hz, 1H), 3.14 (ddd, $J = 12.5$ Hz, $J = 11.5$ Hz, $J = 5.0$ Hz, 1H), 3.02 (td, $J = 12.5$ Hz, $J = 5.5$ Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 173.2, 135.0, 133.85, 133.82, 132.1, 129.7, 127.7, 121.5 (q, $J = 286.5$ Hz), 120.6 (qq, $J = 283.5$ Hz, $J = 3.0$ Hz), 115.7, 94.7 (q, $J = 32.5$ Hz), 78.4, 75.5 (d, $J = 1.0$ Hz), 70.8 (hept, $J = 34.0$ Hz), 42.1, 30.7, 27.1, 26.4; HRMS (ESI^+) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{F}_9\text{NO}_4$ $[\text{M}+\text{H}]^+$ 564.0391, found 564.0386.

(3*S*,4*R*)-1-(3,4-dimethoxyphenethyl)-3,4-dihydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl acetate **9** [*dr* (*R,S,R*):(*S,S,R*) = 89:11]. Colorless oil : IR (film) ν_{max} 727, 754, 1025, 1137, 1227, 1515, 1704, 1755, 2941, 3388 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -80.2 (s, 3F major), -80.6 (s, 3F minor); ^1H NMR (500 MHz, CDCl_3) δ 6.80-6.69 (m, 1H, major and minor), 5.54 (d, $J = 6.0$ Hz, 1H, minor), 5.25 (d, $J = 5.5$ Hz, 1H, major), 4.94 (br s, 1H, major), 4.62 (d, $J = 5.5$ Hz, 1H, major), 4.50 (br s, 1H, minor), 4.49 (d, $J = 6.0$ Hz, 1H, minor), 3.85 (s, 3H, major), 3.83 (s, 3H, minor), 3.82 (s, 3H, major), 3.62 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 4.5$ Hz, 1H, major and minor), 3.42 (ddd, $J = 14.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, major and minor), 2.98 (m, 1H, minor), 2.96 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 6.5$ Hz, 1H major), 2.79 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 4.5$ Hz, 1H major and minor), 2.36 (br s, 1H, major and minor), 2.17 (s, 3H,

major), 2.11 (s, 3H, minor); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 173.2 (minor), 170.5 (major), 169.4 (minor), 169.3 (major), 149.0 (major), 148.9 (major), 147.9 (minor), 147.7 (major), 131.1 (major), 130.9 (minor), 123.2 (q, $J = 285.5$ Hz, major), 122.8 (q, $J = 285.5$ Hz, minor), 121.0 (major and minor), 112.8 (minor), 112.5 (major), 111.6 (major), 111.4 (minor), 87.0 (q, $J = 33.0$ Hz, major), 69.9 (major), 69.2 (minor), 68.0 (minor), 67.1 (major), 56.04 (major), 56.01 (minor), 55.96 (minor), 55.92 (major), 42.5 (major and minor), 33.7 (major), 33.1 (minor), 20.4 (major), 20.2 (minor); HRMS (ESI^+) m/z calcd for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{NO}_7$ $[\text{M}+\text{H}]^+$ 408.1270, found 408.1268.

(3*aR*,6*R*,6*aS*)-4-(3,4-dimethoxyphenethyl)-6-hydroxy-2,2-dimethyl-3*a*-(trifluoromethyl) dihydro-3*aH*-[1,3]dioxolo[4,5-*b*]pyrrol-5(4*H*)-one **10**. Colorless oil : $[\alpha]_{\text{D}}^{20} = +47$ (c 0.96, CHCl_3); IR (film) ν_{max} 727, 884, 1027, 1064, 1141, 1156, 1177, 1515, 1727, 2938, 2992, 3445, 3667 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -77.8 (s, 3F); ^1H NMR (500 MHz, CDCl_3) δ 6.81-6.74 (m, 3H), 4.92 (d, $J = 5.0$ Hz, 1H), 4.41 (t, $J = 5.0$ Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.56-3.47 (m, 2H), 3.42 (ddd, $J = 14.0$ Hz, $J = 12.5$ Hz, $J = 5.0$ Hz, 1H), 2.99 (td, $J = 12.5$ Hz, $J = 5.0$ Hz, 1H), 2.73 (td, $J = 12.5$ Hz, $J = 5.0$ Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 173.2, 149.1, 147.9, 130.9, 122.1 (q, $J = 283.0$ Hz), 120.8, 117.3, 112.1, 111.5, 93.6 (q, $J = 35.0$ Hz), 77.0, 69.4, 56.01, 55.98, 42.7, 33.9, 27.6, 26.1; HRMS (ESI^+) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{F}_3\text{NO}_6$ $[\text{M}+\text{H}]^+$ 406.1477, found 406.1479.

General procedure for the deprotection of the acetonide protecting group. *General Procedure D.* A solution of acetonide-protected compound in a 1 : 1 (v/v) mixture of THF and 10% aq. sol. of HCl was heated at 50°C with a heating mantle. After completion, the reaction mixture was cooled to rt, concentrated under reduced pressure and purified.

(1*R*,2*R*,10*bS*)-1,2-dihydroxy-8,9-dimethoxy-10*b*-(trifluoromethyl)-1,5,6,10*b*-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one **8**. According to General Procedure D, a solution of Pictet-Spengler product **7a** (110 mg, 0.28 mmol) in THF (1 mL) and 10% aq. sol.

of HCl (1 mL) was heated 8h. Purification of the residue on silica gel (EtOAc/Et₂O 1:1) afforded diol **8** (95 mg, 96%) as a colorless amorphous solid : $[\alpha]_D^{20} = +234$ (*c* 1.00, CHCl₃); IR (film) ν_{\max} 777, 924, 1119, 1162, 1261, 1520, 1695, 2940, 3345 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -71.9 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 6.85 (s, 1H), 6.62 (s, 1H), 4.79-4.76 (m, 2H), 4.70 (s, 1H), 4.34 (dd, *J* = 13.0 Hz, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.36 (s, 1H), 3.24 (td, *J* = 13.0 Hz, *J* = 4.5 Hz, 1H), 2.88 (ddd, *J* = 16.0 Hz, *J* = 12.0 Hz, *J* = 6.5 Hz, 1H), 2.73 (dd, *J* = 16.0 Hz, *J* = 3.5 Hz, 1H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 173.5, 149.6, 147.9, 128.4, 125.7 (q, *J* = 288.0 Hz), 117.8, 111.8, 110.5 (q, *J* = 2.5 Hz), 70.4 (q, *J* = 3.0 Hz), 69.3, 68.9 (q, *J* = 26.5 Hz), 56.2, 55.9, 36.1, 27.2; HRMS (ESI⁺) *m/z* calcd for C₁₅H₁₇F₃NO₅ [M+H]⁺ 348.1059, found 348.1061.

(1*R*,2*R*,10*bR*)-1,2-dihydroxy-8,9-dimethoxy-10*b*-(trifluoromethyl)-1,5,6,10*b*-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one *epi*-**8**. According to General Procedure D, a solution of Pictet-Spengler product *epi*-**7a** (110 mg, 0.28 mmol) in THF (1 mL) and 10% aq. sol. of HCl (1 mL) was heated 2h45. Purification of the residue on silica gel (EtOAc/Et₂O 1:1) afforded diol *epi*-**8** (98 mg, 99%) as a pale yellow amorphous solid : $[\alpha]_D^{20} = -124$ (*c* 1.00, CHCl₃); IR (film) ν_{\max} 774, 1117, 1160, 1229, 1260, 1519, 1689, 2851, 2933, 3417 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -68.7 (s, 3F); ¹H NMR (500 MHz, CDCl₃) δ 7.16 (s, 1H), 6.59 (s, 1H), 5.52 (d, *J* = 4.0 Hz, 1H), 4.47 (t, *J* = 8.5, 1H), 4.39 (dd, *J* = 13.5 Hz, *J* = 7.0 Hz, 1H), 4.31 (dd, *J* = 8.5 Hz, *J* = 4.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.80 (d, *J* = 8.5 Hz, 1H), 3.40 (td, *J* = 13.0 Hz, *J* = 5.5 Hz, 1H), 2.87 (m, 1H), 2.77 (dd, *J* = 16.5 Hz, *J* = 4.5 Hz, 1H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 172.8, 149.8, 148.4, 126.3, 125.5 (q, *J* = 288.5 Hz), 122.8, 111.4, 109.7, 74.3, 67.8, 67.6 (q, *J* = 26.5 Hz), 56.3, 56.0, 35.8, 26.7; HRMS (ESI⁺) *m/z* calcd for C₁₅H₁₇F₃NO₅ [M+H]⁺ 348.1059, found 348.1060.

General procedure for the reduction of lactam. *General Procedure E.* To a solution of lactam **7a** or *epi*-**7a** in THF was added dropwise, at rt and under Ar, BH₃.Me₂S (2M sol. in THF). After

full conversion of amide, ethanol (14 mL) was carefully added to the reaction mixture. After 30 min of stirring, the reaction was concentrated under reduced pressure and the residue was purified by chromatographie on silica gel to afford amine **12** or *epi*-**12**.

(*8aS,11aR,11bS*)-2,3-dimethoxy-10,10-dimethyl-11b-(trifluoromethyl)-5,6,8,8a,11a,11b-hexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinoline **12**. According to General Procedure E, lactam **7a** (96 mg, 0.25 mmol) reacted with BH₃.Me₂S (2M in THF, 1.25 mL, 2.50 mmol, 10 equiv) in THF (3 mL) for 5h. Purification of the residue on silica gel (PE/EtOAc 9:1) afforded amine **12** (76 mg, 82%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = +44$ (*c* 1.00, CHCl₃); IR (film) ν_{max} 859, 1132, 1209, 1519, 2835, 2937 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -74.7 (s, 3F) ; ¹H NMR (500 MHz, CDCl₃) δ 6.85 (q, *J* = 1.5 Hz, 1H), 6.59 (s, 1H), 5.07 (d, *J* = 5.5 Hz, 1H), 4.84 (td, *J* = 5.5 Hz, *J* = 2.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58 (ddd, *J* = 12.5 Hz, *J* = 5.0 Hz, *J* = 1.0 Hz, 1H), 3.24-3.11 (m, 3H), 2.79 (ddd, *J* = 15.0 Hz, *J* = 9.0 Hz, *J* = 5.0 Hz, 1H), 2.67 (dt, *J* = 15.0 Hz, *J* = 4.5 Hz, 1H), 1.27 (s, 3H), 1.10 (s, 3H); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 148.5, 146.5, 130.6, 127.0 (q, *J* = 288.0 Hz), 120.9, 114.1 (q, *J* = 2.0 Hz), 112.7, 110.5, 84.2, 80.9, 72.7 (q, *J* = 24.0 Hz), 59.0, 56.3, 55.7, 48.7, 28.8, 26.6, 24.9; HRMS (ESI⁺) *m/z* calcd for C₁₈H₂₃F₃NO₄ [M+H]⁺ 374.1579, found 374.1578.

(*8aS,11aR,11bR*)-2,3-dimethoxy-10,10-dimethyl-11b-(trifluoromethyl)-5,6,8,8a,11a,11b-hexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[2,1-*a*]isoquinoline *epi*-**12**. According to General Procedure E, lactam *epi*-**7a** (260 mg, 0.67 mmol) reacted with BH₃.Me₂S (2M in THF, 6.7 mL, 13.4 mmol, 20 equiv) in THF (8 mL) for 5h. Purification of the residue on silica gel (PE/EtOAc 3:1) afforded amine *epi*-**12** (178 mg, 71%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = -19$ (*c* 0.52, CHCl₃); IR (film) ν_{max} 855, 1104, 1125, 1518, 2849, 2940 cm⁻¹; ¹⁹F NMR (470 MHz, CDCl₃) δ -66.2 (br s, 3F) ; ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 1H), 6.56 (s, 1H), 4.97 (d, *J* = 6.0 Hz, 1H), 4.63 (dd, *J* = 6.0 Hz, *J* = 5.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.41 (td, *J* = 14.0 Hz, *J* = 5.5 Hz, 1H), 3.21 (d, *J* = 11.0 Hz, 1H), 3.14 (dd, *J* = 14.5 Hz, 6.5 Hz, 1H), 3.00

(m, 1H), 2.97 (dd, $J = 11.0$ Hz, $J = 4.5$ Hz, 1H), 2.42 (dd, $J = 17.5$ Hz, $J = 5.5$ Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 149.1, 147.9, 128.4, 125.6 (q, $J = 285.0$ Hz), 121.3, 112.6, 111.7, 111.1 (q, $J = 1.5$ Hz), 87.5, 78.1, 70.5 (q, $J = 26.0$ Hz), 56.2, 55.9, 53.9, 41.5, 25.7, 24.9, 20.4; HRMS (ESI^+) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 374.1579, found 374.1579.

(1*R*,2*S*,10*bS*)-1,2-dihydroxy-8,9-dimethoxy-10*b*-(trifluoromethyl)-2,3,4,5,6,10*b*-hexahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium chloride **13**. According to General Procedure D, a solution of acetonide-protected amine **12** (76 mg, 0.20 mmol) in THF (1 mL) and 10% aq. sol. of HCl (1 mL) was heated 2h. Purification of the residue on reverse-phase chromatography (C-18 silica) ($\text{H}_2\text{O}/\text{MeOH}$ 2:1) afforded amino diol hydrochloride **13** (50 mg, 67%) as a white amorphous solid : $[\alpha]_{\text{D}}^{20} = +57$ (c 0.99, MeOH); IR (film) ν_{max} 1096, 1135, 1256, 1517, 2939, 3436 cm^{-1} ; ^{19}F NMR (470 MHz, MeOD) δ -75.3 (s, 3F); ^1H NMR (500 MHz, MeOD) δ 7.01 (s, 1H), 6.76 (s, 1H), 4.44 (s, 2H), 3.84 (s, 6H), 3.35 (m, 1H), 3.23 (m, 1H), 3.00-2.79 (m, 3H), 2.59 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, MeOD) δ 150.0, 148.1, 132.9, 128.1 (q, $J = 285.0$ Hz), 122.8, 115.2 (q, $J = 2.5$ Hz), 112.5, 75.2, 72.2 (q, $J = 25.0$ Hz), 71.0 (q, $J = 2.5$ Hz), 57.9, 56.7, 56.3, 47.9, 26.4; HRMS (ESI^+) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 334.1266, found 334.1269.

(1*R*,2*S*,10*bR*)-1,2-dihydroxy-8,9-dimethoxy-10*b*-(trifluoromethyl)-2,3,4,5,6,10*b*-hexahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium chloride *epi*-**13**. According to General Procedure D, a solution of acetonide-protected amine *epi*-**12** (84 mg, 0.23 mmol) in THF (1 mL) and 10% aq. sol. of HCl (1 mL) was heated 2h. Purification of the residue on reverse-phase chromatography (C-18 silica) ($\text{H}_2\text{O}/\text{MeOH}$ 2:1) afforded amino diol hydrochloride *epi*-**13** (58 mg, 70%) as a white amorphous solid : $[\alpha]_{\text{D}}^{20} = -52$ (c 1.21, MeOH); IR (film) ν_{max} 708, 1093, 1113, 1150, 1518, 2868, 2945, 3357, 3476 cm^{-1} ; ^{19}F NMR (470 MHz, MeOD) δ -69.2 (s, 3F); ^1H NMR (500 MHz, MeOD) δ 7.10 (d, $J = 1.0$ Hz, 1H), 6.71 (s, 1H), 4.37 (d, $J = 5.0$ Hz, 1H),

3.97 (q, $J = 5.0$ Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.32 (m, 1H), 3.27 (m, 1H), 3.10 (m, 2H), 3.00-2.91 (m, 2H), 2.44 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, MeOD) δ 150.3, 149.1, 130.2, 127.7 (q, $J = 285.5$ Hz), 124.3, 112.9, 112.3 (q, $J = 2.5$ Hz), 82.7, 70.2, 69.7 (q, $J = 25.0$ Hz), 56.7, 56.5, 56.3, 45.2 (q, $J = 1.0$ Hz), 23.0; HRMS (ESI⁺) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_4$ $[\text{M}+\text{H}]^+$ 334.1266, found 334.1266.

(3R,4S,5R)-1-(3,4-dimethoxyphenethyl)-3,4,5-trihydroxy-5-(trifluoromethyl)

pyrrolidin-2-one **14**. From **5a** : According to General Procedure D, a solution of protected *N,O*-acetal **5a** (269 mg, 0.66 mmol) in THF (2 mL) and 10% aq. sol. of HCl (2 mL) was heated 22h. Purification of the residue on silica gel (PE/EtOAc 1:4) afforded triol **14** (240 mg, 99%) as a colorless oil. From **6a** : According to General Procedure D, a solution of protected *O*-acetyl *N,O*-acetal **6a** (151 mg, 0.34 mmol) in THF (1 mL) and 10% aq. sol. of HCl (1 mL) was heated 20h. Purification of the residue on silica gel (hexane/EtOAc 1:4) afforded triol **14** (82 mg, 66%) as a colorless oil. From **9** : According to General Procedure D, a solution of deprotected *O*-acetyl *N,O*-acetal **9** [*dr* (*R,S,R*):(*S,S,R*) = 89:11] (79 mg, 0.19 mmol) in THF (700 μL) and 10% aq. sol. of HCl (700 μL) was heated 20h. Purification of the residue on silica gel (PE/EtOAc 1:4) afforded triol **14** (55 mg, 78%) as a colorless oil : $[\alpha]_{\text{D}}^{20} = +70$ (c 0.94, CHCl_3); IR (film) ν_{max} 728, 1025, 1139, 1171, 1261, 1515, 1692, 3376 cm^{-1} ; ^{19}F NMR (470 MHz, CDCl_3) δ -80.1 (s, 3F) ; ^1H NMR (500 MHz, CDCl_3) δ 6.75 (d, $J = 8.0$ Hz, 1H), 6.72-6.70 (m, 2H), 5.64 (br s, 1H), 5.24 (br s, 1H), 4.82 (br s, 1H), 4.53-4.48 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58 (ddd, $J = 13.5$ Hz, $J = 11.0$ Hz, $J = 5.0$ Hz, 1H), 3.43 (ddd, $J = 13.5$ Hz, $J = 10.5$ Hz, $J = 6.0$ Hz, 1H), 2.91 (ddd, $J = 13.0$ Hz, $J = 11.0$ Hz, $J = 6.0$ Hz, 1H), 2.75 (ddd, $J = 13.0$ Hz, $J = 10.5$ Hz, $J = 5.0$ Hz, 1H) ; $^{13}\text{C}\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ 174.5, 149.0, 147.9, 130.8, 123.2 (q, $J = 285.0$ Hz), 121.0, 112.3, 111.5, 87.4 (q, $J = 33.0$ Hz), 68.9, 68.0, 56.00, 55.97, 42.3, 33.7; HRMS (ESI⁺) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_6$ $[\text{M}+\text{H}]^+$ 366.1164, found 366.1165.

Supporting Information

Copies of all NMR spectra of all new compounds and of X-ray crystallographic data (CIF) for **3**, **4a**, **4b**, **5a**, **7a** and **7f**. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

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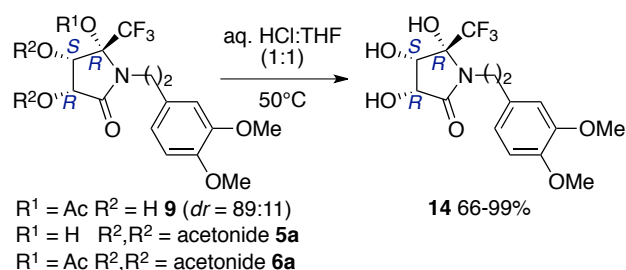
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²¹ Treatment of a 89 :11 mixture of diastereomers of deprotected *O*-acetyl *N,O*-acetal **9** under acidic conditions led mostly to the triol **14** (isolated in 78% yield). Triol **14** was also obtained by acid hydrolysis of the protected *N,O*-acetal **5a** and *O*-acetyl *N,O*-acetal **6a** in 99% and 66% yields, respectively. All these results confirmed unambiguously the configurations of the stereocenters of the major stereoisomer of **9** as *R,S,R* (see experimental section for details). It is noteworthy that HCl is not effective to generate α -CF₃ *N*-acyliminium ions, see for examples ref 7^{a,b}.



²² It is noteworthy that reaction of *N,O*-acetal **5a** with BF₃.Et₂O (10 equiv) in CH₂Cl₂ at rt for 24h or CF₃SO₃H (10 equiv) in HFIP at 0°C for 1h led to the formation of compound **10** as sole

product, no traces of Pictet-Spengler derivatives were detected in the ^{19}F NMR spectra of the crude reaction mixture.

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