JOC The Journal of Organic Chemistry

Article

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Diastereoselective Ritter-like Reaction on Cyclic Trifluoromethylated *N,O*-Acetals Derived from L-Tartaric Acid

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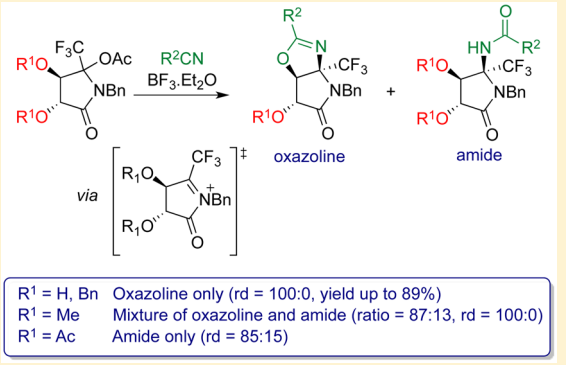
Supporting Information

ABSTRACT: Despite the presence of the highly electron-withdrawing fluorinated substituent, cyclic α-trifluoromethylated *N*-acyliminium ions were successfully generated from fluorinated *O*-acetyl-*N,O*-acetal L-tartaric acid derivatives. The addition of nitriles on these intermediates occurred with high to excellent *syn* diastereoselectivity and led, in most cases, to oxazolines and amides as single diastereomers. The diastereoselectivity of the addition and the nature of the reaction product depend on the substituents on the hydroxyl groups of the tartaric acid scaffold. This methodology gave access to enantiopure, highly functionalized 5-(trifluoromethyl)pyrrolidin-2-one derivatives, bearing the fluorinated substituent on a tetrasubstituted carbon.



INTRODUCTION

Five-membered aza-heterocycles are one of the privileged fragments of synthetic and natural biologically active substances.[1] Of these, 2-pyrrolidone structural motifs exhibit a high potential as a precursor of other *N*-heterocycles, such as pyrrolidines[2] and cyclic amidines,[3] and as a core of small molecules with multiple biological interests.[4] By way of an example, *inter alia*, 2-pyrrolidone derivatives have been described as γ-lactam analogues of prostaglandins by being a potent and selective EP4 receptor agonist and exhibiting a good pharmacological profile.[5]

Many pharmaceuticals and agrochemicals include a fluorine atom or a fluorine-containing group[6] as the introduction of this family of substituents may have a range of beneficial effects on the biological and physicochemical properties of bioactive molecules.[7] For example, the substitution of one or more hydrogen atoms by fluorine close to an amine function not only decreases its basicity but also enhances its metabolic stability.[8] Among all the fluorinated substituents, the trifluoromethyl group is one of the most important.[9]

5-(Trifluoromethyl)-pyrrolidin-2-ones, for which the fluorinated substituent is borne by a tetrasubstituted carbon, have been reported as conformationally restricted amino acids,[10] thrombin inhibitors,[11] and natural product analogues.[12] This family of synthons has been mainly prepared by the construction of the γ-lactam ring.[10,12c,13] A more challenging pathway, scarcely explored, is the elaboration of the tetrasubstituted carbon bearing the trifluoromethyl group by the addition of a nucleophile on a cyclic α-trifluoromethylated *N*-acyliminium ion.[11,12a,b]

N-Acyliminium ions have been widely used in organic synthesis.[14] Due to their highly reactive nature as electrophiles, they have to be generated *in situ* from a more stable precursor, usually an *N,O*-acetal.[14] However, the trifluoromethyl group not only strongly stabilizes *N,O*-acetal functions, and thus renders the formation of the α-trifluoromethyl *N*-acyliminium ions difficult, but also greatly destabilizes and hinders these ions. A few studies dealing with the addition of nucleophiles on these peculiar species have been reported.[11,12a,b,15] To date, only two studies leading to the functionalization of 5-(trifluoromethyl)-pyrrolidin-2-one derivatives have been described, and none are asymmetric.[11,12a,b] Fused nitrogen heterocycles carrying the fluorinated group on the bridgehead position were obtained by an intramolecular Friedel−Craft reaction on 5-silyloxy- or 5-hydroxy-5-(trifluoromethyl)-pyrrolidin-2-ones using an excess of a relatively strong Brønsted acid.[12a,b] The creation of a C−O bond was performed by the addition of methanol in the presence of hydrochloric acid on a α-trifluoromethylated *N,F*-acetal lactam derivative, because the corresponding *N,O*-acetal resisted most deoxygenation procedures except for deoxyfluorination.[11] The creation of a tetrasubstituted stereogenic carbon bearing a sterically demanding trifluoromethyl substituent by the addition of a nucleophile on a α-trifluoromethylated *N*-acyliminium ion is still challenging.

A few years ago, we reported the diastereoselective synthesis of aziridines, morpholines, and oxazepanes bearing a trifluoromethyl group on a tetrasubstituted carbon starting from L-tartaric acid following a strategy based on the ring construction of these aza-heterocycles.[16] We now report a practical way to prepare some original, highly functionalized derivatives of 2-

Received: July 20, 2017

DOI: 10.1021/acs.joc.7b01814
J. Org. Chem. XXXX, XXX, XXX−XXX

trifluoromethylpyrrolidinones using a strategy based on the creation of the tetrasubstituted carbon bearing the fluorinated substituent. For this purpose, we have studied the addition of various nitriles[17] on cyclic α-trifluoromethyl *N*-acyliminium ions derived from L-tartaric acid, which were generated *in situ* under an acidic treatment of the corresponding α-trifluoromethyl *N,O*-acetals. During this work, we have highlighted the influence of the protecting groups of the tartaric acid scaffold alcohols both on the nature of the reaction product and on the diastereoselectivity of the reaction.

RESULTS AND DISCUSSION

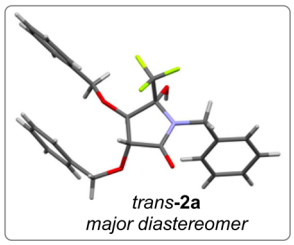
The requisite tartrimides **1a**–**e** were prepared by a one-pot activation–condensation–ring-closure sequence applied to the suitable *O,O′*-diprotected L-tartaric acid derivatives or directly to L-tartaric acid.[18,19]

The nucleophilic trifluoromethylation of various cyclic imides has been reported using trifluoromethyltrimethylsilane in the presence of an activating agent as a trifluoromethide equivalent. Although most studies were performed under conventional conditions, with a fluoride anion as the initiator in THF,[11,12b,20] the use of tri-*tert*-butylphosphine in DMF also enabled this reaction.[21] Our results concerning the nucleophilic trifluoromethylation of tartrimides **1a**–**e** are summarized in Table 1. After screening of a wide variety of fluoride anions, we found that the best yield for the nucleophilic trifluoromethylation of tartrimide **1a**, *O*- and *N*-protected with a benzyl group, was obtained using 2.04 equiv of CF_3SiMe_3 and 0.048 equiv of tetramethylammonium fluoride (TMAF·$4H_2O$) in THF (Table 1, entry 1). The *in situ* hydrolysis of the formed silylether led to *N,O*-acetal **2a** as an 86:14 mixture of two diastereomers, which were isolated in 80% yield. Both diastereomers of **2a** can be easily separated by chromatography on silica gel. Due to *N*-*para*-methoxybenzyl-*O,O′*-dibenzyltartrimide (**1b**) being insoluble in THF, these conditions were not suitable for the preparation of the corresponding *N,O*-acetal **2b**. However, a smooth trifluoromethylation of tartrimide **1b** took place upon treatment with 4 equiv of CF_3SiMe_3 and 0.2 equiv of K_2CO_3 in DMF (Table 1, entry 2).[16a,22] After treatment of the reaction mixture, desilylation was best achieved using fluoride instead of water, and *N,O*-acetal **2b** was isolated in 63% yield as a 71:29 mixture of two diastereomers. Both experimental conditions were applied to *N*-benzyl-*O,O′*-dimethyl tartrimide **1c**. Nucleophilic trifluoromethylation in the presence of TMAF·$4H_2O$ followed by the hydrolysis step led to *N,O*-acetal **2c** as a 84:16 mixture of two diastereomers, albeit in a moderate yield (39%) due to the formation of a considerable amount of a trifluoromethylated byproduct whose structure could not be elucidated (Table 1, entry 3). Using CF_3SiMe_3 and K_2CO_3 in DMF substantially improved the yield of *N,O*-acetal **2c**, which was directly isolated in 77% yield after the trifluoromethylation step but with a slightly lower diastereoselectivity (75:25) (Table 1, entry 4). These latter conditions were successfully applied to *N*-benzyl-tartrimide **1d** containing free alcohol functions (Table 1, entry 5). The desired *N,O*-acetal **2d** was obtained with a very good yield (90%) and a good diastereoselectivity (89:11). Disappointingly, none of the experimental conditions permitted the nucleophilic trifluoromethylation of tartrimide **1e** whose hydroxyl groups were protected as acetyl groups (Table 1, entry 6).

Table 1. Synthesis of α-Trifluoromethylated *N,O*-Acetals 2a–d

1a R^1=Bn R^2=Bn
1b R^1=Bn R^2=PMB
1c R^1=Me R^2=Bn
1d R^1=H R^2=Bn
1e R^1=Ac R^2=Bn

2a R^1=Bn R^2=Bn
2b R^1=Bn R^2=PMB
2c R^1=Me R^2=Bn
2d R^1=H R^2=Bn



entry	tartrimide	conditions[a]	*N,O*-acetal	dr[b] (*trans*/*cis*)	yield[c] (%)
1	**1a**	A	**2a**	86:14	80[d]
2	**1b**	B	**2b**	71:29	63
3	**1c**	A	**2c**	84:16	39
4	**1c**	B	**2c**	75:25	77
5	**1d**	B	**2d**	89:11	90
6	**1e**	A or B[e]			

[a]Reaction conditions A: CF_3TMS (2.04 equiv), TMAF·$4H_2O$ (0.048 equiv), THF, −20 °C then H_2O, rt. Reaction conditions B: CF_3TMS (3.9–4 equiv), K_2CO_3 (0.2 equiv), DMF, rt then TBAF (0.5–1 equiv), THF/H_2O (3:1), rt. [b]Diastereomeric ratios were determined by ^{19}F NMR of the crude mixture. [c]Unless noticed, the diastereomers were not separated. [d]Both diastereomers were separated by chromatography on silica gel (yield major diastereomer *trans*-**2a**, 68%; yield minor diastereomer *cis*-**2a**, 12%). [e]No reaction observed regardless of the experimental conditions.

Since the configuration of the leaving group can have a strong impact on the generation of the iminium ion,[23] the absolute configuration of the created trifluoromethylated stereocenter has been determined for the two diastereomers. The X-ray crystallography of the major diastereomer of **2a**[24] revealed that a *cis*-relationship between the CF_3 group and the neighboring benzyloxy group exists and that the absolute configuration of the new quaternary stereocenter is *R* (Table 1). To rationalize the stereochemical outcome of the reaction, we propose that the attack of the rather bulky CF_3 nucleophile on the carbonyl group of the imide occurred on the face where steric repulsion with the benzyloxy group is minimized according to the Bürgi–Dunitz trajectory,[25] affording the *trans*-isomer as the major diastereomer (Scheme 1).

We first attempted to generate the α-trifluoromethylated *N*-acyliminium ions directly from the trifluoromethylated *N,O*-acetals **2a** and **2d**. *N,O*-Acetals **2a** and **2d** were treated with 3 equiv of BF_3·Et_2O in acetonitrile, standard conditions reported for the reaction of the nitrile with *N*-acyliminium ions derived from (4*S*)-4,5-dihydroxypyrrolidin-2-one[17a] (Table 2). No reaction occurred at room temperature (Table 2, entries 1 and 2). The reaction was then conducted at reflux of the nitrile. Starting from *O,O′*-benzyl-*N,O*-acetal **2a**, only the fully *O*-debenzylated oxazoline derivative **3** was formed and was isolated in 77% yield (Table 2, entry 3). This oxazoline **3** can be obtained in a similar yield (77%) directly from *N,O*-acetal **2d** bearing two nonprotected hydroxyl groups (Table 2, entry 4).

DOI: 10.1021/acs.joc.7b01814
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 1. Proposed Transition State for the Nucleophilic Trifluoromethylation of Tartrimides

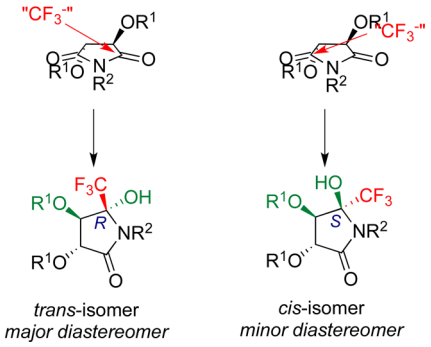
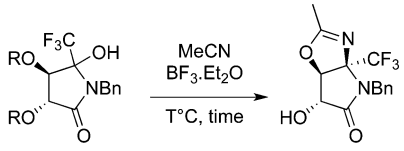


Table 2. Reaction of *N,O*-Acetals 2a and 2d with Acetonitrile in the Presence of $BF_3{\cdot}Et_2O$[a]



2a R=Bn (dr = 86:14)
2d R=H (dr = 89:11)
3

entry	*N,O*-acetal	*T* (°C)	time (h)	yield (%)
1	**2a**	rt	7.5	*b*
2	**2d**	rt	18	*b*
3	**2a**	reflux	5	75
4	**2d**	reflux	2	77

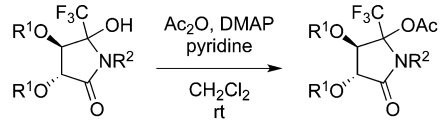
[a]Reaction conditions: $BF_3{\cdot}Et_2O$ (3 equiv) in MeCN. [b]No reaction.

In order to use a milder reaction temperature to generate the *N*-acyliminium ions, *O*-acetyl-*N,O*-acetals **4**, analogues of *N,O*-acetals **2** containing a better leaving group, were thus prepared and evaluated as precursors.

Treatment of each diastereomer of *N,O*-acetal **2a** and the mixture of diastereomers of **2a–c** with 1.7 equiv of acetic anhydride, 1.5 equiv of pyridine, and 0.1 equiv of DMAP in dichloromethane led to the corresponding *O*-acetyl-*N,O*-acetals *trans*-**4a**, *cis*-**4a**, and **4a–c** with very good yields ranging from 83% to 99% (Table 3, entries 1–5). The reaction of **2d**, in which alcohol functions are not protected, was performed using a bigger excess of acetic anhydride (5 equiv) and pyridine (4.51 equiv) in the presence of DMAP (0.3 equiv) in order to esterify the three hydroxyl groups (Table 3, entry 6). Thus, the corresponding peracetyl-*N,O*-acetal **4d** was isolated in 95% yield. Using this procedure circumvented the absence of the reaction of *O,O′*-acyltartrimide **1e** under the nucleophilic trifluoromethylation conditions (Table 1, entry 6)

The experimental conditions for the addition of acetonitrile were optimized on the major diastereomer *trans*-**4a** and 3 equiv of $BF_3{\cdot}Et_2O$ and were utilized in all cases (Table 4, entries 1–4). Using acetonitrile as the solvent at rt, *O*-benzyl oxazoline **5a** was smoothly formed (24 h of reaction) and was then isolated with an excellent yield of 97% (Table 4, entry 1). It is noteworthy that this Ritter-like reaction product **5a** can also be obtained in only 90 min at reflux of acetonitrile but in a slightly lower yield (80%) due to the formation of a small amount of amide **6a** (Table 4, entry 2). Amide **6a** results from the ring opening of oxazoline **5a** with water (see Table 8 for the structure). The reaction could also be performed with only 10 equiv of acetonitrile in dichloromethane as the solvent (Table 4, entries 3 and 4). At rt, the reaction was not complete (90% conversion after 30 h of stirring), and oxazoline **5a** was isolated in only 65% yield due to the concomitant formation of a non-negligible amount of *N,O*-acetals *cis*-**4a** and **2a** (6% and 18% conversion detected, respectively, in the ^{19}F NMR of the crude reaction mixture) (Table 4, entry 3). At reflux of dichloromethane, the reaction was faster (97% conversion after 8 h of stirring), and the yield of oxazoline **5a** was slightly improved to 71%. However, similar amounts of *N,O*-acetals *cis*-**4a** and **2a** were also formed (5% and 17% detected, respectively, in the ^{19}F NMR of the crude reaction mixture) (Table 4, entry 4). The formation of *cis*-**2a**, *trans*-**2a**, and *cis*-**4a** during the course of the reaction can be rationalized by the competitive nucleophilic attack of H_2O and $AcOBF_3$ on the intermediate

Table 3. Synthesis of α-Trifluoromethylated *O*-Acetyl-*N,O*-acetals 4a–d



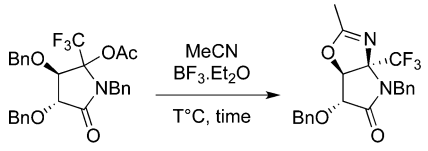
2a R^1=Bn R^2=Bn
2b R^1=Bn R^2=PMB
2c R^1=Me R^2=Bn
2d R^1=H R^2=Bn

4a R^1=Bn R^2=Bn
4b R^1=Bn R^2=PMB
4c R^1=Me R^2=Bn
4d R^1=Ac R^2=Bn

entry	*N,O*-acetal	dr[a] (*trans*/*cis*)	*O*-acetyl-*N,O*-acetal	yield (%)
1	*trans*-**2a**	100:0	*trans*-**4a**	99
2	*cis*-**2a**	0:100	*cis*-**4a**	93
3	**2a**	86:14	**4a**	92
4	**2b**	71:29	**4b**	83
5	**2c**	75:25	**4c**	91
6	**2d**	89:11	**4d**	95

[a]Diastereomeric ratios of starting materials **2a–d** and products **4a–d** were determined by ^{19}F NMR.

Table 4. Optimization of the Ritter-like Reaction Conditions on *N,O*-Acetals *trans*-4a and *cis*-4a[a]



trans-**4a**
cis-**4a**
5a

entry	*N,O*-acetal[b]	MeCN	*T* (°C)	time (h)	yield (%)
1	*trans*-**4a**	solvent	rt	24	97
2	*trans*-**4a**	solvent	reflux	1.5	80[c]
3	*trans*-**4a**	10 equiv	rt	30	65[d]
4	*trans*-**4a**	10 equiv	reflux	8	71[e]
5	*cis*-**4a**	solvent	rt	26	39[f]

[a]Reaction conditions: $BF_3{\cdot}Et_2O$ (3 equiv) in MeCN or $BF_3{\cdot}Et_2O$ (3 equiv), MeCN (10 equiv) in CH_2Cl_2. [b]*trans*-**4a**: From the major diastereomer of **2a**, the absolute configuration of the stereocenter bearing the CF_3 group is *R*. *cis*-**4a**: From the minor diastereomer of **2a**, the absolute configuration of the stereocenter bearing the CF_3 group is *S*. [c]Ratio oxazoline **5a**/amide **6a** 85:15 determined by the ^{19}F NMR spectra of the crude reaction mixture. 12% of amide **6a** was also isolated. [d]90% conversion. 6% of *cis*-**4a** and 18% of **2a** (dr *trans*/*cis* 96:4) were also detected by ^{19}F NMR of the crude reaction mixture. [e]97% conversion. 5% of *cis*-**4a** and 17% of **2a** (dr *trans*/*cis* 99:1) were also detected by ^{19}F NMR of the crude reaction mixture. [f]42% conversion determined by ^{19}F NMR.

DOI: 10.1021/acs.joc.7b01814
J. Org. Chem. XXXX, XXX, XXX–XXX

N-acyliminium ion. It is noteworthy that, when using *O*-acetyl-*N*,*O*-acetal **4a** as the starting material, no traces of debenzylated oxazoline **3** were detected in the ^{19}F NMR spectra of the crude reaction mixture regardless of the reaction conditions. Better conversions in oxazoline **5a** have been obtained using acetonitrile as the solvent (Table 4, entries 1 and 2) instead of only 10 equiv in dichloromethane (Table 4, entries 3 and 4), but these latter conditions will be particularly advantageous for nitriles that cannot be used as a solvent. The best experimental conditions (acetonitrile as the solvent, at rt) were then applied to *N*,*O*-acetal *cis*-**4a**, the minor diastereomer (Table 4, entry 5). Only 42% conversion of *cis*-**4a** in oxazoline **5a** after 18 h of stirring was detected by ^{19}F NMR, and oxazoline **5a** was thus isolated in 39% yield. The slowness of this reaction on *cis*-**4a** might be attributed to the more difficult generation of the intermediate *N*-acyliminium ion from the minor *cis*-**4a** diastereomer in comparison with that of the major *trans*-**4a** for conformational reasons.[23] The structure of **5a** was confirmed by 2D NOESY and ^{19}F,^{1}H HOESY (heteronuclear NOESY) experiments (Figure 1).

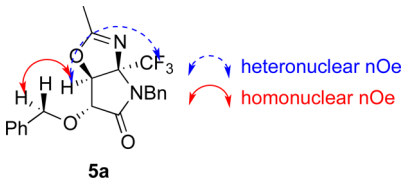


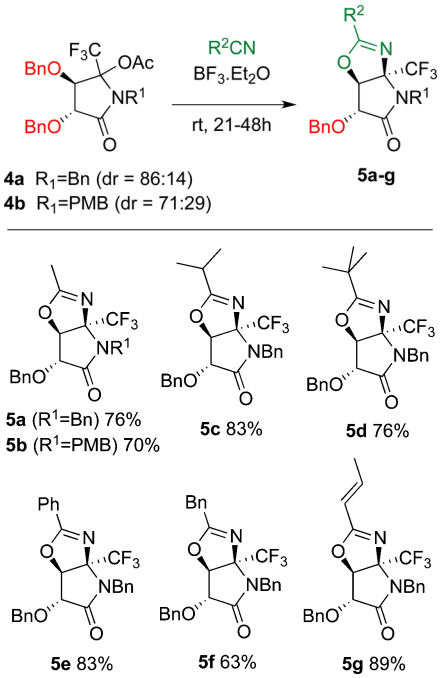
Figure 1. NOE connectivities on oxazoline **5a**.

Even if the Ritter-type reaction was sluggish with the minor diastereomer of *N*,*O*-acetal **4a**, the addition of various nitriles in the presence of 3 equiv of $BF_3{\cdot}Et_2O$ was carried out on a mixture of diastereomers of *O*,*O*′-benzyl-*N*,*O*-acetals **4a** and **4b** at room temperature (Table 5). Optimized conditions, with nitrile as the solvent, were used except for nitrile having a high boiling point, for which only 10 equiv was used in dichloromethane to facilitate the purification of the oxazoline. The addition of various aliphatic nitriles led to the corresponding oxazolines **5a**−**d**, which were isolated in good to very good yields (ranging from 70% to 83%). However, due to the steric hindrance around the electrophilic carbon of the iminium ion function caused by the trifluoromethyl substituent, the addition of sterically hindered *iso*-propyl cyanide or *tert*-butyl cyanide was slower than the addition of acetonitrile (41−48 h instead of 28−31 h). A similar long reaction time (40 h) was necessary to complete the addition of phenyl cyanide on *N*,*O*-acetal **4a**. After purification, oxazoline **5e** was isolated in 83% yield. The reaction with benzyl cyanide was performed in dichloromethane and gave, after 48 h at room temperature, the corresponding oxazoline **5f** in a slightly lower yield (63%). The addition of allyl cyanide resulted in oxazoline **5g**, in which the double bond C=C migrated to be conjugated with the double C=N bond. Oxazoline **5g** was isolated in 89% yield after 21 h of reaction.

The influence of α-trifluoromethylated *N*,*O*-acetals bearing other hydroxyl protecting groups on the course of the reaction was then evaluated.

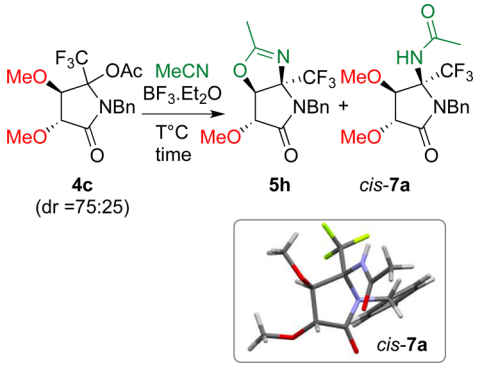
The reaction of *O*,*O*′-methyl-*N*,*O*-acetal **4c** with acetonitrile in the presence of 3 equiv of $BF_3{\cdot}Et_2O$ was first examined (Table 6). The reaction was not complete after 23 h at room temperature (73% conversion) (Table 6, entry 1). Oxazoline **5h**, for which the formation implied a challenging demethylation step during the reaction, was the major compound. As this demethylation step is not favored, *O*,*O*′-methyl amide *cis*-**7a** was also isolated. It is interesting to note that, although the diastereoselectivity of the addition of nucleophiles to the *N*-acyliminium ions generated *in situ* from cyclic imides derived from tartaric acid or malic acid is typically modest,[14c] amide **7a** was formed as a single diastereomer. The *cis*-relationship between the amide group and the adjacent oxygenated

Table 5. Ritter-Type Reaction on Benzyl-Protected *N*,*O*-Acetals 4a and 4b[a]



[a]Reaction conditions for **5a**−**e**,**g**: $BF_3{\cdot}Et_2O$ (3 equiv) in R^2CN, rt, 21−48 h. Reaction conditions for **5f**: BnCN (10 equiv), $BF_3{\cdot}Et_2O$ (3.05 equiv) in CH_2Cl_2, rt, 48 h.

Table 6. Addition of Acetonitrile on *O*,*O*′-Methyl-Protected *N*,*O*-Acetal 4c[a]



entry	*T* (°C)	time (h)	ratio[b] (**5h**/*cis*-**7a**)	yield (%) **5h**	yield (%) *cis*-**7a**
1	rt	23[c]	55:45	29	19
2	50	6	63:37	46	21
3	reflux	1.5	87:13	68	13

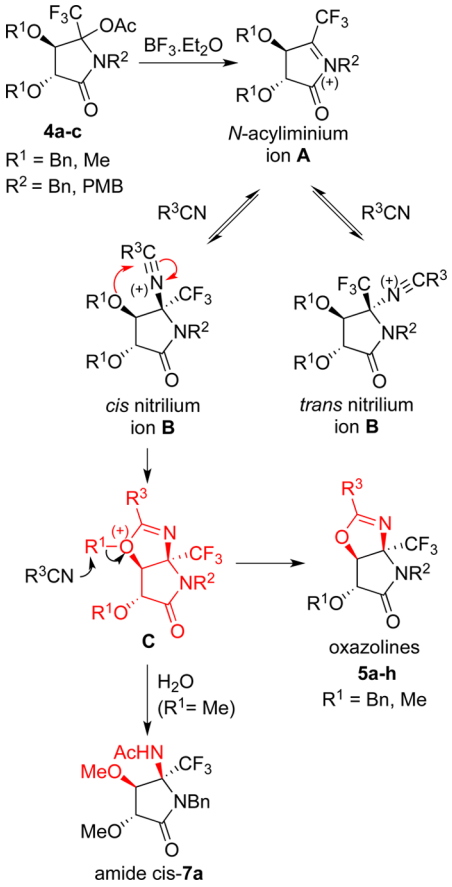
[a]Reaction conditions: $BF_3{\cdot}Et_2O$ (3 equiv) in MeCN. [b]Ratios determined by ^{19}F NMR of the crude reaction mixture. A single diastereomer was detected for each compound, **5h** and *cis*-**7a**. [c]73% conversion determined by ^{19}F NMR of the crude reaction mixture.

DOI: 10.1021/acs.joc.7b01814
J. Org. Chem. XXXX, XXX, XXX−XXX

substituent of **7a**[24] was determined from its X-ray structural analysis. Conducting the reaction at higher temperatures allowed a full conversion of the starting *N,O*-acetal **4c**, increased the intramolecular cyclization rate leading to oxazoline **5h**, and thus decreased the formation of amide *cis*-**7a** (until a 87:13 ratio at reflux of acetonitrile) (Table 6, entries 2 and 3). At reflux of acetonitrile, oxazoline **5h** and amide *cis*-**7a** were isolated in 68% and 13% yields, respectively (Table 6, entry 3).

The excellent *cis* diastereoselectivity for the formation of oxazolines **5a−h** and of amide **7a** can be rationalized on the basis of the mechanism suggested by Pyne[17a] for the addition of nitriles on *N*-acyliminium ions derived from (4*S*)-4,5-dihydroxypyrrolidone and (4*S*)-4-(benzyloxy)-5-hydroxypyrrolidone (Scheme 2). The attack of nitriles on *N*-acyliminium ion

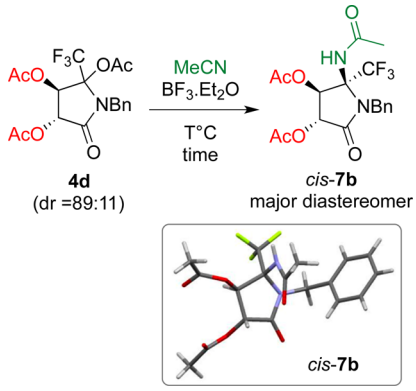
Scheme 2. Proposed Mechanism for the Formation of Oxazolines 5a−h and Amide *cis*-7a from *N,O*-Acetals 4a−c



A giving the *cis*- and *trans*-nitrilium ion **B** might be reversible, and due to its *cis* stereochemistry, the *cis*-nitrilium ion **B** more readily cyclizes to the oxazoline cationic intermediate **C**.[26] Debenzylation or demethylation gives the oxazolines **5a−h**. Due to demethylation being less favorable than debenzylation, and amide **7a** being only obtained as its *cis* isomer, we propose that *cis*-**7a** stems from the concomitant hydrolysis of the methoxy cyclic intermediate **C**, not from the hydrolysis of nitrilium ion **B**.

O,O′-Acetyl-*N,O*-acetal **4d** was treated under the same experimental conditions (Table 7). At room temperature, only a low conversion of the starting *N,O*-acetal **4d** was observed (45%, Table 7, entry 1). Amide **7b** (89:11 mixture of

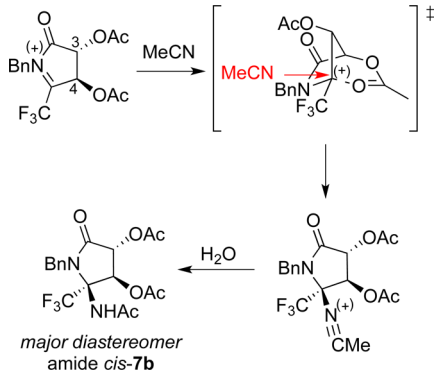
Table 7. Addition of Acetonitrile on *O,O′*-Acetyl-Protected *N,O*-Acetal 4d[a]



				yield (%)	
entry	*T* (°C)	time (h)	dr **7b** (*cis*/*trans*)[b]	*cis*-**7b**	*trans*-**7b**
1	rt	46[c]	89:11	31[d]	31[d]
2	50	30	86:14	73	10
3	reflux	6	85:15	63	13

[a]Reaction conditions: $BF_3{\cdot}Et_2O$ (3 equiv) in MeCN. [b]Diastereomeric ratios of amides **7b** determined by ^{19}F NMR of the crude reaction mixture. [c]45% conversion determined by ^{19}F NMR of the crude reaction mixture. [d]Diastereomers not separated.

Scheme 3. Proposed Mechanism for the *syn* Selectivity of the Addition of Acetonitrile on *O,O′*-Acetyl *N*-Acyliminium Ion Derived from *N,O*-Acetal 4d



cis/*trans* diastereomers) was the only product formed. The *cis*-relationship between the amide group and the adjacent oxygenated substituent of the major diastereomer of **7b**[24] was determined from its X-ray structural analysis. At 50 °C, acetal **4d** was fully converted into *O,O′*-acetyl amides **7b**, which were formed in an 86:14 mixture of diastereomers and isolated in 73% and 10% yields, respectively (Table 7, entry 2). Similar results were obtained at reflux of acetonitrile (Table 7, entry 3). Due to the oxygen atom of the neighboring acetoxy group being less nucleophilic than that of the one of the benzyloxy or methoxy groups, no traces of oxazoline were formed, even at reflux.

The formation of a 85:15 to 89:11 mixture of *cis*- and *trans*-amide **7b** should reflect the prevalent *syn* addition of nitrile on the *N*-acyliminium ion generated from *O,O′*-acetyl-*N,O*-acetal **4d**. Since the neighboring group participation of the 4-*O*-acetyl group in the stereocontrol of the reaction should favor the *anti* addition of the nucleophile,[14d,27] it would appear that the 3-*O*-

DOI: 10.1021/acs.joc.7b01814
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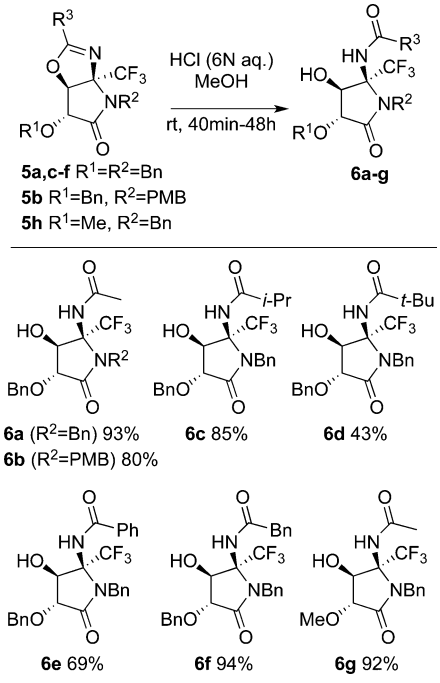
acetyl group provided the anchimeric assistance, leading to the preferential formation of the *cis*-isomer[28] (Scheme 3).

Acid hydrolysis of oxazolines **5a−f,h** with HCl in methanol at room temperature led to the corresponding *cis*-hydroxyamides **6a−g**, in which one alcohol function has been selectively deprotected (Table 8). With most of the substituents on the

Table 8. Hydrolysis of Oxazolines 5a−f,h into Corresponding Hydroxylamides 6a−g



oxazoline ring (methyl, *iso*-propyl, or benzyl), this reaction was complete in a short reaction time (4 h or less), and amides **6a−c,f,g** were isolated with a yield ranging from 80% to 94%. However, the efficiency of the reaction seems to depend on the bulkiness of this substituent. With *tert*-butyl and phenyl groups, the reactions were not complete even after long reaction times (55% and 75% conversion after 46−48 h at room temperature), and the corresponding amides **6d** and **6e** were thus isolated in only 43% and 69% yields, respectively.

The retention of the *cis*-relationship between the hydroxyl group and the *exo* amide function was confirmed by 2D NOESY and $^{19}F,^{1}H$ HOESY (heteronuclear NOESY) experiments on compound **6a** (Figure 2).

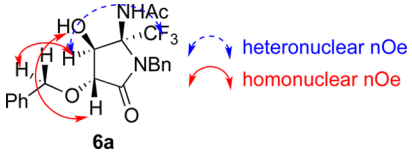


Figure 2. NOE connectivities on hydroxyamide **6a**.

Full deprotection of oxazoline **5a** with HCl in methanol at 60 °C gave, after 29 h of reaction, the conformationally stable *cis*-hydroxyamine **8** in 68% yield (Scheme 4).

Finally, we have shown that the Ritter-like reaction and the hydrolysis step can also be carried out without purification of the intermediate oxazoline (Table 9). Treatment of *N,O*-acetal **4a** with acetonitrile in the presence of 3 equiv of $BF_3{\cdot}Et_2O$ at

Scheme 4. Hydrolysis of Oxazoline 5a into Corresponding Hydroxylamine 8

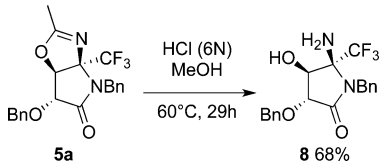
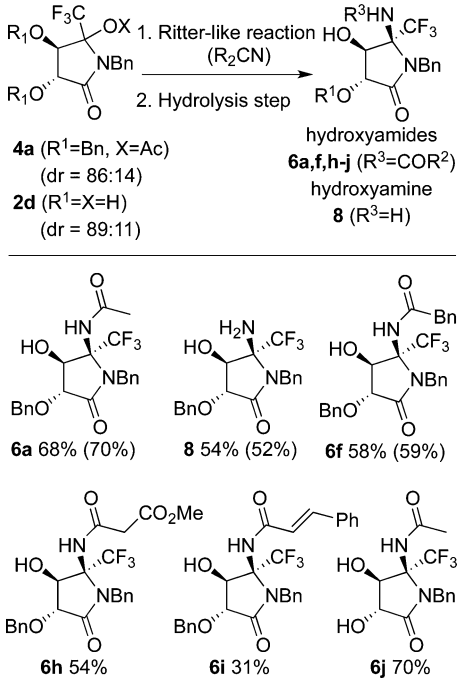


Table 9. Reaction Sequence "Addition of Nitrile−Acid Hydrolysis" on *N,O*-Acetals 4a and 2d[a,b]



[a]Reaction conditions for **6a** and **6f**: RCN (solvent), $BF_3{\cdot}Et_2O$ (3 equiv), rt then HCl (6 N aq), MeOH, rt. Reaction conditions for **8**: MeCN (solvent), $BF_3{\cdot}Et_2O$ (3 equiv), rt then HCl (6 N aq), MeOH, 60 °C. Reaction conditions for **6h−i**: RCN (10 equiv), $BF_3{\cdot}Et_2O$ (3 equiv), CH_2Cl_2, rt then HCl (6 N aq), MeOH, rt. Reaction conditions for **6j**: MeCN (solvent), $BF_3{\cdot}Et_2O$ (3 equiv), reflux then HCl (6 N aq), MeOH, rt. [b]The yield for the whole sequence with purification of the intermediate oxazoline is indicated between brackets.

room temperature followed, after work up, by the hydrolysis under acidic conditions (HCl 6 N aq in methanol) led to hydroxyamide **6a** or hydroxylamine **8** depending on the temperature of the deprotection reaction. These two-step sequences get similar yields to the ones obtained when oxazoline **5a** was purified (64% and 54% instead of 70% and 52%, respectively). This process was particularly convenient for performing the reaction with a nitrile that has a high boiling point, for which purification of the intermediate oxazoline can be difficult. In this case, the Ritter-like reaction step is performed with 10 equiv of a suitable nitrile in dichloromethane as the solvent, and after hydrolysis, the hydroxyamides **6f,h,i**, variously substituted on the amide alkyl chain, were obtained in moderate to good yields (from 31% to 58%). These yields reflect the partial conversion observed for one or both steps of the reaction sequence. The yield of **6f** was identical to that of the global one obtained when oxazoline **5f** was isolated. This approach was also applied directly to *N,O*-acetal **2d**. In this latter case, the Ritter-like reaction step was performed at

DOI: 10.1021/acs.joc.7b01814
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reflux of acetonitrile, and hydroxyamide **6j** was isolated, after the acid hydrolysis reaction, in 70% yield.

CONCLUSION

Although the electron-withdrawing trifluoromethyl group has not only rendered the formation of adjacent *N*-acyliminium ions difficult by strongly stabilizing the *N*,*O*-acetal precursor but also destabilized and hindered these ions, rendering the reactions with nucleophiles arduous, α-trifluoromethylated iminium ions have been successfully generated by the treatment of *O*-acetyl-*N*,*O*-acetals derived from L-tartaric acid with $BF_3 \cdot Et_2O$. Using nitriles as nucleophiles afforded the corresponding 3a-(trifluoromethyl)-pyrrolo[2,3-*d*]-oxazolone and 2-acyl-2-trifluoromethylpyrrolidone derivatives. Hydroxyl groups and ether substituents directed the Ritter-like reaction mostly or exclusively toward the formation of oxazoline derivatives, while esters led to an amide function, which was obtained with high *syn* diastereoselectivity. A small library of original, highly functionalized 5-(trifluoromethyl)-pyrrolidin-2-ones bearing the fluorinated substituent on a tetrasubstituted carbon was thereby obtained.

EXPERIMENTAL SECTION

THF, CH_2Cl_2, and MeCN were dried using a Pure Solv solvent drying system over aluminum oxide under an argon atmosphere. DMF (extra dry, water <0.005%) was purchased from Acros Organics. CF_3SiMe_3 was distilled under Ar prior to use. Thin-layer chromatography using precoated aluminum backed plates (Merck Kieselgel 60F254) was visualized by UV light and by phosphomolybdic acid. Silica gel 40−63 μm (Macherey−Nagel GmbH & Co KG) was used for flash chromatography. NMR spectra were recorded in $CDCl_3$ with 250, 500, or 600 MHz spectrometers. Chemicals shifts (δ) were reported in ppm relative to TMS for ^{1}H and ^{13}C NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. In the ^{13}C NMR data (J-MOD), reported signal multiplicities were related to the 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 (quintet), hept (heptuplet), m (multiplet). COSY, HSQC, and HMBC 2D NMR experiments were used to confirm the NMR peak assignments for compounds **2**−**8**. Diastereomeric ratios (dr) were determined by ^{19}F NMR. HRMS were recorded on an ESI-Q-TOF mass spectrometer using an electrospray source in positive mode. Melting points (mp) were determined on a Tottoli apparatus and were uncorrected. Optical rotations were measured at room temperature (ca. 20 °C).

General Procedure for Preparation of Tartrimides 1a−c by a One-Pot Activation−Condensation−Ring-Closure Sequence.[18] A solution of *O*,*O*′-protected L-tartaric acid in acetyl chloride (8.4−16.5 equiv) was heated at reflux under Ar for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the solid anhydride was dissolved in dichloromethane. The amine (1.08−1.21 equiv) was added dropwise at 0 °C. After 15 min of stirring at 0 °C and 5 h at reflux, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. A solution of amido acid in acetyl chloride (8.4−16.5 equiv) was heated at reflux for 6 h, then cooled to room temperature, and concentrated under reduced pressure. Purification of the residue afforded tartrimide **1**.

*(3R,4R)-1-Benzyl-3,4-bis(benzyloxy)pyrrolidine-2,5-dione (**1a**).* According to a general procedure, a solution of *O*,*O*′-benzyl L-tartaric acid[25] (13.7 g, 41.5 mmol) reacted with acetyl chloride (25 mL, 350.3 mmol, 8.4 equiv). Then the formed anhydride reacted with benzylamine (5.5 mL, 50.3 mmol, 1.2 equiv) in CH_2Cl_2 (23 mL), and finally the obtained amido acid reacted with acetyl chloride (25 mL, 350.3 mmol, 8.4 equiv). Purification by chromatography on silica gel (PE/EtOAC 8:1) afforded the known tartrimide **1a**[29] (12.9 g, 78%) as a white solid: mp 90 °C; $[\alpha]_D^{20}$ +152 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 698, 1022, 1080, 1102, 1337, 1709, 1786, 2863, 3030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.66 (d, *J* = 14.0 Hz, 1H), 4.69 (d, *J* = 14.0 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 2H), 5.02 (d, *J* = 11.5 Hz, 2H), 7.31−7.41 (m, 15H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 42.4, 73.6, 78.9, 128.30, 128.36, 128.37, 128.8, 129.0, 135.1, 136.6, 172.5; HRMS (ESI$^+$) *m*/*z* calcd for $C_{25}H_{23}NNaO_4$ $[M + Na]^+$ 424.1525, found 424.1522.

*(3R,4R)-3,4-Bis(benzyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**1b**).* According to a general procedure, *O*,*O*′-benzyl L-tartaric acid[25] (7.1 g, 21.5 mmol) reacted with acetyl chloride (15 mL, 210.2 mmol, 9.8 equiv). Then the formed anhydride reacted with *p*-methoxybenzylamine (3.4 mL, 26.0 mmol, 1.21 equiv) in CH_2Cl_2 (23 mL), and finally the obtained amido acid reacted with acetyl chloride (20 mL, 280.2 mmol, 13 equiv). Purification by recrystallization in EtOAc afforded the known tartrimide **1b**[18,25] (7.04 g, 76%) as a beige solid: mp 132 °C; $[\alpha]_D^{20}$ +203 (*c* 0.80, CH_2Cl_2); IR (KBr) ν_{max} 699, 746, 1105, 1251, 1342, 1606, 1722, 2062, 2610, 2886, 3427 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.38 (s, 2H), 4.60 (s, 2H), 4.75 (d, *J* = 11.5 Hz, 2H), 5.00 (d, *J* = 11.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 41.9, 55.4, 73.6, 79.0, 114.2, 127.4, 128.4, 128.6, 130.9, 136.6, 159.6, 172.5; HRMS (ESI$^+$) *m*/*z* calcd for $C_{26}H_{25}NNaO_5$ $[M + Na]^+$ 454.1630, found 454.1614.

*(3R,4R)-1-Benzyl-3,4-dimethoxypyrrolidine-2,5-dione (**1c**).* According to a general procedure, *O*,*O*′-methyl L-tartaric acid[30] (3.32 g, 18.6 mmol) reacted with acetyl chloride (22 mL, 308.3 mmol, 16.5 equiv). Then the formed anhydride reacted with benzylamine (2.2 mL, 20.1 mmol, 1.08 equiv) in CH_2Cl_2 (25 mL), and finally the obtained amino acid reacted with acetyl chloride (22 mL, 308.3 mmol, 16.5 equiv). Purification by chromatography on silica gel (PE/EtOAC 4:1) afforded tartrimide **1c** (2.19 g, 47%) as a white solid: mp 126 °C; $[\alpha]_D^{20}$ +190 (*c* 1.01, $CHCl_3$); IR (KBr) ν_{max} 703, 961, 1074, 1118, 1152, 1340, 1431, 1716, 2834, 2951, 2987, 3486 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.68 (s, 6H), 4.12 (s, 2H), 4.63 (s, 2H), 7.30 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 42.3, 59.8, 81.4, 128.3, 128.8, 129.0, 135.1, 172.2; HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{15}NNaO_4$ $[M + Na]^+$ 272.0899, found 272.0893.

*(3R,4R)-1-Benzyl-2,5-dioxopyrrolidine-3,4-diyl Diacetate (**1e**).* A solution of L-tartaric acid (15 g, 100 mmol) in acetyl chloride (73 mL, 1023 mmol, 10.2 equiv) was heated at reflux under Ar for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the solid residue was dissolved in anhydrous THF (120 mL). Benzylamine (12 mL, 109.9 mmol, 1.1 equiv) was added dropwise at 0 °C. After 15 min of stirring at 0 °C and 3 h at reflux, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. A solution of the residue in acetyl chloride (70 mL, 981 mmol, 9.8 equiv) was heated at reflux for 5 h, then cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and an aq solution of 10% (v/v) HCl , dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the known tartrimide **1e**[31] (25.2 g, 82%) as a white solid: mp 121 °C; $[\alpha]_D^{20}$ +113 (*c* 1.01, CH_2Cl_2); IR (KBr) ν_{max} 705, 1023, 1072, 1174, 1224, 1354, 1439, 1720, 3007, 3492 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.17 (s, 6H), 4.67 (d, *J* = 14.0 Hz, 1H), 4.76 (d, *J* = 14.0 Hz, 1H), 5.53 (s, 2H), 7.30−7.38 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.4, 43.2, 72.8, 128.4, 128.9, 134.6, 169.2, 169.9; HRMS (ESI$^+$) *m*/*z* calcd for $C_{15}H_{15}NNaO_6$ $[M + Na]^+$ 328.0797, found 328.0798.

*(3R,4R)-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (**1d**).* A solution of tartrimide **1e** (20 g, 65.5 mmol) and acetyl chloride (14 mL, 196 mmol, 3 equiv) was stirred for 15 min at 0 °C and 24 h at rt and was then concentrated under reduced pressure to give the known tartrimide **1d**[32] (14.4 g, 99%) as a yellowish solid: mp 201 °C; $[\alpha]_D^{20}$ +135 (*c* 2.00, MeOH); IR (KBr) ν_{max} 693, 1007, 1162, 1348, 1711, 2922, 3287 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD) δ 4.27 (s, 2H), 4.39 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 6.18 (br s, 2H), 7.14 (m, 5H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 50.7, 84.0, 137.0, 138.1, 145.5, 184.1; HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{11}NNaO_4$ $[M + Na]^+$ 244.0586, found 244.0583.

DOI: 10.1021/acs.joc.7b01814
J. Org. Chem. XXXX, XXX, XXX−XXX

General Procedure for the Preparation of *N,O*-Acetals 2a–d by Nucleophilic Trifluoromethylation of Tartrimides 1a–d. *General Procedure A.* To a solution of tartrimide **1** in THF were slowly added, at −20 °C under Ar, TMAF·4H_2O (0.048 equiv) and CF_3TMS (2.04 equiv). The reaction was stirred at this temperature until the full conversion of the starting tartrimide (reaction monitored by TLC and ^{19}F NMR). Water was added, and the reaction was stirred at room temperature. After the complete conversion of the silyl ether intermediate (reaction monitored by TLC and ^{19}F NMR), the reaction was extracted three times with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel afforded *N,O*-acetals **2**.

General Procedure B. To a solution of tartrimide **1** and K_2CO_3 (0.1 equiv) in DMF was slowly added, at 0 °C under Ar, CF_3TMS (2 equiv). After 20 min of stirring at 0 °C and 2 h at room temperature, supplementary amounts of K_2CO_3 (0.1 equiv) and CF_3TMS (2 equiv) were added. After the complete conversion of the starting tartrimide (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then dissolved in a mixture of THF/H_2O (3:1), and a solution of *tetra-n*-butylammonium fluoride (1 M in THF, 0.1 equiv) was added at room temperature. After the complete conversion of the silyl ether intermediate (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel afforded *N,O*-acetals **2**.

*(3R,4R)-1-Benzyl-3,4-bis(benzyloxy)-5-hydroxy-5-(trifluoromethyl)pyrrolidin-2-one (**2a**).* According to General Procedure A, a solution of tartrimide **1a** (4.8 g, 12.0 mmol), TMAF·4H_2O (95 mg, 0.58 mmol, 0.048 equiv), and CF_3TMS (3.6 mL, 24.5 mmol, 2.04 equiv) in THF (115 mL) was stirred for 1.5 h and was then hydrolyzed with H_2O (100 mL) for 21 h. Purification of the residue (dr = 86:14) on silica gel (CH_2Cl_2/Et_2O 10:0 to 19:1) afforded the minor diastereomer *cis*-**2a** (650 mg, 12%) followed by the major diastereomer *trans*-**2a** (3.86 g, 68%). *cis*-**2a**: pale yellow solid; mp 73 °C; $[\alpha]_D^{20}$ +79 (*c* 1.01, $CHCl_3$); IR (KBr) ν_{max} 701, 948, 1031, 1112, 1180, 1321, 1454, 1735, 2951, 3033, 3357 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −80.6 (s, 3F, CF_3); ^{19}F NMR (CD_3OD, 235.5 MHz) δ −80.6 (s, 3F, CF_3); ^1H NMR (CD_3OD, 500 MHz) δ 4.19 (d, ^3J = 5.0 Hz, 1H, CH—C—CF_3), 4.29 (d, ^3J = 5.0 Hz, 1H, CH—C═O), 4.48 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.60 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C—CF_3), 4.63 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.74 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C═O), 4.76 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C—CF_3), 4.86 (br s, 1H, OH), 4.92 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C═O), 7.20–7.37 (m, 15H, 15 CHar (aromatic)); ^{13}C NMR (CD_3OD, 125.7 MHz) δ 44.9 (N—CH_2), 73.8 (CH_2—O—CH—C═O), 74.3 (CH_2—O—CH—C—CF_3), 79.0 (CH—C—CF_3), 80.2 (CH—C═O), 88.3 (q, $^1J_{CF}$ = 32.5 Hz, C—CF_3), 124.4 (q, $^2J_{CF}$ = 286.0 Hz, CF_3), 128.1 (CHar), 128.7 (CHar), 129.07 (CHar), 129.15 (CHar), 129.18 (CHar), 129.4 (CHar), 137.9 (C_{IV}ar, N—Bn), 138.3 (C_{IV}ar, CF_3—C—CH—O—Bn), 138.6 (C_{IV}ar, O═C—CH—O—Bn), 173.8 (C═O); HRMS (ESI^+) *m*/*z* calcd for $C_{26}H_{24}F_3NNaO_4$ $[M + Na]^+$ 494.1555, found 494.1556. *trans*-**2a**: white solid; mp 104 °C; $[\alpha]_D^{20}$ +80 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 694, 738, 1025, 1062, 1163, 1197, 1256, 1358, 1451, 1498, 1690, 3031, 3184 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −78.6 (s, 3F, CF_3); ^{19}F NMR (CD_3OD, 235.5 MHz) δ −74.6 (s, 3F, CF_3); ^1H NMR (CD_3OD, 500 MHz) δ 4.29 (d, ^3J = 8.0 Hz, 1H, CH—C—CF_3), 4.40 (d, ^3J = 8.0 Hz, 1H, CH—C═O), 4.52 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.61 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.70 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3), 4.75 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O), 4.93 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3), 4.97 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O), 7.20–7.36 (m, 15H, 15 CHar); ^{13}C NMR (CD_3OD, 125.7 MHz) δ 44.0 (N—CH_2), 74.2 (CH_2—O—CH—C═O), 75.0 (CH_2—O—CH—C—CF_3), 79.5 (CH—C═O), 88.5 (CH—C—CF_3), 88.6 (q, $^2J_{CF}$ = 30.5 Hz, C—CF_3), 124.9 (q, $^2J_{CF}$ = 288.0 Hz, CF_3), 128.1 (CHar), 128.6 (CHar), 128.9 (CHar), 129.1 (CHar), 129.2 (CHar), 129.3 (CHar), 129.4 (CHar), 138.4 (C_{IV}ar, N—Bn), 138.6 (C_{IV}ar, CF_3—C—CH—O—Bn), 138.8 (C_{IV}ar, O═C—CH—O—Bn), 172.3 (C═O); HRMS (ESI^+) *m*/*z* calcd for $C_{26}H_{24}F_3NNaO_4$ $[M + Na]^+$ 494.1555, found 494.1548. An analytical sample of *trans*-**2a** was crystallized from Et_2O/PE.

*(3R,4R)-3,4-Bis(benzyloxy)-5-hydroxy-1-(4-methoxybenzyl)-5-(trifluoromethyl)pyrrolidin-2-one (**2b**).* According to General Procedure B, a mixture of tartrimide **1b** (1.5 g, 3.47 mmol), K_2CO_3 (98 mg, 0.71 mmol, 0.2 equiv), and CF_3TMS (2 mL, 13.53 mmol, 3.9 equiv) in DMF (28 mL) was stirred for 21 h. After treatment, a solution of the residue and TBAF (1.75 mL, 1.75 mmol, 0.5 equiv) in a mixture of THF/H_2O (40 mL) was stirred for 1 h. Purification of the residue (dr = 71:29) on silica gel (PE/EtOAc 4:1) afforded *N,O*-acetal **2b** (1.1 g, 63%, dr = 71:29) as a yellow oil: IR (film) ν_{max} 699, 754, 1029, 1111, 1193, 1250, 1353, 1454, 1514, 1613, 1699, 2935, 3032, 3273 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −76.9 (s, 3F, CF_3, major), −79.4 (s, 3F, CF_3, minor); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 3H, OCH_3, major), 3.76 (s, 3H, OCH_3, minor), 3.89 (br s, 1H, OH, major), 4.06 (d, ^3J = 5.0 Hz, 1H, CH—C═O, minor), 4.16 (m, 1H, CH—C—CF_3, major), 4.17 (m, 1H, CH—C—CF_3, minor), 4.22 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 4.31 (d, ^3J = 8.0 Hz, 1H, CH—C═O, major), 4.38 (br s, 1H, OH, minor), 4.46 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 4.56 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 4.63 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, major), 4.65 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, minor), 4.73 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, major), 4.74 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, minor), 4.76 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 4.79 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, minor), 4.81 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, major), 5.01 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, minor), 5.04 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, major), 6.78 (m, 2H, 2 CHar, major), 6.81 (m, 2H, 2 CHar, minor), 7.22–7.38 (m, 12H, 12 CHar, major and minor); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 43.1 (N—CH_2, major), 44.1 (N—CH_2, minor), 55.3 (OCH_3, minor), 55.4 (OCH_3, major), 73.0 (CH_2—O—CH—C═O, minor), 73.6 (CH_2—O—CH—C═O, major), 73.9 (CH_2—O—CH—C—CF_3, major), 74.0 (CH_2—O—CH—C—CF_3, minor), 77.2 (CH—C—CF_3, minor), 78.1 (CH—C—C═O, minor), 78.4 (CH—C—C═O, major), 85.9 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3, minor), 87.1 (CH—C—CF_3, major), 88.0 (q, $^2J_{CF}$ = 31.0 Hz, C—CF_3, major), 113.8 (CHar, minor), 114.2 (CHar, major), 122.9 (q, $^1J_{CF}$ = 288.5 Hz, CF_3, minor), 123.3 (q, $^1J_{CF}$ = 286.0 Hz, CF_3, major), 128.0 (CHar, major), 128.1 (CHar, minor), 128.2 (CHar, major), 128.4 (CHar, minor), 128.48 (CHar, minor), 128.53 (CHar, major), 128.6 (CHar, major), 128.7 (CHar, minor), 128.83 (CHar, major), 128.86 (CHar, minor), 129.4 (C_{IV}ar, N—CH_2—Ph, major), 129.7 (CHar, major), 129.9 (CHar, minor), 135.7 (C_{IV}ar, CF_3—C—CH—O—Bn, minor), 137.00 (C_{IV}ar, O═C—CH—O—Bn, minor), 137.04 (C_{IV}ar, CF_3—C—CH—O—Bn, major), 137.4 (C_{IV}ar, O═C—CH—O—Bn, major), 159.00 (C_{IV}ar, CH_3—O—Ph, major), 159.03 (C_{IV}ar, CH_3—O—Ph, minor), 170.6 (C═O, major), 171.8 (C═O, minor); HRMS (ESI^+) *m*/*z* calcd for $C_{27}H_{26}F_3NNaO_5$ $[M + Na]^+$ 524.1661, found 524.1656.

*(3R,4R)-1-Benzyl-5-hydroxy-3,4-dimethoxy-5-(trifluoromethyl)-pyrrolidin-2-one (**2c**).* According to General Procedure B, a mixture of tartrimide **1c** (1.2 g, 4.81 mmol), K_2CO_3 (135 mg, 0.98 mmol, 0.2 equiv), and CF_3TMS (2.86 mL, 19.34 mmol, 4 equiv) in DMF (25 mL) was stirred for 7.5 h. After treatment, *N,O*-acetal **2c** (dr = 75:25) was directly purified on silica gel (PE/EtOAc 3:1) to afford *N,O*-acetal **2c** (1.18 g, 77%, dr = 75:25) as a yellow oil: IR (film) ν_{max} 699, 757, 1075, 1199, 1265, 1350, 1449, 1709, 2841, 2941, 3004, 3280 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.4 (s, 3F, CF_3, major), −79.7 (s, 3F, CF_3, minor); ^1H NMR ($CDCl_3$, 600 MHz) δ 3.53 (s, 3H, CH_3—O—CH—C—CF_3, major), 3.60 (s, 3H, CH_3—O—CH—C═O, major), 3.61 (s, 3H, CH_3—O—CH—C—CF_3, minor), 3.64 (s, 3H, CH_3—O—CH—C═O, minor), 3.84 (d, ^3J = 5.0 Hz, 1H, CH—C═O, minor), 3.88 (d, ^3J = 5.0 Hz, 1H, CH—C—CF_3, minor), 3.93 (d, ^3J = 8.0 Hz, 1H, CH—C—CF_3, major), 4.01 (d, ^3J = 8.0 Hz, 1H, CH—

DOI: 10.1021/acs.joc.7b01814
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C=O, major), 4.32 (d, ^2J = 15.5 Hz, 1H, N—C$\underline{H}_a$H$_b$, major), 4.36 (br s, 1H, OH, minor), 4.52 (d, ^2J = 15.5 Hz, 1H, N—C$\underline{H}_a$H$_b$, minor), 4.59 (d, ^2J = 15.5 Hz, 1H, N—CH$_a\underline{H}_b$, minor), 4.70 (d, ^2J = 15.5 Hz, 1H, N—CH$_a\underline{H}_b$, major), 4.80 (br s, 1H, OH, major), 7.20–7.29 (m, 5H, 5 CHar, major and minor); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 43.4 (N—CH_2, major), 44.6 (N—CH_2, minor), 59.3 ($\underline{C}H_3$—O—CH—C=O, minor), 59.64 ($\underline{C}H_3$—O—CH—C—CF_3, minor), 59.7 ($\underline{C}H_3$—O—CH—C=O, major), 60.2 ($\underline{C}H_3$—O—CH—C—CF_3, major), 79.1 ($\underline{C}$H—C—CF_3, minor), 80.3 ($\underline{C}$H—C=O, major), 80.8 ($\underline{C}$H—C=O, minor), 85.7 (q, $^2J_{CF}$ = 33.5 Hz, $\underline{C}$—CF_3, minor), 87.8 (q, $^2J_{CF}$ = 31.0 Hz, $\underline{C}$—CF_3, major), 89.7 ($\underline{C}$H—C—CF_3, major), 122.7 (q, $^1J_{CF}$ = 286.0 Hz, CF_3, minor), 123.2 (q, $^1J_{CF}$ = 288.5 Hz, CF_3, major), 127.6 (CHar, major), 127.8 (CHar, major), 128.2 (CHar, minor), 128.4 (CHar, minor), 128.7 (CHar, major), 136.2 (C_{IV}ar, minor), 137.0 (C_{IV}ar, major), 170.6 (C=O, major), 171.7 (C=O, minor); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}F_3NNaO_4$ [M + Na]$^+$ 342.0929, found 342.0921.

*(3R,4R)-1-Benzyl-3,4,5-trihydroxy-5-(trifluoromethyl)pyrrolidin-2-one (**2d**).* According to General Procedure B, a mixture of tartrimide **1d** (2 g, 9.04 mmol), K_2CO_3 (252 mg, 1.82 mmol, 0.2 equiv), and CF_3TMS (5.40 mL, 36.53 mmol, 4 equiv) in DMF (50 mL) was stirred for 5 h. After treatment, a solution of the residue and TBAF (9 mL, 9 mmol, 1 equiv) in a mixture of THF/H_2O (40 mL) was stirred for 2 h. Purification of the residue (dr = 89:11) on silica gel (PE/EtOAc 3:1) afforded *N,O*-acetal **2d** (2.37 g, 90%, dr = 89:11) as a beige solid: IR (KBr) ν_{max} 698, 959, 1114, 1191, 1354, 1415, 1704, 2925, 3339 cm^{-1}; ^{19}F NMR (CD_3OD, 235.5 MHz) δ −78.0 (s, 3F, CF_3, major), −80.6 (s, 3F, CF_3, minor); ^{1}H NMR (CD_3OD, 500 MHz), major isomer, δ 4.18 (m, 1H, CH—C—CF_3), 4.29 (d, ^3J = 8.5 Hz, 1H, CH—C=O), 4.49 (d, ^2J = 15.5 Hz, 1H, N—C$\underline{H}_a$H$_b$), 4.55 (d, ^2J = 15.5 Hz, 1H, N—CH$_a\underline{H}_b$), 7.19–7.22 (m, 1H, CHar), 7.25–7.30 (m, 4H, 4 CHar); ^{13}C NMR (CD_3OD, 125.7 MHz), major isomer, δ 44.2 (N—CH_2), 74.1 ($\underline{C}$H—C=O), 83.4 ($\underline{C}$H—C—CF_3), 88.5 (q, $^2J_{CF}$ = 30.0 Hz, $\underline{C}$—CF_3), 125.0 (q, $^1J_{CF}$ = 288.0 Hz, CF_3), 128.0 (CHar), 128.6 (CHar), 129.2 (CHar), 138.6 (C_{IV}ar), 174.1 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{12}H_{12}F_3NNaO_4$ [M + Na]$^+$ 314.0616, found 314.0612.

General Procedure for the Preparation of Oxazoline 3 from *N,O*-Acetals 2a and 2d. A solution of α-trifluoromethylated *N,O*-acetals **2a** and **2d** and $BF_3{\cdot}Et_2O$ (3 equiv) in acetonitrile was heated at reflux under Ar. The reaction mixture was cooled to rt, quenched with a saturated aqueous solution of $NaHCO_3$, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel.

*(3aR,6R,6aS)-4-Benzyl-6-hydroxy-2-methyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (**3**).* From **2a**, according to a general procedure, a solution of *N,O*-acetal **2a** (80 mg, 0.17 mmol) and $BF_3{\cdot}OEt_2$ (65 μL, 0.53 mmol, 3 equiv) in acetonitrile (5 mL) was stirred for 5 h at reflux. Purification on silica gel (PE/EtOAc 7:1) afforded oxazoline **3** (40 mg, 75%) as a white solid. From **2d**, according to a general procedure, a solution of *N,O*-acetal **2d** (80 mg, 0.27 mmol) and $BF_3{\cdot}OEt_2$ (101 μL, 0.82 mmol, 3 equiv) in acetonitrile (5 mL) was stirred for 2 h at reflux. Purification on silica gel (PE/EtOAc 7:1) afforded oxazoline **3** (66 mg, 77%) as a white solid. Oxazoline **3**: mp 114 °C; $[\alpha]_D^{20}$ +6 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max} 735, 969, 1014, 1127, 1174, 1202, 1337, 1658, 1710, 3390 cm^{-1}; ^{19}F NMR (CD_3OD, 235.5 MHz) δ −78.9 (s, 3F, CF_3); ^{1}H NMR (CD_3OD, 500 MHz) δ 2.09 (s, 3H, CH_3), 4.39 (d, ^3J = 1.5 Hz, 1H, CH—C=O), 4.49 (d, ^2J = 16.0 Hz, 1H, N—C$\underline{H}_a$H$_b$), 4.72 (d, ^2J = 16.0 Hz, 1H, N—CH$_a\underline{H}_b$), 4.95 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 7.23–7.31 (m, 5H, 5 CHar); ^{13}C NMR (CD_3OD, 125.7 MHz) δ 14.0 (CH_3), 46.6 (N—CH_2), 74.0 ($\underline{C}$H—C=O), 85.9 ($\underline{C}$H—C—CF_3), 93.3 (q, $^2J_{CF}$ = 33.0 Hz, $\underline{C}$—CF_3), 124.3 (q, $^1J_{CF}$ = 283.0 Hz, CF_3), 128.3 (CHar), 128.6 (CHar), 129.2 (CHar), 137.6 (C_{IV}ar, N—Bn), 174.4 (C=N), 174.9 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{13}F_3N_2NaO_3$ [M + Na]$^+$ 337.0776, found 337.0768.

General Procedure for the Preparation of *O*-Acetyl-*N,O*-acetals 4a–d from 2a–d. A solution of α-trifluoromethylated *N,O*-acetals **2a–d**, pyridine, acetic anhydride, and DMAP in dichloromethane was stirred at rt under Ar. After the complete conversion of the starting *N,O*-acetal (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with an aqueous solution of hydrochloric acid (10%) and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (PE/EtOAc).

*(2R,3R,4R)-1-Benzyl-3,4-bis(benzyloxy)-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl Acetate (trans-**4a**).* According to a general procedure, a solution of *N,O*-acetal *trans*-**2a** (1.50 g, 3.18 mmol), pyridine (387 μL, 4.80 mmol, 1.5 equiv), acetic anhydride (510 μL, 5.40 mmol, 1.7 equiv), and DMAP (40 mg, 0.33 mmol, 0.1 equiv) in CH_2Cl_2 (23 mL) was stirred for 1.5 h. Purification on silica gel (PE/EtOAc 4:1) afforded *O*-acetyl-*N,O*-acetal *trans*-**4a** (1.63 g, 99%) as a colorless oil: $[\alpha]_D^{20}$ +33 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 699, 1038, 1118, 1206, 1363, 1425, 1741, 2874, 2929, 3032, 3065 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −75.5 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.74 (s, 3H, CH_3), 4.39 (d, ^2J = 15.5 Hz, 1H, N—C$\underline{H}_a$H$_b$), 4.40 (d, ^3J = 7.0 Hz, 1H, C$\underline{H}$—C=O), 4.60 (d, ^2J = 11.5 Hz, 1H, C$\underline{H}_a$H$_b$—O—CH—C—CF_3), 4.63 (d, ^2J = 15.5 Hz, 1H, N—CH$_a\underline{H}_b$), 4.69 (d, ^2J = 11.5 Hz, 1H, CH$_a\underline{H}_b$—O—CH—C—CF_3), 4.81 (d, ^2J = 11.5 Hz, 1H, C$\underline{H}_a$H$_b$—O—CH—C=O), 5.05 (d, ^2J = 11.5 Hz, 1H, CH$_a\underline{H}_b$—O—CH—C=O), 5.22 (d, ^3J = 7.0 Hz, 1H, C$\underline{H}$—C—CF_3), 7.25–7.39 (m, 15H, 15 CHar); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 21.4 (CH_3), 44.5 (N—CH_2), 72.8 ($\underline{C}H_2$—O—CH—C=O), 74.2 ($\underline{C}H_2$—O—CH—C—CF_3), 78.9 ($\underline{C}$H—C=O), 80.6 ($\underline{C}$H—C—CF_3), 92.1 (q, $^2J_{CF}$ = 32.0 Hz, $\underline{C}$—CF_3), 122.1 (q, $^2J_{CF}$ = 288.0 Hz, CF_3), 127.7 (CHar), 128.0 (CHar), 128.2 (CHar), 128.3 (CHar), 128.50 (CHar), 128.54 (CHar), 128.55 (CHar), 128.6 (CHar), 135.5 (C_{IV}ar, N—Bn), 136.8 (C_{IV}ar, CF_3—C—CH—O—Bn), 137.8 (C_{IV}ar, O=C—CH—O—Bn), 168.2 (CH_3—$\underline{C}$=O), 171.6 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{28}H_{26}F_3NNaO_5$ [M + Na]$^+$ 536.1661, found 536.1669.

*(2S,3R,4R)-1-Benzyl-3,4-bis(benzyloxy)-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl Acetate (cis-**4a**).* According to a general procedure, a solution of *N,O*-acetal *cis*-**2a** (725 mg, 1.54 mmol), pyridine (188 μL, 2.32 mmol, 1.52 equiv), acetic anhydride (249 μL, 2.63 mmol, 1.7 equiv), and DMAP (19 mg, 0.16 mmol, 0.1 equiv) in CH_2Cl_2 (15 mL) was stirred for 3 h. Purification by chromatography (PE/EtOAc 4:1) afforded *O*-acetyl-*N,O*-acetal *cis*-**4a** (732 mg, 93%) as a colorless oil: $[\alpha]_D^{20}$ +43 (*c* 0.41, $CHCl_3$); IR (film) ν_{max} 700, 744, 1026, 1137, 1194, 1312, 1353, 1455, 1737, 1770, 2944, 3033, 3064 cm^{-1}; ^{19}F NMR (CD_3OD, 235.5 MHz) δ −75.6 (s, 3F, CF_3); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.61 (s, 3H, CH_3), 4.27 (d, ^2J = 15.5 Hz, 1H, N—C$\underline{H}_a$H$_b$), 4.34 (d, ^3J = 5.0 Hz, 1H, C$\underline{H}$—C—CF_3), 4.48 (d, ^3J = 5.0 Hz, 1H, C$\underline{H}$—C=O), 4.53 (d, ^2J = 11.5 Hz, 1H, C$\underline{H}_a$H$_b$—O—CH—C—CF_3), 4.60 (d, ^2J = 11.5 Hz, 1H, CH$_a\underline{H}_b$—O—CH—C—CF_3), 4.79 (d, ^2J = 11.5 Hz, 1H, C$\underline{H}_a$H$_b$—O—CH—C=O), 4.89 (d, ^2J = 15.5 Hz, 1H, N—CH$_a\underline{H}_b$), 5.04 (d, ^2J = 11.5 Hz, 1H, CH$_a\underline{H}_b$—O—CH—C=O), 7.19–7.21 (m, 2H, 2 CHar), 7.26–7.39 (m, 13H, 13 CHar); ^{13}C NMR (CD_3OD, 125.7 MHz) δ 20.9 (CH_3), 45.1 (N—CH_2), 73.9 ($\underline{C}H_2$—O—C=O), 74.2 ($\underline{C}H_2$—O—CH—C—CF_3), 79.4 ($\underline{C}$H—C—CF_3), 80.7 ($\underline{C}$H—C=O), 91.6 (q, $^2J_{CF}$ = 32.5 Hz, $\underline{C}$—CF_3), 123.5 (q, $^1J_{CF}$ = 285.5 Hz, CF_3), 128.8 (CHar), 128.9 (CHar), 129.08 (CHar), 129.12 (CHar), 129.4 (CHar), 129.5 (CHar), 129.6 (CHar), 129.9 (CHar), 136.8 (C_{IV}ar, N—Bn), 138.2 (C_{IV}ar, CF_3—C—CH—O—Bn), 138.6 (C_{IV}ar, O=C—CH—O—Bn), 170.6 (CH_3—$\underline{C}$=O), 174.9 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{28}H_{26}F_3NNaO_5$ [M + Na]$^+$ 536.1661, found 536.1658.

*(3R,4R)-1-Benzyl-3,4-bis(benzyloxy)-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl Acetate (**4a**).* According to a general procedure, a mixture of *N,O*-acetal **2a** (1.51 g, 3.20 mmol, dr = 86:14), pyridine (390 μL, 4.83 mmol, 1.5 equiv), acetic anhydride (515 μL, 5.45 mmol, 1.7 equiv), and DMAP (39 mg, 0.32 mmol, 0.1 equiv) in CH_2Cl_2 (25 mL) was stirred for 5.5 h. Purification on silica gel (PE/EtOAc 7:1) afforded *O*-acetyl-*N,O*-acetal **4a** (1.52 g, 92%, dr = 86:14) as a colorless oil: HRMS (ESI$^+$) m/z calcd for $C_{28}H_{26}F_3NNaO_5$ [M + Na]$^+$ 536.1661, found 536.1670.

*(3R,4R)-3,4-Bis(benzyloxy)-1-(4-methoxybenzyl)-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl Acetate (**4b**).* According to a general procedure, a solution of *N,O*-acetal **2b** (1.08 g, 2.15 mmol, dr =

DOI: 10.1021/acs.joc.7b01814
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71:29), pyridine (260 μL, 3.22 mmol, 1.5 equiv), acetic anhydride (345 μL, 3.65 mmol, 1.7 equiv), and DMAP (27 mg, 0.22 mmol, 0.1 equiv) in CH_2Cl_2 (18 mL) was stirred for 19 h. Purification on silica gel (PE/EtOAc 6:1) afforded *O*-acetyl-*N*,*O*-acetal **4b** (972 mg, 83%, dr = 71:29) as a yellow oil: IR (film) ν_{max} 699, 741, 1032, 1112, 1205, 1317, 1514, 1612, 1736, 1767, 2939, 3032, 3415 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −75.4 (s, 3F, CF_3, major), −78.0 (s, 3F, CF_3, minor); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.59 (s, 3H, CH_3, minor), 1.78 (s, 3H, CH_3, major), 3.783 (s, 3H, OCH_3, major), 3.786 (s, 3H, OCH_3, minor), 4.12 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 4.29 (d, ^3J = 5.5 Hz, 1H, CH—C—CF_3, minor), 4.34 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, major), 4.39 (d, ^3J = 7.0 Hz, 1H, CH—C═O, major), 4.55 (d, ^3J = 5.5 Hz, 1H, CH—C═O, minor), 4.56 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, minor), 4.59 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, major), 4.61 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, major), 4.62 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, minor), 4.70 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C—CF_3, major), 4.78 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, minor), 4.82 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C═O, major), 4.99 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 5.06 (d, ^2J = 12.0 Hz, 1H, CH_aH_b—O—CH—C═O, major), 5.18 (d, ^2J = 11.5 Hz, 1H, CH_aH_b—O—CH—C═O, minor), 5.22 (d, ^3J = 7.0 Hz 1H, CH—C—CF_3, major), 6.83 (m, 2H, 2 CHar, major and minor), 7.20−7.40 (m, 12H, 12 CHar, major and minor); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.0 (CH_3, minor), 21.5 (CH_3, major), 43.6 (N—CH_2, minor), 44.0 (N—CH_2, major), 55.3 (O—CH_3, major), 55.4 (O—CH_3, minor), 72.7 (CH_2—O—CH—C═O, major), 73.2 (CH_2—O—CH—C═O, minor), 73.3 (CH_2—O—CH—C—CF_3, minor), 74.2 (CH_2—O—CH—C—CF_3, major), 78.3 (CH—C—CF_3, minor), 78.9 (CH—C—C═O, major), 79.8 (CH—C—C═O, minor), 80.6 (CH—C—CF_3, major), 90.4 (q, $^2J_{CF}$ = 32.5 Hz, C—CF_3, minor), 92.1 (q, $^2J_{CF}$ = 32.0 Hz, C—CF_3, major), 112.1 (q, $^1J_{CF}$ = 288.1 Hz, CF_3, major), 112.3 (q, $^1J_{CF}$ = 286.0 Hz, CF_3, minor), 113.8 (CHar, minor), 113.9 (CHar, major), 127.60 (C_{IV}ar, N—CH_2—Ph, major), 127.66 (C_{IV}ar, N—CH_2—Ph, minor), 127.7 (CHar, minor), 128.0 (CHar, major), 128.06 (CHar, minor), 128.13 (CHar, major), 128.15 (CHar, major), 128.3 (CHar, minor), 128.46 (CHar, minor), 128.48 (CHar, minor), 128.5 (CHar, major), 128.6 (CHar, major), 130.0 (CHar, major), 130.6 (CHar, minor), 136.8 (C_{IV}ar, CF_3—C—CH—O—Bn, major), 137.0 (C_{IV}ar, CF_3—C—CH—O—Bn, minor), 137.4 (C_{IV}ar, O═C—CH—O—Bn, minor), 137.5 (C_{IV}ar, O═C—CH—O—Bn, major), 159.1 (C_{IV}ar, CH_3—O—Ar, major), 159.3 (C_{IV}ar, CH_3—O—Ar, minor), 168.2 (CH_3—C═O, major), 168.5 (CH_3—C═O, minor), 171.6 (C═O, major), 173.0 (C═O, minor); HRMS (ESI^+) m/z calcd for $C_{29}H_{28}F_3NNaO_6$ $[M + Na]^+$ 566.1766, found 566.1765.

*(3R,4R)-1-Benzyl-3,4-dimethoxy-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl acetate (**4c**).* According to a general procedure, a solution of *N*,*O*-acetal **2c** (1.17 g, 3.67 mmol, dr = 74:26), pyridine (445 μL, 5.51 mmol, 1.5 equiv), acetic anhydride (590 μL, 6.24 mmol, 1.7 equiv), and DMAP (45 mg, 0.37 mmol, 0.1 equiv) in CH_2Cl_2 (18 mL) was stirred for 4 h. Purification on silica gel (PE/EtOAc 5:1) afforded *O*-acetyl-*N*,*O*-acetal **4c** (1.20 g, 91%, dr = 75:25) as a colorless oil: IR (neat) ν_{max} 700, 1014, 1037, 1125, 1180, 1315, 1736, 1767, 2840, 2940 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −75.8 (s, 3F, CF_3, major), −78.1 (s, 3F, CF_3, minor); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 3H, CH_3—C═O, minor), 1.82 (s, 3H, CH_3—C═O, major), 3.49 (s, 3H, CH_3—O—CH—C—CF_3, minor), 3.53 (s, 3H, CH_3—O—CH—C—CF_3, major), 3.70 (s, 3H, CH_3—O—CH—C═O, major), 3.73 (s, 3H, CH_3—O—CH—C═O, minor), 3.97 (d, ^3J = 5.0 Hz, 1H, CH—C—CF_3, minor), 4.10 (d, ^3J = 7.0 Hz, 1H, CH—C═O, major), 4.12 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 4.26 (d, ^3J = 5.0 Hz, 1H, CH—C═O, minor), 4.38 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 4.64 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 4.95 (d, ^3J = 7.0 Hz, 1H, CH—C—CF_3, major), 5.02 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 7.23−7.30 (m, 5H, 5 CHar, major and minor); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.7 (CH_3—C═O, minor), 21.5 (CH_3—C═O, major), 44.1 (N—CH_2, minor), 44.4 (N—CH_2, major), 59.2 (CH_3—O—CH—C═O, major), 59.3 (CH_3—O—CH—C═O, minor), 59.6 (CH_3—O—CH—C—CF_3, minor), 60.3 (CH_3—O—CH—C—CF_3, major), 80.6 (CH—C—CF_3, minor), 80.8 (CH—C═O, major), 82.0 (CH—C═O, minor), 83.7 (CH—C—CF_3, major), 90.1 (q, $^2J_{CF}$ = 32.5 Hz, C—CF_3, minor), 92.2 (q, $^2J_{CF}$ = 32.0 Hz, C—CF_3, major), 122.1 (q, $^1J_{CF}$ = 288.0 Hz, CF_3, major), 122.2 (q, $^1J_{CF}$ = 286.0 Hz, CF_3, minor), 127.7 (CHar, major), 127.9 (CHar, minor), 128.47 (CHar, minor), 128.52 (CHar, major), 128.54 (CHar, major), 129.3 (CHar, minor), 135.3 (C_{IV}ar, minor), 135.5 (C_{IV}ar, major), 168.37 (CH_3—C═O, major), 168.38 (CH_3—C═O, minor), 171.2 (C═O, major), 172.7 (C═O, minor); HRMS (ESI^+) m/z calcd for $C_{16}H_{18}F_3NNaO_5[M + Na]^+$ 384.1035, found 384.1024.

*(3R,4R)-1-Benzyl-5-oxo-2-(trifluoromethyl)pyrrolidine-2,3,4-triyl Triacetate (**4d**).* According to a general procedure, a solution of *N*,*O*-acetal **2d** (500 mg, 1.72 mmol, dr = 89:11), pyridine (625 μL, 7.75 mmol, 4.51 equiv), acetic anhydride (810 μL, 8.57 mmol, 5 equiv), and DMAP (62 mg, 0.51 mmol, 0.3 equiv) in CH_2Cl_2 (10 mL) was stirred for 4 h. Purification on silica gel (PE/EtOAc 4:1) afforded *O*-acetyl-*N*,*O*-acetal **4d** (680 mg, 95%, dr = 89:11) as a pale yellow oil: IR (film) ν_{max} 702, 754, 975, 1039, 1227, 1369, 1434, 1760, 2945, 3029, 3497 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −75.9 (s, 3F, CF_3, major), −78.7 (s, 3F, CF_3, minor); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 3H, CH_3, minor), 1.81 (s, 3H, CH_3, major), 2.07 (s, 3H, CH_3, minor), 2.13 (s, 3H, CH_3, major), 2.16 (s, 3H, CH_3, minor), 2.19 (s, 3H, CH_3, major), 4.15 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 4.41 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 4.75 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b, major), 5.15 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b, minor), 5.71 (d, ^3J = 6.0 Hz, 1H, CH—C═O, minor), 5.77 (d, ^3J = 6.0 Hz, 1H, CH—C—CF_3, minor), 5.78 (d, ^3J = 7.0 Hz, 1H, CH—C═O, major), 6.41 (d, ^3J = 6.0 Hz, 1H, CH—C—CF_3, major), 7.25−7.32 (m, 5H, 5 CHar, major and minor); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.5 (CH_3, major), 20.6 (CH_3, minor), 20.7 (CH_3, major), 21.1 (CH_3, major), 44.6 (N—CH_2, minor), 45.9 (N—CH_2, major), 69.5 (CH—C—CF_3, minor), 71.2 (CH—C═O, major), 72.6 (CH—C—CF_3, major), 73.7 (CH—C═O, minor), 91.0 (q, $^2J_{CF}$ = 32.0 Hz, C—CF_3, major), 121.9 (q, $^1J_{CF}$ = 286.5 Hz, CF_3, minor), 123.9 (q, $^1J_{CF}$ = 288.0 Hz, CF_3, major), 128.0 (CHar, major), 128.2 (CHar, minor), 128.63 (CHar, major), 128.66 (CHar, minor), 128.9 (CHar, major), 129.4 (CHar, minor), 134.8 (C_{IV}ar, minor), 135.0 (C_{IV}ar, major), 168.1 (C═O, major), 168.2 (O—C═O, minor), 168.5 (O—C═O, major), 168.6 (O—C═O, minor), 169.3 (C═O, minor), 169.8 (O—C═O, major), 169.9 (O—C═O, major), 170.0 (O—C═O, minor); HRMS (ESI^+) m/z calcd for $C_{18}H_{18}F_3NNaO_7$ $[M + Na]^+$ 440.0933, found 440.0925.

General Procedures for the Addition of Nitriles on *O*-Acetyl-*N*,*O*-acetals 4a−d. *General Procedure C (with Nitrile as a Solvent).* To a solution of *O*-acetyl-*N*,*O*-acetals **4a**−**d** in nitrile was slowly added, at rt under Ar, $BF_3{\cdot}OEt_2$ (3 equiv). After stirring of the reaction mixture at room temperature (with acetals **4a** and **4b**) or at reflux (with acetals **4c** and **4d**) (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (PE/EtOAc).

General Procedure D (using 10 Equiv of Nitrile in Dichloromethane). To a solution of *O*-acetyl-*N*,*O*-acetal **4a** and nitrile (10 equiv) in dichloromethane was slowly added, at rt under Ar, $BF_3{\cdot}OEt_2$ (3 equiv). After stirring at room temperature (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (PE/EtOAc).

*(3aR,6R,6aS)-4-Benzyl-6-(benzyloxy)-2-methyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (**5a**).* According to General Procedure C, a solution of *N*,*O*-acetal **4a** (100 mg, 0.19 mmol) and $BF_3{\cdot}OEt_2$ (72 μL, 0.59 mmol, 3 equiv) in acetonitrile (4 mL) was stirred for 31 h at rt. Purification on silica gel (PE/EtOAc 3:1) afforded oxazoline **5a** (60 mg, 76%) as a colorless oil: $[\alpha]_D^{20}$ +50 (*c* 0.40, $CHCl_3$); IR (film) ν_{max} 704, 738, 978, 1027, 1113, 1195, 1268,

DOI: 10.1021/acs.joc.7b01814
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1338, 1402, 1659, 1721, 2927, 3060, 3329 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.2 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 600 MHz) δ 2.07 (s, 3H, CH_3), 4.19 (d, ^3J = 1.5 Hz, 1H, CH—C═O), 4.56 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.78 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.91 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 4.92 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 5.03 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 7.26−7.45 (m, 10H, 10 CHar); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 14.3 (CH_3), 45.7 (N—CH_2), 72.9 (O—CH_2), 77.6 (CH—C═O), 82.4 (CH—C—CF_3), 92.4 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 122.8 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.5 (CHar), 127.9 (CHar), 128.30 (CHar), 128.36 (CHar), 128.39 (CHar), 128.7 (CHar), 136.1 (C_{IV}ar, N—Bn), 136.6 (C_{IV}ar, O—Bn), 171.1 (C═N), 171.8 (C═O); HRMS (ESI^+): m/z calcd for $C_{21}H_{19}F_3N_2NaO_3$ $[M + Na]^+$ 427.1245, found 427.1241.

(3aR,6R,6aS)-6-(Benzyloxy)-4-(4-methoxybenzyl)-2-methyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5b)***. According to General Procedure C, a solution of *N,O*-acetal **4b** (250 mg, 0.46 mmol) and $BF_3{\cdot}OEt_2$ (170 μL, 1.38 mmol, 3 equiv) in acetonitrile (6 mL) was stirred for 28 h at rt. Purification on silica gel (PE/EtOAc 2:1) afforded oxazoline **5b** (140 mg, 70%) as a yellow oil: $[\alpha]_D^{20}$ +35 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 702, 978, 1029, 1111, 1176, 1247, 1303, 1338, 1400, 1513, 1695, 1722, 2935, 3418 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.2 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (s, 3H, CH_3), 3.78 (s, 3H, O—CH_3), 4.13 (d, ^3J = 1.0 Hz, 1H, CH—C═O), 4.47 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b), 4.67 (d, ^2J = 15.0 Hz, 1H, N—CH_aH_b), 4.86 (s, 1H, CH—C—CF_3), 4.87 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 4.99 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 6.83 (m, 2H, 2 CHar), 7.27 (m, 2H, 2 CHar), 7.31−7.42 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.3 (CH_3), 45.3 (N—CH_2), 55.3 (O—CH_3), 72.9 (O—CH_2), 77.6 (CH—C═O), 82.5 (CH—C—CF_3), 92.4 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 113.7 (CHar), 122.9 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 128.3 (CHar), 128.32 (C_{IV}ar, N—CH_2—Ph), 128.4 (CHar), 128.7 (CHar), 129.6 (CHar), 136.6 (C_{IV}ar, O—Bn), 159.0 (C_{IV}ar, CH_3—O—Ph), 170.9 (C═O), 171.7 (C═N); HRMS (ESI^+) m/z calcd for $C_{22}H_{21}F_3N_2NaO_4$ $[M + Na]^+$ 457.1351, found 457.1342.

(3aR,6R,6aS)-4-Benzyl-6-(benzyloxy)-2-isopropyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5c)***. According to General Procedure C, a solution of *N,O*-acetal **4a** (250 mg, 0.49 mmol) and $BF_3{\cdot}OEt_2$ (180 μL, 1.46 mmol, 3 equiv) in isobutyronitrile (4 mL) was stirred for 48 h at rt. Purification on silica gel (PE/EtOAc 9:1) afforded oxazoline **5c** (175 mg, 83%) as a colorless oil: $[\alpha]_D^{20}$ +18 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 700, 979, 1028, 1189, 1330, 1400, 1650, 1723, 2879, 2979, 3033, 3426 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.2 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, ^3J = 7.0 Hz, 3H, CH_3), 1.13 (d, ^3J = 7.0 Hz, 3H, CH_3), 2.56 (hept, ^3J = 7.0 Hz, 1H, C$H(CH_3)_2$), 4.13 (d, ^3J = 1.5 Hz, 1H, CH—C═O), 4.46 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.67 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.87 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 4.88 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.00 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 7.23−7.35 (m, 6H, 6 CHar), 7.37−7.43 (m, 4H, 4 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.2 (CH_3), 19.3 (CH_3), 28.5 ($CH(CH_3)_2$), 45.7 (N—CH_2), 72.9 (O—CH_2), 77.8 (CH—C═O), 82.1 (CH—C—CF_3), 92.4 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 123.0 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.5 (CHar), 128.2 (CHar), 128.3 (CHar), 128.33 (CHar), 128.7 (CHar), 136.4 (C_{IV}ar, N—Bn), 136.7 (C_{IV}ar O—Bn), 170.9 (C═O), 178.5 (C═N); HRMS (ESI+) m/z calcd for $C_{23}H_{23}F_3N_2NaO_3$ $[M + Na]^+$ 455.1558, found 455.1552.

(3aR,6R,6aS)-4-Benzyl-6-(benzyloxy)-2-(tert-butyl)-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5d)***. According to General Procedure C, a solution of *N,O*-acetal **4a** (300 mg, 0.58 mmol) and $BF_3{\cdot}OEt_2$ (216 μL, 1.75 mmol, 3 equiv) in trimethylacetonitrile (4 mL) was stirred for 41 h at rt. Purification on silica gel (PE/EtOAc 10:1) afforded oxazoline **5d** (199 mg, 76%) as a yellow oil: $[\alpha]_D^{20}$ +2 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 699, 980, 1028, 1106, 1197, 1338, 1400, 1643, 1723, 2875, 2976, 3034, 3423 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.2 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (s, 9H, 3 CH_3), 4.10 (d, ^3J = 1.5 Hz, 1H, CH—C═O), 4.61 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.71 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.85 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 4.87 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.00 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 7.21−7.42 (m, 10H, 10 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 27.4 (CH_3), 33.8 (C_{IV}), 45.7 (N—CH_2), 72.9 (O—CH_2), 78.0 (CH—C═O), 82.2 (CH—C—CF_3), 92.6 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 123.1 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.5 (CHar), 128.31 (CHar), 128.32 (CHar), 128.7 (CHar), 136.5 (C_{IV}ar, N—Bn), 136.7 (C_{IV}ar, O—Bn), 170.9 (C═O), 180.5 (C═N); HRMS (ESI^+) m/z calcd for $C_{24}H_{25}F_3N_2NaO_3$ $[M + Na]^+$ 469.1715, found 469.1714.

(3aR,6R,6aS)-4-Benzyl-6-(benzyloxy)-2-phenyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5e)***. According to General Procedure C, a solution of *N,O*-acetal **4a** (200 mg, 0.39 mmol) and $BF_3{\cdot}OEt_2$ (150 μL, 1.22 mmol, 3.1 equiv) in benzonitrile (5 mL) was stirred for 40 h at rt. Purification on silica gel (PE/EtOAc 10:1) afforded oxazoline **5e** (150 mg, 83%) as a colorless oil: $[\alpha]_D^{20}$ +72 (*c* 0.51, $CHCl_3$); IR (film) ν_{max} 701, 735, 1027, 1121, 1197, 1349, 1452, 1496, 1581, 1640, 1724, 2926, 3033, 3065 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −76.8 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 600 MHz) δ 4.27 (d, ^3J = 1.5 Hz, 1H, CH—C═O), 4.71 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.73 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.92 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.05 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.07 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 7.21−7.45 (m, 12H, 12 CHar), 7.56 (t, ^3J = 7.5 Hz, 1H, 1 CHar), 7.87 (m, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 45.8 (N—CH_2), 73.0 (O—CH_2), 77.8 (CH—C═O), 82.5 (CH—C—CF_3), 92.7 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 123.1 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 125.4 (C_{IV}ar, N═C—Ph), 127.5 (CHar), 128.2 (CHar), 128.36 (CHar), 128.38 (CHar), 128.4 (CHar), 128.72 (CHar), 128.73 (CHar), 129.3 (CHar), 133.4 (CHar), 136.3 (C_{IV}ar, N—Bn), 136.7 (C_{IV}ar, O—Bn), 169.2 (C═N), 170.9 (C═O); HRMS (ESI^+) m/z calcd for $C_{26}H_{21}F_3N_2NaO_3$ $[M + Na]^+$ 489.1402, found 489.1408.

(3aR,6R,6aS)-2,4-Dibenzyl-6-(benzyloxy)-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5f)***. According to General Procedure D, a solution of *N,O*-acetal **4a** (150 mg, 0.29 mmol), benzyl cyanide (340 μL, 2.95 mmol, 10 equiv), and $BF_3{\cdot}OEt_2$ (108 μL, 0.88 mmol, 3.05 equiv) in CH_2Cl_2 (3 mL) was stirred for 48 h at rt. Purification on silica gel (PE/EtOAc 7:1) afforded oxazoline **5f** (88 mg, 63%) as a pale yellow oil: $[\alpha]_D^{20}$ +14 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 700, 980, 1026, 1110, 1175, 1337, 1398, 1455, 1497, 1653, 1724, 2928, 3033, 3064 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.1 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 600 MHz) δ 3.62 (d, ^2J = 15.0 Hz, 1H, N═C—CH_aH_b), 3.66 (d, ^2J = 15.0 Hz, 1H, N═C—CH_aH_b), 4.07 (d, ^3J = 1.5 Hz, 1H, CH—C═O), 4.62 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.70 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.83 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 4.90 (d, ^3J = 1.5 Hz, 1H, CH—C—CF_3), 4.96 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 7.15 (m, 2H, 2 CHar), 7.27−7.37 (m, 13H, 13 CHar); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 34.8 (CH_2—C═N), 45.8 (N—CH_2), 72.9 (O—CH_2), 77.6 (CH—C═O), 82.6 (CH—C—CF_3), 92.4 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 122.9 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.6 (CHar), 127.7 (CHar), 128.1 (CHar), 128.3 (CHar), 128.35 (CHar), 128.4 (CHar), 128.7 (CHar), 128.9 (CHar), 129.0 (CHar), 133.1 (C_{IV}ar, N═C—Bn), 136.1 (C_{IV}ar, N—Bn), 136.5 (C_{IV}ar, O—Bn), 170.9 (C═O), 172.8 (C═N); HRMS (ESI^+) m/z calcd for $C_{27}H_{23}F_3N_2NaO_3$ $[M + Na]^+$ 503.1558, found 503.1550.

(3aR,6R,6aS)-4-Benzyl-6-(benzyloxy)-2-((E)-prop-1-en-1-yl)-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one ***(5g)***. According to General Procedure C, a solution of *N,O*-acetal **4a** (205 mg, 0.40 mmol) and $BF_3{\cdot}OEt_2$ (149 μL, 1.20 mmol, 3 equiv) in allyl cyanide (3 mL) was stirred for 21 h at rt. Purification of the residue by chromatography (PE/EtOAc 6:1) afforded oxazoline **5g** (152 mg, 89%) as a colorless oil: $[\alpha]_D^{20}$ +22 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 701, 736, 973, 1031, 1113, 1191, 1351, 1398, 1605, 1670, 1722, 2923, 3034, 3422 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.1 (s, 3F, CF_3); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.92 (dd, ^3J = 7.0 Hz, ^4J = 1.5 Hz, 3H, CH_3), 4.18 (s, 1H, CH—C═O), 4.55 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.75 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.89 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 4.91 (s, 1H, CH—C—CF_3), 5.02 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.95 (dq, ^3J = 16.0 Hz, ^4J = 1.5 Hz, 1H, CH═CH—CH_3), 6.81 (dq, ^3J = 16.0 Hz, ^3J = 7.0 Hz, 1H, CH═CH—CH_3), 7.24−7.35 (m, 6H, 6 CHar), 7.40 (m, 4H, 4 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (CH_3), 45.8 (N—CH_2), 72.9 (O—CH_2), 77.8 (CH—C═O), 81.9 (CH—C—CF_3), 92.3 (q, $^2J_{CF}$ =

DOI: 10.1021/acs.joc.7b01814
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33.0 Hz, C—CF_3), 117.4 (CH=CH—CH_3), 123.0 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.4 (CHar), 128.0 (CHar), 128.31 (CHar), 128.34 (CHar), 128.4 (CHar), 128.7 (CHar), 136.2 (C_{IV}ar, N—Bn), 136.7 (C_{IV}ar, O—Bn), 145.3 (CH—CH_3), 168.3 (C=N), 171.1 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{23}H_{21}F_3N_2NaO_3$ $[M + Na]^+$ 453.1402, found 453.1408.

*(3aR,6R,6aR)-4-Benzyl-6-methoxy-2-methyl-3a-(trifluoromethyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (**5h**) and (2R,3S,4R)-N-1-Benzyl-3,4-dimethoxy-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl)acetamide (cis-**7a**).* According to General Procedure C, a solution of *N,O*-acetal **4c** (160 mg, 0.44 mmol) and $BF_3{\cdot}OEt_2$ (165 μL, 1.34 mmol, 3 equiv) in acetonitrile (4 mL) was stirred for 1.5 h at reflux. Purification of the residue (**5h**/*cis*-**7a** 87:13) on silica gel (PE/EtOAc 4:1 to 3:2) afforded oxazoline **5h** (98 mg, 68%) followed by amide *cis*-**7a** (21 mg, 13%). Oxazoline **5h**: white solid; mp 66 °C; $[\alpha]_D^{20}$ +5 (*c* 0.41, $CHCl_3$); IR (neat) ν_{max} 696, 709, 727, 963, 1016, 1171, 1192, 1314, 1651, 1724, 2925 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.3 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06 (s, 3H, N=C—CH_3), 3.66 (s, 3H, O—CH_3), 3.98 (d, ^3J = 1.0 Hz, 1H, CH—C=O), 4.50 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.75 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.84 (d, ^3J = 1.0 Hz, 1H, CH—C—CF_3), 7.22−7.31 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.3 (N=C—CH_3), 45.7 (N—CH_2), 59.2 (CH_3), 80.6 (CH—C=O), 81.9 (CH—C—CF_3), 92.4 (q, $^2J_{CF}$ = 33.0 Hz, C—CF_3), 122.8 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.5 (CHar), 127.9 (CHar), 128.4 (CHar), 136.0 (C_{IV}ar, N—Bn), 170.8 (C=O), 171.8 (C=N); HRMS (ESI$^+$) m/z calcd for $C_{15}H_{15}F_3N_2NaO_3$ $[M + Na]^+$ 351.0932, found 351.0925. Amide *cis*-**7a**: pale yellow solid; mp 148 °C; $[\alpha]_D^{20}$ +44 (*c* 0.41, $CHCl_3$); IR (neat) ν_{max} 696, 720, 1085, 1115, 1155, 1179, 1263, 1307, 1696, 2923, 3051, 3210 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.5 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.66 (s, 3H, H_3C—C=O), 3.47 (s, 3H, H_3C—O—CH—C—CF_3), 3.74 (s, H_3C—O—CH—C=O), 3.93 (d, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.23 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.40 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.76 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.77 (s, 1H, NH), 7.21−7.27 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 23.5 (H_3C—C=O), 44.3 (N—CH_2), 59.22 (H_3C—O—CH—C—CF_3), 59.23 (H_3C—O—CH—C=O), 76.1 (q, $^2J_{CF}$ = 30.0 Hz, C—CF_3), 80.9 (CH—C—CF_3), 82.2 (CH—C=O), 123.5 (q, $^1J_{CF}$ = 287.0 Hz, CF_3), 127.5 (CHar), 128.4 (CHar), 128.5 (CHar), 136.1 (C_{IV}ar, N—Bn), 170.7 (H_3C—C=O), 172.9 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{16}H_{19}F_3N_2NaO_4$ $[M + Na]^+$ 383.1195, found 383.1189. An analytical sample of *cis*-**7a** was crystallized from $CHCl_3$/pentane.

*(3S,4R)-2-Acetamido-1-benzyl-5-oxo-2-(trifluoromethyl)-pyrrolidine-3,4-diyl Diacetate (**7b**).* According to General Procedure C, a solution of *N,O*-acetal **4d** (130 mg, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (115 μL, 0.93 mmol, 3 equiv) in acetonitrile (5 mL) was stirred for 6 h at reflux. Purification of the residue (dr = 15:85) on silica gel (PE/EtOAc 1:1) afforded amide *trans*-**7b** (8 mg, 6%) followed by amide *cis*-**7b** (82 mg, 63%). Amide *trans*-**7b**: white solid; mp 196 °C; $[\alpha]_D^{20}$ −4 (*c* 0.50, CH_2Cl_2); IR (KBr) ν_{max} 702, 1070, 1184, 1231, 1370, 1554, 1716, 1761, 2939, 3045, 3214, 3283 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −75.0 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.87 (s, 3H, CH_3—(C=O)—NH), 2.11 (s, 3H, CH_3—(C=O)—O—CH—C=O), 2.18 (s, 3H, CH_3—(C=O)—O—CH—C—CF_3), 4.48 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.51 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.82 (d, ^3J = 7.5 Hz, 1H, CH—C=O), 6.08 (s, 1H, NH), 6.55 (d, ^3J = 7.5 Hz, 1H, CH—C—CF_3), 7.23−7.30 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.6 (CH_3—(C=O)—O—CH—C—CF_3), 20.8 (CH_3—(C=O)—O—CH—C=O), 23.7 (CH_3—(C=O)—NH), 44.7 (N—CH_2), 70.8 (CH—C=O), 73.0 (CH—C—CF_3), 76.5 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 122.9 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 127.7 (CHar), 128.1 (CHar), 128.6 (CHar), 135.6 (C_{IV}ar, N—Bn), 168.1 (C=O), 170.10 (O=C—O—CH—C=O), 170.12 (O=C—CH—C—CF_3), 170.8 (O=C—NH); HRMS (ESI$^+$) m/z calcd for $C_{18}H_{19}F_3N_2NaO_6$ $[M + Na]^+$ 439.1093, found 439.1099. Amide *cis*-**7b**: white solid; mp 199 °C; $[\alpha]_D^{20}$ +33 (*c* 0.51, CH_2Cl_2); IR (KBr) ν_{max} 707, 1020, 1089, 1183, 1234, 1303, 1370, 1414, 1548, 1709, 1759, 3056, 3309 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −77.8 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.64 (s, 3H, CH_3—(C=O)—NH), 2.06 (s, 3H, CH_3—(C=O)—O—CH—C—CF_3), 2.15 (s, 3H, CH_3—(C=O)—O—CH—C=O), 4.23 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.90 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.75 (d, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 5.82 (s, 1H, NH), 5.85 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 7.26−7.31 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.6 (CH_3—(C=O)—O—CH—C—CF_3), 20.7 (CH_3—(C=O)—O—CH—C=O), 23.1 (CH_3—(C=O)—NH), 44.6 (N—CH_2), 70.0 (CH—C—CF_3), 74.2 (CH—C=O), 75.6 (q, $^2J_{CF}$ = 30.5 Hz, C—CF_3), 123.2 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 127.9 (CHar), 128.5 (CHar), 128.6 (CHar), 135.5 (C_{IV}ar, N—Bn), 169.1 (O=C—CH—C—CF_3), 169.4 (C=O), 170.1 (O=C—O—CH—C=O), 170.5 (O=C—NH); HRMS (ESI$^+$) m/z calcd for $C_{18}H_{19}F_3N_2NaO_6$ $[M + Na]^+$ 439.1093, found 439.1097. An analytical sample of *cis*-**7b** was crystallized from hexane/CH_2Cl_2.

General Procedures for the Synthesis of Amides 6a−j and Amine 8. *General Procedure E (Acid Hydrolysis of Oxazolines **5a−f,h**).* A solution of oxazolines **5a−f,h** in MeOH and 6 N aqueous HCl (1:1 mixture) was stirred at room temperature (synthesis of amides **6**) or at 60 °C (synthesis of amine **8**). After completion of the reaction (reaction monitored by TLC and ^{19}F NMR), the mixture was neutralized with solid $NaHCO_3$ and extracted five times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (PE/EtOAc).

*General Procedure F (Reaction Sequence "Addition of Nitrile−Acid Hydrolysis" on N,O-Acetal **4a** or **2d**).* To a solution of α-trifluoromethylated *N,O*-acetal **4a** or **2d** in nitrile or a solution of α-trifluoromethylated *O*-acetyl-*N,O*-acetal **4a** and nitrile (10 equiv) in dichloromethane was slowly added, at rt under Ar, $BF_3{\cdot}OEt_2$ (3 equiv). After stirring at room temperature (with **4a**) or at reflux (with **2d**) (reaction monitored by TLC and ^{19}F NMR), the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was then dissolved in MeOH and 6 N aq HCl (1:1 mixture) at room temperature (reaction monitored by TLC and ^{19}F NMR). The reaction mixture was neutralized with solid $NaHCO_3$ and extracted five times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (PE/EtOAc).

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)acetamide (**6a**).* From **5a**, according to General Procedure E, a solution of oxazoline **5a** (70 mg, 0.38 mmol) in MeOH and 6 N aq HCl (8 mL) was stirred for 40 min at rt. Purification on silica gel (PE/EtOAc 1:1) afforded hydroxylamide **6a** (68 mg, 93%) as a white solid. From **4a**, according to General Procedure F, a solution of *N,O*-acetal **4a** (2.5 g, 4.87 mmol) and $BF_3{\cdot}OEt_2$ (1.80 μL, 14.58 mmol, 3 equiv) in acetonitrile (40 mL) was stirred for 28 h at rt. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 1 h at rt. Purification on silica gel (PE/EtOAc 1:1) afforded hydroxylamide **6a** (1.40 g, 68%) as a white solid. Hydroxylamide **6a**: mp 141 °C; $[\alpha]_D^{20}$ +17 (*c* 0.50, CH_2Cl_2); IR (KBr) ν_{max} 702, 751, 1016, 1118, 1168, 1297, 1573, 1681, 1714, 2930, 3094, 3290 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.4 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 600 MHz) δ 1.40 (s, 3H, CH_3), 2.99 (d, ^3J = 11.0 Hz, 1H, OH), 3.97 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.46 (dd, ^3J = 11.0 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.64 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.92 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.11 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.22 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.80 (s, 1H, NH), 7.25−7.32 (m, 6H, 6 CHar), 7.36 (t, ^3J = 7.5 Hz, 2H, 2 CHar), 7.45 (d, ^3J = 7.5 Hz, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 151 MHz) δ 23.1 (CH_3), 44.1 (N—CH_2), 73.2 (O—CH_2), 74.6 (CH—C—CF_3), 76.7 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 80.7 (CH—C=O), 123.8 (q, $^1J_{CF}$ = 283.5 Hz, C—CF_3), 128.0 (CHar), 128.1 (CHar), 128.2 (CHar), 128.4 (CHar), 128.6 (CHar), 129.0 (CHar), 136.3 (C_{IV}ar, N—Bn), 137.5 (C_{IV}ar, O—Bn), 171.8 (C=O),

DOI: 10.1021/acs.joc.7b01814
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172.9 (NH—C=O); HRMS (ESI$^+$) m/z calcd for $C_{21}H_{21}F_3N_2NaO_4$ [M + Na]$^+$ 445,1351, found 445.1351.

*N-((2R,3S,4R)-4-(Benzyloxy)-3-hydroxy-1-(4-methoxybenzyl)-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)acetamide (**6b**).* According to General Procedure E, a solution of oxazoline **5b** (110 mg, 0.25 mmol) in MeOH and 6 N aq HCl (10 mL) was stirred for 3.5 h at rt. Purification on silica gel (PE/EtOAc 1:2) afforded hydroxylamide **6b** (92 mg, 80%) as a white solid: mp 168 °C; $[\alpha]_D^{20}$ +8 (c 0.50, CH_2Cl_2); IR (KBr) ν_{max} 1025, 1109, 1177, 1253, 1301, 1514, 1675, 1711, 3102, 3234, 3297 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.5 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 500 MHz) δ 1.47 (s, 3H, CH_3), 2.94 (d, ^3J = 11.0 Hz, 1H, OH), 3.76 (s, 3H, O—CH_3), 3.92 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.44 (dd, ^3J = 11.0 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.62 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.91 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.10 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.16 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.79 (s, 1H, NH), 6.83 (m, 2H, 2 CHar), 7.18 (m, 2H, 2 CHar), 7.30 (m, 1H, CHar), 7.37 (m, 2H, 2 CHar), 7.44 (m, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 125.7 MHz) δ 23.3 (CH_3), 43.5 (N—CH_2), 55.5 (O—CH_3), 73.2 (O—CH_2), 74.6 (CH—C—CF_3), 76.7 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 80.7 (CH—C=O), 114.3 (CHar), 123.8 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.1 (CHar), 128.2 (CHar), 128.4 (C_{IV}ar, N—CH_2—Ph), 128.6 (CHar), 129.7 (CHar), 137.5 (C_{IV}ar, O—Bn), 159.3 (C_{IV}ar, CH_3—O—Ph), 171.7 (C=O), 172.7 (NH—C=O); HRMS (ESI$^+$) m/z calcd for $C_{22}H_{23}F_3N_2NaO_5$ [M + Na]$^+$ 475.1457, found 475.1465.

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)isobutyramide (**6c**).* According to General Procedure E, a solution of oxazoline **5c** (125 mg, 0.29 mmol) in MeOH and 6 N aq HCl (10 mL) was stirred for 4 h at rt. Purification on silica gel (PE/EtOAc 3:1) afforded hydroxylamide **6c** (111 mg, 85%) as a white solid: mp 127 °C; $[\alpha]_D^{20}$ +25 (c 0.50, CH_2Cl_2); IR (KBr) ν_{max} 700, 1109, 1182, 1230, 1295, 1551, 1667, 1707, 2975, 3067, 3282 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.6 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 500 MHz) δ 0.80 (d, ^3J = 7.0 Hz, 3H, CH_3), 0.93 (d, ^3J = 7.0 Hz, 3H, CH_3), 1.86 (hept, ^3J = 7.0 Hz, 1H, CH(CH_3)$_2$), 2.97 (d, ^3J = 10.5 Hz, 1H, OH), 4.08 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.49 (dd, ^3J = 10.5 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.68 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.90 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.03 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.14 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.84 (s, 1H, NH), 7.24–7.31 (m, 6H, 6 CHar), 7.36 (t, ^3J = 7.5 Hz, 2H, 2 CHar), 7.45 (m, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 125.7 MHz) δ 18.5 (CH_3), 19.5 (CH_3), 35.5 (CH(CH_3)$_2$), 44.2 (N—CH_2), 73.4 (O—CH_2), 74.6 (CH—C—CF_3), 76.6 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 81.0 (CH—C=O), 123.8 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.9 (CHar), 128.0 (CHar), 128.15 (CHar), 128.2 (CHar), 128.6 (CHar), 128.8 (CHar), 136.3 (C_{IV}ar, N—Bn), 136.7 (C_{IV}ar, O—Bn), 172.0 (C=O), 179.2 (NH—C=O); HRMS (ESI$^+$) m/z calcd for $C_{23}H_{25}F_3N_2NaO_4$ [M + Na]$^+$ 473.1664, found 473.1655.

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)pivalamide (**6d**).* According to General Procedure E, a solution of oxazoline **5d** (160 mg, 0.36 mmol) in MeOH and 6 N aq HCl (12 mL) was stirred for 48 h at rt. Purification on silica gel (PE/EtOAc 4:1) afforded hydroxylamide **6d** (71 mg, 43%) as a colorless oil: $[\alpha]_D^{20}$ +2 (c 0.50, CH_2Cl_2); IR (film) ν_{max} 701, 739, 1113, 1168, 1301, 1404, 1453, 1521, 1710, 2967, 3034, 3451 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.6 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 600 MHz) δ 0.92 (s, 9H, C(CH_3)$_3$), 2.89 (t, ^3J = 11.0 Hz, 1H, OH), 4.11 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.52 (dd, ^3J = 10.0 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.72 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.93 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.05 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.20 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 6.01 (s, 1H, NH), 7.26–7.46 (m, 10H, 10 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 151 MHz) δ 27.0 (CH_3), 39.6 (C(CH_3)$_3$), 44.1 (N—CH_2), 73.4 (O—CH_2), 74.7 (CH—C—CF_3), 76.5 (q, $^2J_{CF}$ = 29.0 Hz, C—CF_3), 81.1 (CH—C=O), 123.9 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.9 (CHar), 128.0 (CHar), 128.2 (CHar), 128.6 (CHar), 128.8 (CHar), 136.4 (C_{IV}ar, N—Bn), 137.7 (C_{IV}ar, O—Bn), 172.0 (C=O), 180.7 (NH—C=O); HRMS (ESI$^+$) m/z calcd for $C_{24}H_{27}F_3N_2NaO_4$ [M + Na]$^+$ 487.1821, found 487.1817.

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)benzamide (**6e**).* According to General Procedure E, a solution of oxazoline **5e** (168 mg, 0.36 mmol) in MeOH and 6 N aq HCl (12 mL) was stirred for 46 h at rt. Purification on silica gel (PE/EtOAc 3:1) afforded hydroxylamide **6e** (120 mg, 69%) as a white solid: mp 74 °C; $[\alpha]_D^{20}$ +72 (c 0.40, CH_2Cl_2); IR (KBr) ν_{max} 701, 1000, 1113, 1178, 1279, 1532, 1713, 2930, 3064, 3387 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.4 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 600 MHz) δ 3.10 (d, ^3J = 10.5 Hz, 1H, OH), 4.07 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.58 (dd, ^3J = 10.5 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.81 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.96 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.17 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.19 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 6.35 (s, 1H, NH), 6.91 (t, ^3J = 7.5 Hz, 1H, CHar), 7.05 (t, ^3J = 7.5 Hz, 2H, 2 CHar), 7.21 (t, ^3J = 7.5 Hz, 3H, 3 CHar), 7.29 (m, 5H, 5 CHar), 7.38 (t, ^3J = 7.5 Hz, 2H, 2 CHar), 7.48 (m, 3H, 3 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 151 MHz) δ 44.3 (N—CH_2), 73.4 (O—CH_2), 74.8 (CH—C—CF_3), 77.2 (q, $^2J_{CF}$ = 29.0 Hz, C—CF_3), 80.9 (CH—C=O), 123.9 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.0 (CHar), 127.7 (CHar), 128.0 (CHar), 128.1 (CHar), 128.2 (CHar), 128.58 (CHar), 128.61 (CHar), 128.8 (CHar), 131.8 (C_{IV}ar, NH—CO—Ph), 132.9 (CHar), 135.9 (C_{IV}ar, N—Bn), 137.6 (C_{IV}ar, O—Bn), 168.8 (NH—C=O), 172.0 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{26}H_{23}F_3N_2NaO_4$ [M + Na]$^+$ 507.1508, found 507.1516.

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)-2-phenylacetamide (**6f**).* From **5f**, according to General Procedure E, a solution of oxazoline **5f** (90 mg, 0.19 mmol) in MeOH and 6 N aq HCl (8 mL) was stirred for 4 h at rt. Purification on silica gel (PE/EtOAc 2:1) afforded hydroxylamide **6f** (88 mg, 94%) as a white solid. From **4a**, according to General Procedure F, a solution of *N,O*-acetal **4a** (250 mg, 0.486 mmol), benzyl cyanide (560 μL, 4.85 mmol, 10 equiv), and $BF_3{\cdot}OEt_2$ (180 μL, 1.46 mmol, 3 equiv) in dichloromethane (40 mL) was stirred for 48 h at rt. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 2 h at rt. Purification on silica gel (PE/EtOAc 3:1) afforded hydroxylamide **6f** (140 mg, 58%) as a white solid. Hydroxylamide **6f**: mp 98 °C; $[\alpha]_D^{20}$ +8 (c 0.50, CH_2Cl_2); IR (KBr) ν_{max} 699, 1079, 1112, 1177, 1299, 1549, 1707, 2928, 3034, 3064, 3300, 3403 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.9 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 600 MHz) δ 2.87 (d, ^3J = 10.5 Hz, 1H, OH), 2.96 (d, ^2J = 16.5 Hz, 1H, CH_aH_b—C=O), 3.06 (d, ^2J = 16.5 Hz, 1H, CH_aH_b—C=O), 4.00 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.47 (dd, ^3J = 10.5 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.71 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.92 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.09 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.15 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.82 (s, 1H, NH), 6.93 (dd, ^3J = 7.5 Hz, ^4J = 2.0 Hz, 2H, 2 CHar), 7.26–7.42 (m, 11H, 11 CHar), 7.47 (d, ^3J = 7.0 Hz, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 151 MHz) δ 43.1 (CH_2—CO—NH), 44.1 (N—CH_2), 73.3 (O—CH_2), 74.5 (CH—C—CF_3), 76.6 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 80.8 (CH—C=O), 123.6 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.0 (CHar), 128.05 (CHar), 128.07 (CHar), 128.2 (CHar), 128.3 (CHar), 128.6 (CHar), 128.9 (CHar), 129.3 (CHar), 129.4 (CHar), 132.8 (C_{IV}ar, O=C—Bn), 136.3 (C_{IV}ar, N—Bn), 137.5 (C_{IV}ar, O—Bn), 171.9 (NH—C=O), 173.3 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{27}H_{25}F_3N_2NaO_4$ [M + Na]$^+$ 521.1664, found 521.1671.

*N-((2R,3S,4R)-1-Benzyl-3-hydroxy-4-methoxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)acetamide (**6g**).* According to General Procedure E, a solution of oxazoline **5h** (83 mg, 0.25 mmol) in MeOH and 6 N aq HCl (8 mL) was stirred for 1 h at rt. Purification on silica gel (PE/EtOAc 1:2) afforded hydroxylamide **6g** (80 mg, 92%) as a white solid: mp 181 °C; $[\alpha]_D^{20}$ +91 (c 0.50, EtOAc); IR (neat) ν_{max} 604, 663, 721, 971, 1117, 1129, 1169, 1274, 1403, 1678, 1697, 3326 cm^{-1}; ^{19}F NMR (CD_3COCD_3, 235.5 MHz) δ −74.2 (s, 3F, CF_3); ^{1}H NMR (CD_3COCD_3, 600 MHz) δ 1.82 (s, 3H, O=C—CH_3), 3.65 (s, 3H, O—CH_3), 4.27 (d, ^3J = 6.0 Hz, 1H, CH—C=O),

DOI: 10.1021/acs.joc.7b01814
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4.36 (dd, ^3J = 7.5 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.41 (d, ^2J = 16.0 Hz, 1H, N—CH_aH_b), 4.47 (d, ^2J = 16.0 Hz, 1H, N—CH_aH_b), 5.09 (d, ^3J = 7.5 Hz, 1H, OH), 7.23 (m, 1H, CHar), 7.28 (d, ^3J = 7.5 Hz, 4H, 4 CHar), 7.86 (s, 1H, NH); ^{13}C NMR (CD_3COCD_3, 151 MHz) δ 23.3 (O=C—CH_3), 44.8 (N—CH_2), 59.0 (O—CH_3), 74.1 (CH—C—CF_3), 77.6 (q, $^2J_{CF}$ = 29.0 Hz, C—CF_3), 84.3 (CH—C=O), 124.8 (q, $^1J_{CF}$ = 283.5 Hz, CF_3), 127.9 (CHar), 128.89 (CHar), 128.91 (CHar), 138.0 (C_{IV}ar, N—Bn), 172.1 (O=C—CH_3), 173.9 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{15}H_{17}F_3N_2NaO_4$ [M + Na]$^+$ 369.1038, found 369.1041.

*Methyl 3-(((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)amino)-3-oxopropanoate (**6h**).* According to General Procedure F, a solution of *N,O*-acetal **4a** (250 mg, 0.49 mmol), methyl cyanoacetate (430 μL, 4.87 mmol, 10 equiv), and $BF_3{\cdot}OEt_2$ (180 μL, 1.46 mmol, 3 equiv) in CH_2Cl_2 (4 mL) was stirred for 28 h at rt. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 1 h at rt. Purification on silica gel (PE/EtOAc 2:1) afforded hydroxylamide **6h** (125 mg, 54%) as a colorless oil: $[\alpha]_D^{20}$ +24 (c 0.50, CH_2Cl_2); IR (film) ν_{max} 701, 1019, 1081, 1113, 1171, 1271, 1353, 1407, 1442, 1556, 1720, 2953, 3066, 3310 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.7 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 500 MHz) δ 2.37 (d, ^2J = 19.5 Hz, 1H, O=C—CH_aH_b), 2.85 (d, ^3J = 10.5 Hz, 1H, OH), 2.89 (d, ^2J = 19.5 Hz, 1H, O=C—CH_aH_b), 3.68 (s, 3H, CH_3), 3.96 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.48 (dd, ^3J = 10.5 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.64 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.92 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.12 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.26 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 7.23−7.31 (m, 6H, 6 CHar), 7.36 (m, 2H, 2 CHar), 7.45 (m, 2H, 2 CHar), 8.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 125.7 MHz) δ 38.9 (O=C—CH_2), 44.1 (N—CH_2), 52.9 (O—CH_3), 73.3 (O—CH_2), 74.4 (CH—C—CF_3), 76.4 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 80.8 (CH—C=O), 123.8 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.7 (CHar), 128.1 (CHar), 128.2 (CHar), 128.57 (CHar), 128.59 (CHar), 128.8 (CHar), 136.1 (C_{IV}ar, N—Bn), 137.5 (C_{IV}ar, O—Bn), 167.2 (HN—C=O), 170.1 (O—C=O), 171.7 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{23}H_{23}F_3N_2NaO_6$ [M + Na]$^+$ 503.1406, found 503.1408.

*N-((2R,3S,4R)-1-Benzyl-4-(benzyloxy)-3-hydroxy-5-oxo-2-(trifluoromethyl)pyrrolidin-2-yl)cinnamamide (**6i**).* According to General Procedure F, a solution of *N,O*-acetal **4a** (250 mg, 0.49 mmol), cinnamonitrile (610 μL, 4.86 mmol, 10 equiv), and $BF_3{\cdot}OEt_2$ (180 μL, 1.46 mmol, 3 equiv) in CH_2Cl_2 (4 mL) was stirred for 48 h at rt. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 30 h at rt. Purification on silica gel (PE/EtOAc 3:1) afforded hydroxylamide **6i** (78 mg, 31%) as a colorless oil; $[\alpha]_D^{20}$ +70 (c 0.50, CH_2Cl_2); IR (film) ν_{max} 699, 976, 1110, 1169, 1216, 1349, 1549, 1627, 1710, 2929, 3063, 3302 cm^{-1}; ^{19}F NMR ($CDCl_3$ neutralized on basic Al_2O_3, 235.5 MHz) δ −77.4 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$ neutralized on basic Al_2O_3, 600 MHz) δ 3.22 (d, ^3J = 11.0 Hz, 1H, OH), 4.05 (d, ^2J = 15.5 Hz, 1H, NCH_aH_b), 4.54 (dd, ^3J = 11.0 Hz, ^3J = 6.0 Hz, 1H, CH—C—CF_3), 4.76 (d, ^3J = 6.0 Hz, 1H, CH—C=O), 4.96 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.15 (d, ^2J = 11.5 Hz, 1H, O—CH_aH_b), 5.19 (d, ^2J = 15.5 Hz, 1H, NCH_aH_b), 5.77 (d, ^3J = 15.5 Hz, 1H, O=C—CH=CH), 5.83 (s, 1H, NH), 7.05 (t, ^3J = 7.5 Hz, 1H, CHar), 7.19 (t, ^3J = 7.5 Hz, 2H, 2 CHar), 7.26 (d, ^3J = 7.5 Hz, 1H, CHar), 7.29−7.40 (m, 9H, 9 CHar), 7.33 (d, ^3J = 15.5 Hz, 1H, O=C—CH=CH), 7.46 (d, ^3J = 7.5 Hz, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$ neutralized on basic Al_2O_3, 151 MHz) δ 44.3 (N—CH_2), 73.3 (O—CH_2), 74.9 (CH—C—CF_3), 77.2 (q, $^2J_{CF}$ = 29.5 Hz, C—CF_3), 80.9 (CH—C=O), 117.9 (CH=CH—Ph), 123.8 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.7 (CHar), 128.1 (CHar), 128.2 (CHar), 128.25 (CHar), 128.28 (CHar), 128.6 (CHar), 128.9 (CHar), 129.1 (CHar), 130.7 (CHar), 133.8 (C_{IV}ar, HC=CH—Ph), 136.1 (C_{IV}ar, N—Bn), 137.5 (C_{IV}ar, O—Bn), 144.2 (CH=CH—Ph), 167.8 (NH—C=O), 172.0 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{28}H_{25}F_3N_2NaO_4$ [M + Na]$^+$ 533.1664, found 533.1670.

*N-((2R,3S,4R)-1-Benzyl-3,4-dihydroxy-5-oxo-2-(trifluoromethyl)-pyrrolidin-2-yl)acetamide (**6j**).* According to General Procedure F, a solution of *N,O*-acetal **2d** (250 mg, 0.86 mmol) and $BF_3{\cdot}OEt_2$ (317 μL, 2.57 mmol, 3 equiv) in acetonitrile (6 mL) was stirred for 2.5 h at reflux. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 4 h at rt. Purification on silica gel (EtOAc 100%) afforded hydroxylamide **6j** (200 mg, 70%) as a white solid: mp 165 °C; $[\alpha]_D^{20}$ +58 (c 0.50, MeOH); IR (KBr) ν_{max} 1105, 1184, 1296, 1413, 1575, 1674, 1710, 2398, 3089, 3225, 3279, 3399 cm^{-1}; ^{19}F NMR (CD_3OD, 235.5 MHz) δ −78.6 (s, 3F, CF_3); ^{1}H NMR (CD_3OD, 600 MHz) δ 1.74 (s, 3H, CH_3), 4.28 (d, ^3J = 6.5 Hz, 1H, CH—C—CF_3), 4.32 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.55 (d, ^3J = 6.5 Hz, 1H, CH—C=O), 4.62 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 7.21−7.27 (m, 5H, 5 CHar); ^{13}C NMR (CD_3OD, 151 MHz) δ 22.9 (CH_3), 45.5 (N—CH_2), 75.6 (CH—C—CF_3), 76.4 (CH—C=O), 78.1 (q, $^2J_{CF}$ = 29.0 Hz, C—CF_3), 125.0 (q, $^1J_{CF}$ = 286.0 Hz, CF_3), 128.3 (CHar), 129.1 (CHar), 129.4 (CHar), 137.5 (C_{IV}ar, N—Bn), 174.3 (NH—C=O), 176.8 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{15}F_3N_2NaO_4$ [M + Na]$^+$ 355.0882, found 355.0878.

*(3R,4S,5R)-5-Amino-1-benzyl-3-(benzyloxy)-4-hydroxy-5-(trifluoromethyl)pyrrolidin-2-one (**8**).* From **5a**, according to General Procedure E, a solution of oxazoline **5a** (100 mg, 0.25 mmol) in MeOH and 6 N aq HCl (10 mL) was stirred for 29 h at 60 °C. Purification on silica gel (PE/EtOAc 2:1) afforded hydroxylamine **8** (64 mg, 68%) as a colorless oil. From **4a**, according to General Procedure F, a solution of *N,O*-acetal **4a** (200 mg, 0.39 mmol) and $BF_3{\cdot}OEt_2$ (145 μL, 1.17 mmol, 3 equiv) in MeCN (4 mL) was stirred for 48 h at rt. A solution of the resulting residue in MeOH and 6 N aq HCl (12 mL) was stirred for 48 h at 60 °C. Purification on silica gel (PE/EtOAc 2:1) afforded hydroxylamine **8** (80 mg, 54%) as a colorless oil. Hydroxylamine **8**: $[\alpha]_D^{20}$ +12 (c 0.41, CH_2Cl_2); IR (KBr) ν_{max} 701, 746, 1110, 1165, 1264, 1415, 1609, 1700, 2931, 3033, 3402 cm^{-1}; ^{19}F NMR ($CDCl_3$, 235.5 MHz) δ −78.4 (s, 3F, CF_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (br s, 2H, NH_2), 3.62 (br s, 1H, OH), 4.13 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 4.18 (d, ^3J = 7.0 Hz, 1H, CH—C=O), 4.33 (d, ^3J = 7.0 Hz, 1H, CH—C—CF_3), 4.84 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 5.01 (d, ^2J = 15.5 Hz, 1H, N—CH_aH_b), 5.07 (d, ^2J = 12.0 Hz, 1H, O—CH_aH_b), 7.26−7.34 (m, 8H, 8 CHar), 7.41 (m, 2H, 2 CHar); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 44.2 (N—CH_2), 72.4 (CH—C—CF_3), 73.1 (O—CH_2), 75.2 (q, $^2J_{CF}$ = 30.0 Hz, C—CF_3), 79.1 (CH—C=O), 124.2 (q, $^1J_{CF}$ = 287.0 Hz, CF_3), 128.0 (CHar), 128.1 (CHar), 128.22 (CHar), 128.23 (CHar), 128.6 (CHar), 128.8 (CHar), 136.6 (C_{IV}ar, N—Bn), 137.3 (C_{IV}ar, O—Bn), 171.4 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{19}H_{19}F_3N_2NaO_3$ [M + Na]$^+$ 403.1245, found 403.1247.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01814.

X-ray structural data for *trans*-**2a**, *cis*-**7a**, and *cis*-**7b** (CIF)
Copies of all 1D NMR spectra for compounds **1**−**8** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the "région Champagne-Ardenne" for financial support and the CNRS, the Conseil Régional de Champagne-Ardenne, and the EU-program FEDER for the facilities of the analytical platform (PlAneT CPER project). We thank A. Martinez (NMR analyses including NOE measurements), S. Lanthony (chiral HPLC analyses and HRMS), Dr. S. Chevreux (X-ray crystallographic structure determination), Dr.

DOI: 10.1021/acs.joc.7b01814
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D. Harakat (HRMS), A. Robert (NMR analyses), and A. Vallée and L. Lepolard (synthesis of some of the tartrimides **1**). We also thank the French Fluorine Network (GIS CNRS).

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