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Stereoselective Access to Fluorinated and Non-fluorinated Quaternary Piperidines: Synthesis of Pipecolic Acid and Iminosugar Derivatives

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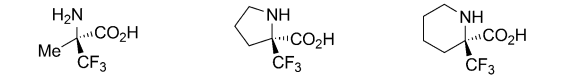
Abstract: The preparation of optically pure quaternary piperidines, both fluorinated and non-fluorinated, has been achieved from a chiral imino lactone derived from (*R*)-phenylglycinol. In the case of the fluorinated derivatives, the addition of (trifluoromethyl)trimethylsilane ($TMSCF_3$) followed by iodoamination and migration of the CF_3 group allowed access to four derivatives of α-(trifluoromethyl)pipecolic acid. A theoretical study of the CF_3-group rearrangement has been carried out to help establish the reaction mechanism of this uncommon transformation. Moreover, a route to trifluoromethyl-substituted iminosugars was also developed through the diastereoselective dihydroxylation of suitable synthetic intermediates. Conversely, alkylation of the starting substrate and subsequent cross-metathesis and aza-Michael reactions led to α-alkyl derivatives of the target compounds.

Keywords: amino acids · density functional calculations · fluorine · iminosugars · quaternary stereocenters

Introduction

Nowadays fluorinated analogues of proteinogenic amino acids are common synthetic targets due to their highly recognized biological properties.[1] Particularly, the selective introduction of trifluoromethyl groups into peptidic compounds may contribute to an enhancement of their chemical and thermal stabilities and, as a result, to an improvement of their bioavailability.[2] However, 3,3,3-trifluoroalanine-containing peptides possess low chemical and configurational stabilities at pH >7; therefore, the α-CF_3 groups are usually located within a quaternary center to avoid these drawbacks.[3] Acyclic derivatives such as α-(trifluoromethyl)alanine (Scheme 1) have been widely used for the design of antitumor drugs[4] or as suitable molecular labels in ^{19}F NMR spectroscopic studies.[5] In contrast, the preparation of cyclic analogues has been much scarcer, despite the importance of quaternary cyclic amino acids in the discovery of new peptidomimetic structures.[6,7] The most representative example is the synthesis of optically active α-(trifluoromethyl)proline developed by Brigaud and co-workers,[8] whereas the preparation of α-(trifluoromethyl)pipecolic acid derivatives has been achieved only in racemic form.[9,10]



(*S*)-α-(trifluoromethyl)-alanine (*S*)-α-(trifluoromethyl)-proline (*S*)-α-(trifluoromethyl)-pipecolic acid

Scheme 1. Quaternary α-(trifluoromethyl)amino acids.

We recently studied the nucleophilic trifluoromethylation[11] of chiral imino lactones such as **1** with the Ruppert–Prakash reagent $TMSCF_3$,[12] thus leading to trifluoromethyl lactol **2** as a single diastereoisomer[13] (Scheme 2). As it turned out, the cyclization of **2** by reaction with iodine and NaH proceeded through a 6-*exo-trig* ring closure, although the initially formed iodoamination product **3** underwent an unexpected rearrangement toward trifluoromethyl lactone **4** by the addition of a second iodine atom in a one-pot process, with the concomitant stereoselective creation of a quaternary center containing a CF_3 group.[14]

Intrigued by the result of this unusual transformation,[15] we decided to study the reaction mechanism in depth with the aid of density functional calculations. Next, we envisioned **4** as a versatile precursor to the synthesis of several 2,6-disubstituted 2-(trifluoromethyl)piperidines, such as pi-

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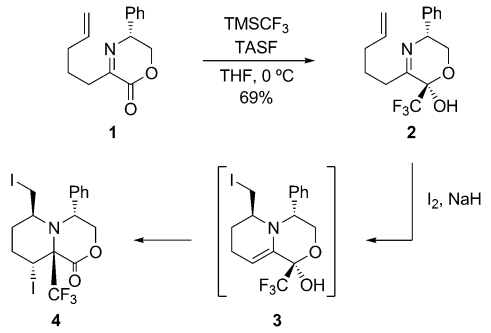
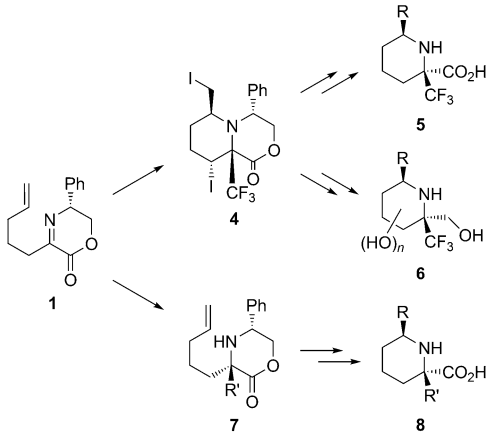


Scheme 2. Iodoamination of imino lactol **2** and rearrangement of the CF_3 group. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, $TMSCF_3$ = (trifluoromethyl)trimethylsilane.

pecolic acids **5**, by functional-group manipulations and removal of the chiral auxiliary (Scheme 3). Furthermore, the stereoselective introduction of hydroxy groups within the piperidine ring would afford iminosugars **6** containing a quaternary CF_3 group.



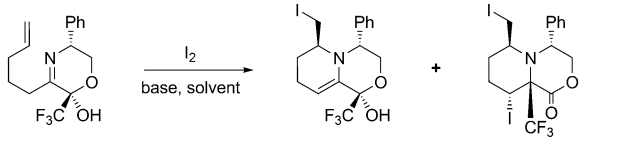
Scheme 3. Synthetic plan for the preparation of quaternary pipecolic acids **5** and **8** and iminosugars **6**.

Based on our previous studies concerning the synthesis of α-methyl quaternary dipeptide mimics,[16] we additionally developed an alternative route to prepare the corresponding non-fluorinated derivatives **8** (R′ = alkyl). By starting again from unsaturated imino lactone **1**, key steps would include the diastereoselective alkylation at the iminic carbon atom[17] and a further cyclization based on a cross-metathesis/intramolecular aza-Michael protocol.

Results and Discussion

Mechanism of the CF_3 rearrangement: Iodocyclization of imino lactol **2**[13] was first tested using two equivalents of I_2 and an excess of $NaHCO_3$ in CH_2Cl_2/H_2O (Table 1, entry 1). A moderate yield of the expected product **3** was obtained and isolated as a single diastereoisomer,[18] together with a small amount of a new compound, which was characterized

Table 1. Synthesis of trifluoromethyl lactol **3** and lactone **4**.



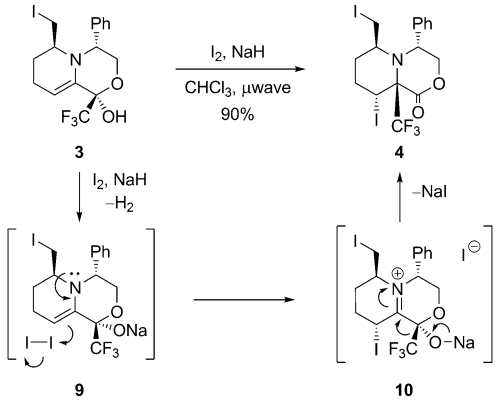
2 **3** **4**

Entry	I_2 [equiv]	Base (equiv)	Solvent	T [°C]	t [h]	Yield of **3** [%]	Yield of **4** [%]
1	2	$NaHCO_3$ (excess)	CH_2Cl_2/H_2O	25	15	46	9
2	3	Et_3N (2)	$CHCl_3$	25	48	40	18
3	4	NaH (2)	$CHCl_3$	25	60	25	39
4	5	NaH (2.5)	$CHCl_3$	60[a]	0.5		60
5	5	NaH (2.5)	THF	60[a]	0.5		80
6	1.5	none	$CHCl_3$	25	3	83	–
7	5	none	THF	60[a]	2	62	–

[a] The reaction was performed under microwave irradiation.

as the rearranged lactone **4**. Further attempts to increase the yield of **4** involved the use of other bases, such as Et_3N or NaH (Table 1, entries 2 and 3). In practice, the exclusive formation of **4** was made possible by using NaH as the base, a greater amount of I_2 (5 equiv), and microwave heating (Table 1, entry 4); although, the best yield was achieved when the solvent was changed from $CHCl_3$ to THF (Table 1, entry 5). It should be mentioned that the reaction did not proceed further in the absence of the base and enamino lactol **3** was formed as the only product (Table 1, entries 6 and 7). Moreover, we confirmed that lactone **4** was also formed from **3** under the same reaction conditions (Scheme 4).

These experimental results seem to indicate that the [1,2]-shift of the CF_3 group takes place when sodium alkoxide **9** reacts with iodine, thus leading to the iminium ion **10**, which evolves to lactone **4** (Scheme 4). We carried out a theoretical study of these reactions by using density-functional theory (DFT) to substantiate this mechanistic proposal. The calculations were carried out with the B3LYP functional, the 6-31G* basis set was employed for the carbon, hydrogen, oxygen, nitrogen, fluorine, and sodium atoms and the



3 **4** **9** **10**

Scheme 4. Transformation of enamino lactol **3** into lactone **4** and tentative mechanism.

LANL2DZ pseudopotential was used for the iodine atoms. All the stationary points located were fully optimized and characterized as a minimum or first-order saddle point by calculating their harmonic vibrational frequencies (full details of the geometries and energies of the located stationary points are given in the Supporting Information).

First, the potential-energy surface that corresponds to the *6-exo-trig* ring iodocyclization of imino lactol **1**, in the absence of a base, to give bicyclic enamine **3** was studied, and the transition structures **TS1** and **TS2** were located (Figure 1). The predicted activation energies are 14.3 and

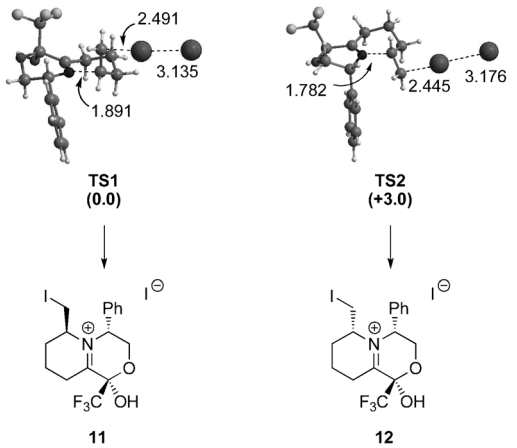


Figure 1. Transition structures located for the iodocyclization of imino lactol **2** to give iminium intermediates **11** and **12**. Bond lengths and relative energies are given in Å and kcal mol^{-1}, respectively.

17.3 kcal mol^{-1}, respectively. **TS1**, which leads to bicyclic iminium intermediate **11**, has an *anti* disposition between the phenyl and the iodomethyl groups and is clearly favored by 3.0 kcal mol^{-1} relative to **TS2**, which leads to the *syn* iminium intermediate **12**. The normal mode associated with the imaginary frequency of the transition structures **TS1** and **TS2** is dominated by the stretching movement that corresponds to the formation of the N–C bond associated with the ring closure. The comparison of both transition structures shows that **TS1** is an earlier transition structure, as reflected in the bond lengths of the formed C–N bonds: 1.891 and 1.782 Å in **TS1** and **TS2**, respectively. The preference of **TS1** appears to be related to the higher steric interaction between the phenyl ring and the iodomethyl group in **TS2**.

Although the alternative *7-endo-trig* ring closure was also favored according to the Baldwin rules,[19] the corresponding transition structures were located, and, in agreement with the experiments, this route was clearly unfavored relative to the *6-exo-trig* cyclization (see the Supporting Information for details).

Bicyclic enamine **3** was formed by tautomerization of the iminium intermediate **11** promoted by the iodide anion. The reaction takes place through transition-structure **TS3** (Figure 2), which corresponds to a proton abstraction from the α-methylene group by the iodide anion, and has a predicted activation energy of 13.9 kcal mol^{-1}. The imaginary

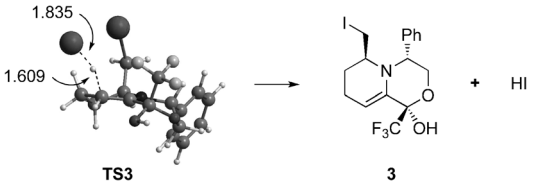


Figure 2. Transition structure located for the tautomerization of iminium intermediate **10**. Bond lengths are given in Å.

frequency of **TS3** corresponds to the stretching movement of the breaking C–H bond and the forming I–H bond. According to these calculations, the rate-determining step for the reaction of imino lactol **1** with iodine to give bicycle **3** is the iodoamination reaction, which has an activation energy of 14.3 kcal mol^{-1}.

The treatment of bicyclic enamine **3** with sodium hydride and iodine resulted in the rearranged bicycle **4** (Scheme 4). It seems plausible that the reaction of **3** with NaH to give sodium alkoxide **9** and molecular hydrogen (Scheme 4) is faster than iodination of the double bond, so we propose that the diiodinated alkoxide **10** is formed and then undergoes a [1,2]-shift of the CF_3 group. Thus, we found the transition-structure **TS4** for the addition of iodine to the alkoxide **9** (Figure 3). The imaginary normal mode of **TS4** corresponds to the formation and breaking of the C–I and I–I bonds, respectively. The coordination of the iodine molecule with the sodium cation directs the addition of the iodine atom to the double bond of **9**, that is, *anti* to the CF_3 group. The potential-energy barrier for the iodination of **9** presented a quite low value of 3.4 kcal mol^{-1}.

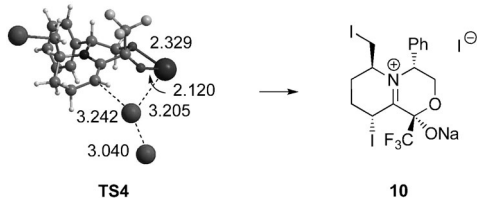


Figure 3. Transition structure located for the iodination of sodium alkoxide **9**. Bond lengths are given in Å.

According to our calculations, iodinated alkoxide **10** is a minimum on the potential-energy surface and can experience the [1,2]-shift of the CF_3 group toward the electrophilic iminium carbon atom through the transition-structure **TS5** (Figure 4), which leads to lactone **4**. The imaginary normal

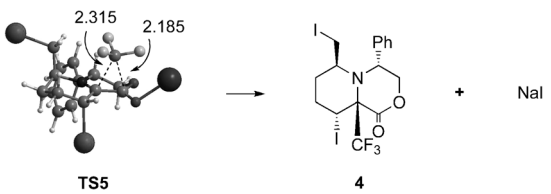


Figure 4. Transition structure for the [1,2]-shift of the CF_3 group. Bond lengths are given in Å.

mode of **TS5** corresponds to the simultaneous processes of bond breaking and bond formation between the CF_3 group and the carbon atoms and the subsequent shortening of the C–O bond. The barrier of the [1,2]-shift was 12.3 kcal mol^{-1}.

The full reaction profile for the transformation of alkoxide **9** into lactone **4** is shown in Figure 5. According to these data, the rate-determining step of the process is the CF_3 rearrangement, and the whole transformation is exothermic.

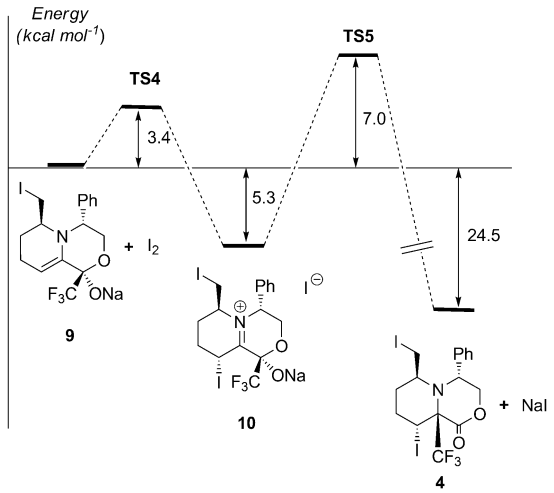
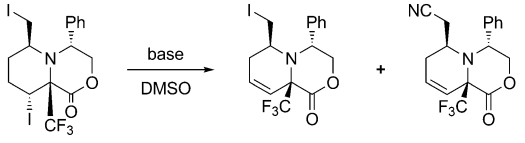


Figure 5. Energy-reaction profile for the transformation of **9** into lactone **4**.

Synthesis of α-(trifluoromethyl)pipecolic acid derivatives: Starting from diiodide **4**, we attempted the displacement of the primary iodine atom with several nucleophilic reagents. However, we soon found that elimination of the secondary iodine atom was a faster process; for example, the reaction with NaCN afforded a mixture of iodide **13**, nitrile **14**, and starting material (Table 2, entry 1). When using non-nucleophilic basic reagents, such as NaH or DBU, **13** was obtained as the only product (Table 2, entries 2 and 3), and the reaction time could be efficiently decreased by using microwave heating without affecting the yield (Table 2, entry 4). In the event, the treatment of **4** with NaCN under extended reaction times or microwave irradiation promoted both the elimination and the introduction of a nitrile group to give **14** exclusively (Table 2, entries 5 and 6).

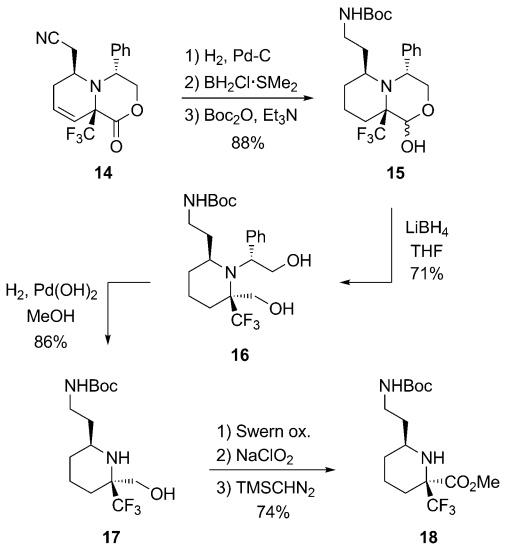
Table 2. Synthesis of bicyclic lactones **13** and **14**.



Entry	Base	t [h]	T [°C]	Yield of **13** [%]	Yield of **14** [%]
1[a]	NaCN	12	25	63	16
2	NaH	12	25	65	–
3	DBU	12	25	85	–
4	DBU	1	60[b]	92	–
5	NaCN	48	25	–	95
6	NaCN	1	90[b]	–	84

[a] Starting material **4** was isolated in 12% yield. [b] The reaction was performed under microwave irradiation. DBU = 1,8-diazabicycloundec-7-ene, DMSO = dimethyl sulfoxide.

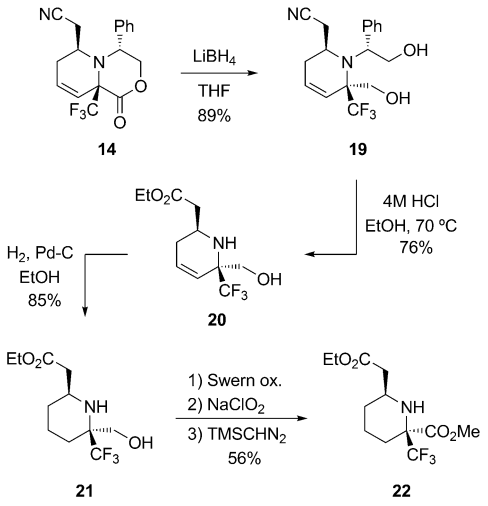
Access to a target amino acid derivative was first evaluated by starting from nitrile **14**. After hydrogenation of the double bond, the CN group was reduced with $BH_2Cl{\cdot}SMe_2$, and the resulting crude amine was protected with a Boc group (Scheme 5). In this transformation, the lactone ring also experienced a partial reduction to afford a mixture of diastereomeric lactols **15**, which were fully reduced with $LiBH_4$ to produce diol **16**. The phenylglycinol moiety was removed by hydrogenation in the presence of the Pearlman catalyst, and finally alcohol **17** was converted into ester **18** in a three-step sequence, namely, the Swern oxidation[20] followed by Pinnick oxidation[21] and esterification with $TMSCHN_2$ without purification of the corresponding intermediates.



Scheme 5. Synthesis of amino ester **18**. Boc = *tert*-butyloxycarbonyl, $TMSCHN_2$ = trimethylsilyldiazomethane.

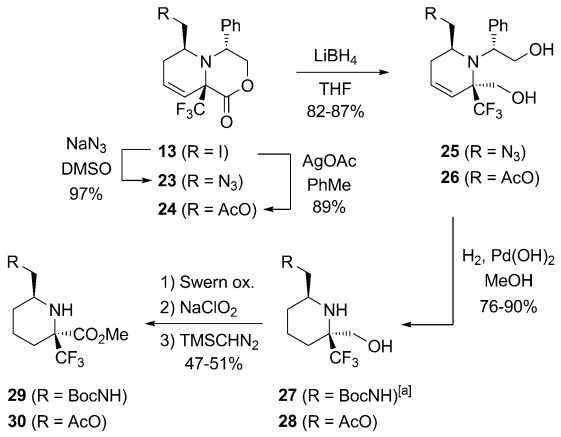
Nitrile **14** also served as the precursor to a diester derivative. Accordingly, reduction to diol **19** was followed by hydrolysis with HCl in EtOH to furnish ethyl ester **20** (Scheme 6). Interestingly, the chiral auxiliary was fully removed probably due to the high lability of the benzylic C–N bond under acidic conditions, which is attributable to the presence of the trifluoromethyl group.[22] Alcohol **20** was hydrogenated to afford its saturated derivative **21** and finally transformed into diester **22**.

Two more derivatives containing aminomethyl or hydroxymethyl substituents at the C2 position were obtained from primary iodide **13**. Thus, the treatment of **13** with either sodium azide or silver acetate yielded substitution products **23** and **24**, respectively, which were subsequently reduced



Scheme 6. Synthesis of amino diester **22**.

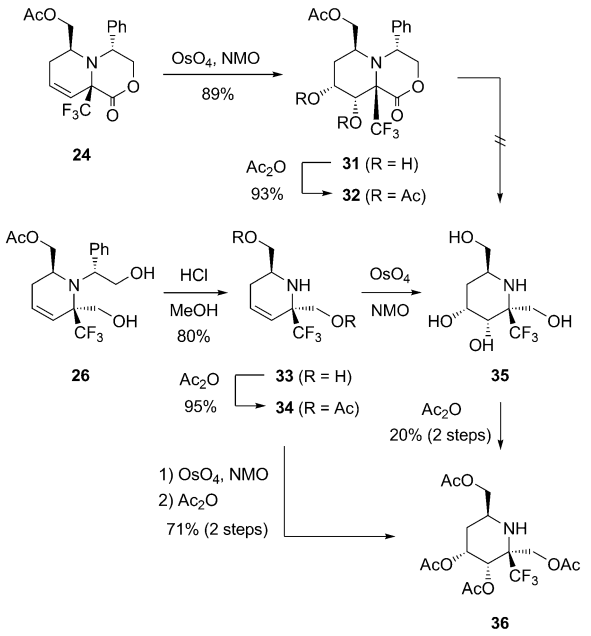
with $LiBH_4$ to give diols **25** and **26** (Scheme 7). Further hydrogenation of the phenylglycinol species and the double bond led to amino alcohols **27** and **28**. In the case of **27**, the azido moiety was also converted into an amine group and protected in situ with a Boc group. As above, a final oxidation and esterification led to amino esters **29** and **30**.



Scheme 7. Synthesis of amino esters **29** and **30**.[a] The reaction was performed in the presence of Boc_2O.

Synthesis of an α-(trifluoromethyl)iminosugar: The versatility of our synthetic intermediates was demonstrated by the straightforward access to a fluorinated analogue of an iminosugar.[23] Although several fluorinated derivatives of iminosugars have been described as glycosidase inhibitors,[24] trifluoromethyl analogues have not been reported to date.

We first envisioned **24** as a suitable precursor for the synthesis of (trifluoromethyl)iminosugar frameworks. For this purpose, osmylation of **24** proceeded through the less sterically demanding double-bond face to produce diol **31** as a single diastereoisomer (Scheme 8). The stereochemistry of this diol was confirmed by coupling-constant calculations



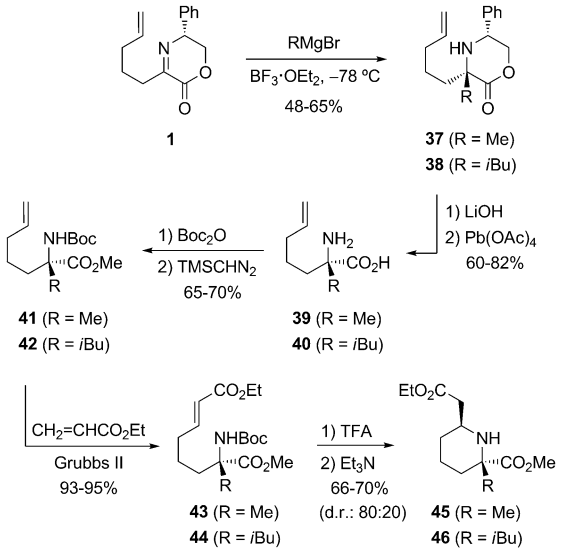
Scheme 8. Synthesis of fluorinated iminosugar **36**. NMO = *N*-Methylmorpholine-*N*-oxide.

and ^1H–^{19}F NOE interaction studies carried out on triacetate derivative **32** (see the Supporting Information). Disappointingly, the phenylglycinol moiety could not be effectively removed from any of these compounds to reveal the target iminosugar **35**.

Next, we attempted the double-bond dihydroxylation of the derived diol **26**, which proved unsuccessful, and the starting material was recovered. Access to the final product was ultimately achieved when the phenylglycinol fragment was removed prior to the double-bond functionalization. Thus, treatment of **26** with acid furnished diol **33** by elimination of the chiral auxiliary and the acetyl group. The reaction of **33** with OsO_4 resulted again in full diastereoselectivity to give iminosugar **35**, which was best isolated as its corresponding tetraacetyl derivative **36**, albeit in low yield. A more efficient sequence involved the osmylation of diacetylated olefin **34** to produce tetraacetate **36** finally and again as a single diastereoisomer in good overall yield. Coupling-constant analysis from the ^1H NMR spectrum established the stereochemical configuration of **36** because the origin of this diastereoselectivity is attributable to the blocking effect of the allylic trifluoromethyl group.

Synthesis of α-alkylpipecolic acid derivatives: As we had achieved the preparation of several quaternary α-(trifluoromethyl)pipecolates, we considered access to their corresponding non-fluorinated counterparts. Accordingly, our previous synthesis of α-methyl quaternary dipeptide mimics[16] was conveniently adapted to introduce diverse alkyl substituents besides the methyl group at the quaternary center in a stereoselective manner, bearing in mind that the volume of a trifluoromethyl moiety is significantly larger than a methyl group.[25]

Thus, starting again from imino lactone **1**, alkylation at the iminic carbon atom by reaction with methyl- or isobutylmagnesium bromide in the presence of $BF_3{\cdot}OEt_2$ produced amines **37** and **38**, respectively, as single diastereoisomers (Scheme 9). Removal of the phenylglycinol moiety by lactone opening and treatment with $Pb(OAc)_4$ revealed unsaturated amino acids **39**[26] and **40**, which were further protected to furnish **41** and **42**. Next, a tandem cross-metathesis/intramolecular aza-Michael process[27] was first attempted on amino ester **41** by reaction with ethyl acrylate under a variety of conditions,[28] but afforded only complex mixtures and the cyclized product remained undetectable. Therefore, a two-step sequence was carried out. Hence, cross-metathesis of **41** and **42** with ethyl acrylate in the presence of a Grubbs second-generation catalyst led to Michael acceptors **43** and **44**, essentially as single *trans* isomers as shown by analysis of their NMR spectroscopic data. The subsequent intramolecular aza-Michael reaction was unsuccessful with these Boc-protected amines under various basic reaction conditions. However, removal of the Boc group prior to treatment with Et_3N under microwave heating cleanly afforded methyl α-alkylpipecolates **45** and **46** with high diastereoselectivity (80:20 as determined by GC analysis). The configuration of the newly created stereocenter was deduced with the aid of NOE interaction studies performed on the diastereoisomeric pair **45**/epi-**45** (see the Supporting Information for details). Therefore, the major diastereoisomers possess the same stereochemical arrangement as the fluorinated amino diester **22**.



Scheme 9. Synthesis of amino diesters **45** and **46**. TFA = trifluoroacetic acid.

Conclusions

The synthetic potential of imino lactones derived from phenylglycinol has been confirmed by the diastereoselective preparation of several examples of polysubtituted piperidines. In one case, the (trifluoromethyl)lactol that resulted from the addition of $TMSCF_3$ to the starting material experienced an unusual rearrangement of the CF_3 group, which served to produce a key diiodide intermediate for the synthesis of α-(trifluoromethyl)pipecolic acid derivatives and CF_3-containing iminosugar analogues. A detailed study of the rearrangement process was carried out with the aid of theoretical DFT calculations, which established that migration of the CF_3 group took place on an iminium ion intermediate. In a different approach, non-fluorinated compounds were also prepared from the same starting molecule by using the alkylation of the iminic carbon atom, a cross-metathesis reaction, and an intramolecular aza-Michael addition as key steps. The resulting final products in both series are compounds with further potential utility as building blocks of more complex peptidomimetic structures.

Experimental Section

General methods: All the reactions were carried out in an argon or nitrogen atmosphere. The solvents were purified prior to use, that is, THF was distilled from sodium/benzophenone and CH_2Cl_2 was distilled from calcium hydride. All the other solvents and reagents were used as received. The reactions were monitored with the aid of TLC analysis on precoated silica gel plates (0.25 mm; E. Merck). Visualization was carried out with UV light and vainillin or potassium permanganate stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1020 polarimeter. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer. Chemical shifts (δ) are given in ppm and referenced to the residual proton resonances of the solvents or fluorotrichloromethane in the ^{19}F NMR spectroscopic experiments. Coupling constants (J) are given in Hertzs (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively, and br indicates that the signal is broad. High-resolution mass spectra were carried out by the Universidad de Valencia Mass Spectrometry Service. Microwave experiments were carried out in sealed vials with an Initiator 2.0 (Biotage). The equipment contains an IR probe to control the internal temperature of the reaction mixture. The solutions were prestirred before irradiation was started. The absorbance of the solvent was set as "normal" and the reaction time was initiated as soon as the system reached the input temperature. After irradiation, the reaction mixture was cooled to room temperature with air flow and the pressure was vented with a needle before removing the vial cap.

(−)-(4*R*,6*S*,9a*S*)-6-(Iodomethyl)-4-phenyl-9a-(trifluoromethyl)-3,4,6,7-tetrahydropyrido[2,1-*c*][1,4]oxazin-1(9a*H*)-one (13): DBU (0.23 mL, 1.52 mmol) was added to a solution of **4**[13] (430 mg, 0.76 mmol) in DMSO (3.8 mL). The reaction mixture was heated under microwave irradiation at 60 °C for 1 h and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel to afford **13** (305 mg, 92%) as a colorless oil. $R_f = 0.17$ (hexane/EtOAc, 15:1); $[\alpha]^{25}_D = -73.8$ ($c = 0.2$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.21$–2.29 (m, 2H), 3.00–3.09 (m, 1H), 3.20 (dd, $J = 10.0$, 8.3 Hz, 1H), 3.29 (dd, $J = 10.1$, 4.9 Hz, 1H), 4.35–4.41 (m, 1H), 4.57 (t, $J = 2.9$ Hz, 1H), 5.05 (dd, $J = 11.4$, 3.4 Hz,

1H), 6.27 (dt, $J=10.2$, 4.5 Hz, 1H), 6.52 (d, $J=10.2$ Hz, 1H), 7.11–7.16 (m, 2H), 7.30–7.40 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.1$ (q, $^5J_{CF}=3.1$ Hz), 26.8, 53.8, 59.7, 65.1 (q, $^2J_{CF}=28.4$ Hz), 71.1 (q, $^5J_{CF}=3.4$ Hz), 122.1 (q, $^4J_{CF}=1.0$ Hz), 124.2 (q, $^1J_{CF}=290.1$ Hz), 127.1, 128.5, 129.1, 129.6, 138.4, 165.1 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-72.8$ ppm (s, 3F); HRMS (EI): *m/z* calcd for $C_{16}H_{15}F_3INO_2$: 437.0100 [M^+]; found: 437.0096.

(−)-(4*R*,6*S*,9a*S*)-6-(Cyanomethyl)-4-phenyl-9a-(trifluoromethyl)-3,4,6,7-tetrahydropyrido[2,1-*c*][1,4]oxazin-1(9a*H*)-one (14): NaCN (86 mg, 1.74 mmol) was added to a solution of **4**[13] (246 mg, 0.44 mmol) in DMSO (2.2 mL). The reaction mixture was heated under microwave irradiation at 90 °C for 1 h and quenched with saturated aqueous NaCl. The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel to afford **14** (123 mg, 84%) as a colorless oil. $R_f=0.21$ (hexane/EtOAc, 3:1); $[\alpha]^{25}_D=-171.4$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.97$–2.08 (m, 1H), 2.21–2.33 (m, 1H), 2.43 (dd, $J=16.8$, 7.2 Hz, 1H), 2.61 (dd, $J=16.8$, 7.3 Hz, 1H), 3.38 (qd, $J=7.2$, 3.7 Hz, 1H), 4.36–4.42 (m, 1H), 4.63 (t, $J=3.0$ Hz, 1H), 5.06 (dd, $J=11.6$, 3.5 Hz, 1H), 6.25 (ddd, $J=10.4$, 5.3, 3.5 Hz, 1H), 6.44 (d, $J=10.3$ Hz, 1H), 7.13–7.18 (m, 2H), 7.34–7.42 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta=24.1$ (q, $^5J_{CF}=3.3$ Hz), 26.9, 49.8, 60.3, 64.6 (q, $^2J_{CF}=28.5$ Hz), 71.0 (q, $^5J_{CF}=3.4$ Hz), 117.7, 122.4 (c, $^4J_{CF}=1.1$ Hz), 124.2 (q, $^1J_{CF}=291.4$ Hz), 127.1, 128.4, 128.8. 129.2, 138.2, 164.7 ppm (q, $^3J_{CF}=1.3$ Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-72.4$ ppm (s, 3F); HRMS (EI): *m/z* calcd for $C_{17}H_{15}F_3N_2O_2$: 336.1086 [M^+]; found: 336.1092.

(4*R*,6*S*,9a*S*)-6-[2-(*tert*-Butoxycarbonylamino)ethyl]-4-phenyl-9a-(trifluoromethyl)octahydropyrido[2,1-*c*][1,4]oxazin-1-ol (15): Pd/C (10% wt, 46 mg, 0.044 mmol) was added to a solution of **14** (29 mg, 0.086 mmol) in MeOH (0.9 mL). The reaction mixture was stirred in a hydrogen atmosphere (1 atm) for 12 h, filtered, and concentrated under reduced pressure. The crude mixture was dissolved in THF (1.7 mL), and $BH_2Cl{\cdot}SMe_2$ (0.027 mL, 0.261 mmol) was added dropwise. The reaction mixture was stirred at under reflux for 12 h and cooled at room temperature. A solution of HCl in MeOH (1.25 M, 0.695 mL, 0.869 mmol) was added dropwise, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOH and re-evaporated three times until complete disappearance of residual borates. Et_3N (0.018 mL, 0.130 mmol) and Boc_2O (28 mg, 0.130 mmol) were added to the crude mixture dissolved in THF (1.7 mL). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel to afford a 7:1 mixture of diastereomeric lactols **15** (34 mg, 88%) as a colorless oil. $R_f=0.23$ (hexane/EtOAc, 5:1); data of major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.39$ (s, 9H), 1.46–1.86 (m, 7H), 2.42–2.59 (m, 1H), 2.67–2.91 (m, 2H), 3.65 (dd, $J=11.4$, 3.4 Hz, 1H), 3.84–3.94 (m, 1H), 4.01 (t, $J=11.7$ Hz, 1H), 4.16 (d, $J=5.1$ Hz, 1H), 4.61–4.71 (m, 1H), 5.03 (d, $J=5.0$ Hz, 1H), 7.29–7.43 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=15.5$ (q, $^3J_{CF}=8.4$ Hz), 25.4, 27.2, 27.3, 28.3, 38.3, 49.0, 57.6 (q, $^4J_{CF}=2.6$ Hz), 61.6 (q, $^2J_{CF}=21.2$ Hz), 63.8, 79.0, 90.9 (q, $^3J_{CF}=3.9$ Hz), 128.1, 128.6, 128.7 (q, $^1J_{CF}=297.4$ Hz), 129.1, 138.3 (q, $^5J_{CF}=0.9$ Hz), 155.6 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-64.1$ ppm (s, 3F); data of minor diastereoisomer: ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-59.5$ ppm (s, 3F); HRMS (EI): *m/z* calcd for $C_{22}H_{31}F_3N_2O_4$: 444.2236 [M^+]; found: 444.2208.

General procedure for reduction with $LiBH_4$ (general procedure A): $LiBH_4$ (3 equiv) was added to a solution of the corresponding lactol or lactone (1 equiv) in THF (0.1 M) and stirred at room temperature for the time indicated in each case. The reaction was quenched with saturated aqueous NH_4Cl, the aqueous layer was extracted with Et_2O (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel with the appropriate solvents as the eluent.

(+)-(2*S*,6*S*)-6-[2-(*tert*-Butoxycarbonylamino)ethyl]-2-(hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]-2-(trifluoromethyl)piperidine (16): General procedure A and **15** (144 mg, 0.32 mmol) were employed with stirring for 36 h to obtain **16** (103 mg, 71%) as a white solid. $R_f=0.14$ (hexane/EtOAc, 2:1); m.p. 51–53 °C; $[\alpha]^{25}_D=+2.4$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.62$–0.79 (m, 1H), 1.43 (s, 9H), 1.47–2.07 (m, 7H), 2.65–2.93 (m, 2H), 3.11–3.26 (m, 1H), 3.61 (d, $J=12.2$ Hz, 1H), 3.70 (dd, $J=10.7$, 3.2 Hz, 1H), 3.94–4.06 (m, 1H), 4.19 (d, $J=12.2$ Hz, 1H), 4.23 (t, $J=10.8$ Hz, 1H), 4.55 (dd, $J=10.0$, 3.8 Hz, 1H), 7.22–7.36 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=15.0$, 26.0, 26.4, 28.4, 35.3, 38.7, 47.2, 60.4, 61.7, 62.7, 63.3 (q, $^2J_{CF}=22.2$ Hz), 79.2, 127.3 (q, $^1J_{CF}=291.4$ Hz), 127.6, 128.2, 128.6, 139.8, 155.9 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-73.3$ ppm (s, 3F); HRMS (FAB): *m/z* calcd for $C_{22}H_{33}F_3N_2O_4$: 446.2392 [M^+]; found: 446.2404.

General procedure for the hydrogenation of *N*-protected amines (general procedure B): $Pd(OH)_2$ (0.7 equiv) was added to a solution of the corresponding *N*-protected amine (1 equiv) in MeOH (0.04 M). The reaction mixture was stirred in a hydrogen atmosphere (5 atm) for the time indicated, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel with the appropriate solvents as the eluent.

(+)-(2*S*,6*S*)-6-[2-(*tert*-Butoxycarbonylamino)ethyl]-2-(hydroxymethyl)-2-(trifluoromethyl)piperidine (17): General procedure B and **16** (84 mg, 0.19 mmol) were employed with stirring for 6 h to obtain **17** (53 mg, 86%) as a white solid. $R_f=0.34$ (hexane/EtOAc, 3:1); m.p. 120–121 °C; $[\alpha]^{25}_D=+8.1$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.03$–1.19 (m, 1H), 1.41 (s, 9H), 1.40–1.75 (m, 5H), 2.36 (br, 1H), 2.66–2.76 (m, 1H), 2.95–3.08 (m, 1H), 3.30–3.48 (m, 1H), 3.61 (d, $J=11.9$ Hz, 1H), 3.74 (br, 1H), 3.92 (d, $J=11.9$ Hz, 1H), 4.99 ppm (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=19.9$, 24.7, 28.3, 31.7, 36.4, 38.5, 46.6, 58.5, 59.9 (q, $^2J_{CF}=23.9$ Hz), 79.8, 126.9 (q, $^1J_{CF}=282.9$ Hz), 157.1 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-79.9$ ppm (s, 3F); HRMS (FAB): *m/z* calcd for $C_{14}H_{26}F_3N_2O_3$: 327.1896 [$M+H^+$]; found: 327.1907.

General procedure for the oxidation and esterification of amino alcohols (general procedure C): DMSO (6 equiv) was added dropwise to a stirred solution of $(COCl)_2$ (3 equiv) in CH_2Cl_2 (0.025 M) cooled to −78 °C. After 10 min, a solution of the corresponding amino alcohol (1 equiv) in CH_2Cl_2 (0.1 M) was added and the reaction mixture was stirred at −78 °C for 1 h. Et_3N (9 equiv) was added to the reaction mixture, which was allowed to reach 0 °C. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated under reduced pressure, and the residue was filtered through a short pad of silica gel with 1:1 hexane/EtOAc as the eluent. The resulting aldehyde was dissolved in 2:1 *t*BuOH/THF (0.03 M). 2-Methyl-2-butene (30 equiv) was added to the reaction mixture followed by a solution of $NaClO_2$ (10 equiv) and NaH_2PO_4 (10 equiv) in H_2O (0.05 M). The reaction mixture was stirred a room temperature for 30 min and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated under reduced pressure, and the crude acid was dissolved in toluene/MeOH (2.5:1, 0.03 M). The solution was cooled to 0 °C and $TMSCHN_2$ (2 M in hexane, 1.5 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and quenched with some drops of AcOH and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel with the appropriate solvents as the eluent.

(+)-(2*S*,6*S*)-6-[2-(*tert*-Butoxycarbonylamino)ethyl]-2-(methoxycarbonyl)-2-(trifluoromethyl)piperidine (18): General procedure C and **17** (63 mg, 0.193 mmol) were employed to obtain **18** (51 mg, 74%) as a colorless oil. $R_f=0.30$ (hexane/EtOAc, 5:1); $[\alpha]^{25}_D=+7.1$ ($c=0.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.11$–1.35 (m, 2H), 1.44 (s, 9H), 1.53–1.72 (m, 4H), 1.76–1.87 (m, 1H), 2.30–2.38 (m, 1H), 2.56–2.69 (m, 1H), 3.09–3.33 (m, 2H), 3.83 (s, 3H), 4.80 ppm (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=20.8$, 25.9 (q, $^3J_{CF}=1.5$ Hz), 28.4, 29.9, 36.6, 37.0, 50.9, 53.1, 66.9 (q, $^2J_{CF}=26.3$ Hz), 79.2, 124.1 (q, $^1J_{CF}=282.3$ Hz), 155.9, 169.6 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-78.9$ ppm (s, 3F); HRMS (EI): *m/z* calcd for $C_{15}H_{26}F_3N_2O_4$: 355.1845 [$M+H^+$]; found: 355.1844.

(+)-(2*S*,6*S*)-2-(Cyanomethyl)-6-(hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (19): General procedure A and **14** (58 mg, 0.173 mmol) were employed with stirring for 3 h to obtain **19** (52 mg, 89%) as a white solid. $R_f=0.34$ (hexane/EtOAc, 1:4); m.p. 114–116 °C; $[\alpha]^{25}_D=+33.7$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): $\delta=1.33$ (d, $J=16.7$ Hz, 1H), 2.27 (dd, $J=16.7$, 11.1 Hz, 1H), 2.34 (dd, $J=16.7$, 6.6 Hz, 1H), 2.45–2.58 (m, 1H), 3.57 (d, $J=12.1$ Hz, 1H), 3.71 (dd, $J=11.1$, 3.4 Hz, 1H), 3.81 (br, 1H), 3.88–3.97 (m, 1H), 4.14 (d, $J=12.1$ Hz, 1H), 4.26 (t, $J=10.4$ Hz, 1H), 4.56 (dd, $J=10.5$, 3.2 Hz, 1H), 4.77 (br, 1H), 5.71 (dd, $J=10.2$, 2.8 Hz, 1H), 6.21–6.29 (m, 1H), 7.31–7.49 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.1$ (q, $^5J_{CF}=4.4$ Hz), 29.2, 46.4, 60.2, 60.4 (q, $^5J_{CF}=1.4$ Hz), 62.3, 64.9 (q, $^2J_{CF}=23.3$ Hz), 118.9 (q, $^6J_{CF}=1.3$ Hz), 123.9 (q, $^4J_{CF}=2.7$ Hz), 125.8 (q, $^1J_{CF}=289.1$ Hz), 128.0 (q, $^6J_{CF}=1.4$ Hz), 128.5, 129.1, 129.8, 137.6 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-72.0$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{17}H_{20}F_3N_2O_2$: 341.1477 $[M+H^+]$; found: 341.1471.

(−)-(2*S*,6*S*)-2-(Ethoxycarbonylmethyl)-6-(hydroxymethyl)-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (20): AcCl (0.78 mL, 10.97 mmol) was added dropwise to EtOH (2 mL) at room temperature (caution: exothermic reaction). An aliquot of the resulting solution of HCl in EtOH (4 M, 0.60 mL, 2.35 mmol) was added to **19** (20 mg, 0.059 mmol). The reaction mixture was stirred at 75 °C for 4 h, cooled to room temperature, and then saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel to afford **20** (12 mg, 76%) as a white solid. $R_f=0.28$ (hexane/EtOAc, 1:1); m.p. 82–83 °C; $[\alpha]^{25}_D=-25.8$ ($c=0.8$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.26$ (t, $J=7.1$ Hz, 3H), 1.92–2.08 (m, 2H), 2.42–2.56 (m, 2H), 2.67 (br, 2H), 3.28–3.37 (m, 1H), 3.77 (d, $J=12.5$ Hz, 1H), 3.84 (d, $J=12.3$ Hz, 1H), 4.16 (q, $J=7.1$ Hz, 2H), 5.54 (ddd, $J=10.2$, 2.5, 1.4 Hz, 1H), 6.09 ppm (ddd, $J=10.1$, 5.2, 2.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=14.1$, 30.8, 40.0, 44.5, 60.9, 61.9 (q, $^2J_{CF}=25.3$ Hz), 62.0, 121.5 (q, $^4J_{CF}=2.0$ Hz), 125.9 (q, $^1J_{CF}=284.2$ Hz), 131.2, 172.4 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-77.3$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{11}H_{17}F_3NO_3$: 268.1161 $[M+H^+]$; found: 268.1159.

(+)-(2*S*,6*S*)-6-(Ethoxycarbonylmethyl)-2-(hydroxymethyl)-2-(trifluoromethyl)piperidine (21): Pd/C (10% wt, 56 mg, 0.052 mmol) was added to a solution of **20** (28 mg, 0.105 mmol) in EtOH (2.6 mL). The reaction mixture was stirred in a hydrogen atmosphere (1 atm) for 2 h, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford **21** (24 mg, 85%) as a colorless oil. $R_f=0.27$ (hexane/EtOAc, 1:1); $[\alpha]^{25}_D=+16.6$ ($c=1.2$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.13$–1.22 (m, 1H), 1.25 (t, $J=7.1$ Hz, 3H), 1.45–1.68 (m, 4H), 1.73–1.78 (m, 1H), 2.29–2.47 (m, 3H), 3.05–3.13 (m, 1H), 3.75 (d, $J=12.6$ Hz, 1H), 3.95 (d, $J=12.6$ Hz, 1H), 4.15 ppm (q, $J=7.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=14.1$, 19.7, 24.0 (q, $^3J_{CF}=2.0$ Hz), 30.6, 41.1, 47.0, 58.6, 59.7 (q, $^2J_{CF}=24.2$ Hz), 60.8, 127.0 (q, $^1J_{CF}=284.6$ Hz), 172.4 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-80.1$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{11}H_{19}F_3NO_3$: 270.1317 $[M+H^+]$; found: 270.1316.

(+)-(2*S*,6*S*)-6-(Ethoxycarbonylmethyl)-2-(methoxycarbonyl)-2-(trifluoromethyl)piperidine (22): General procedure C and **21** (65 mg, 0.241 mmol) were employed to obtain **22** (40 mg, 56%) as a colorless oil. $R_f=0.30$ (hexane/EtOAc, 5:1); $[\alpha]^{25}_D=+0.9$ ($c=0.8$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.16$ (qd, $J=12.1$, 3.5 Hz, 1H), 1.27 (t, $J=7.1$ Hz, 3H), 1.28–1.40 (m, 1H), 1.55–1.62 (m, 1H), 1.66 (td, $J=12.8$, 4.1 Hz, 1H), 1.75–1.83 (m, 1H), 2.30–2.38 (m, 1H), 2.40 (d, $J=6.4$ Hz, 2H), 2.90–3.00 (m, 1H), 3.14 (br, 1H), 3.84 (s, 3H), 4.16 ppm (q, $J=7.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=14.2$, 20.6, 25.7 (q, $^3J_{CF}=1.6$ Hz), 30.5, 41.5, 49.4, 53.1, 60.6, 66.7 (q, $^2J_{CF}=26.7$ Hz), 124.2 (q, $^1J_{CF}=283.8$ Hz), 169.5, 171.7 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-78.4$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{12}H_{19}F_3NO_4$: 298.1266 $[M+H^+]$; found: 298.1262.

(−)-(4*R*,6*S*,9a*S*)-6-(Azidomethyl)-4-phenyl-9a-(trifluoromethyl)-3,4,6,7-tetrahydropyrido[2,1-c][1,4]oxazin-1(9a*H*)-one (23): NaN_3 (50 mg, 0.771 mmol) was added to a solution of **13** (169 mg, 0.385 mmol) in DMF (1.9 mL). The reaction mixture was stirred at 65 °C for 4 h, concentrated under reduced pressure, and purified by column chromatography on silica gel to afford **23** (131 mg, 97%) as a white solid. $R_f=0.27$ (hexane/EtOAc, 15:1); m.p. 47–49 °C; $[\alpha]^{25}_D=-137.2$ ($c=1.5$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.98$–2.26 (m, 2H), 3.07 (qd, $J=6.7$, 4.4 Hz, 1H), 3.22 (dd, $J=12.4$, 6.4 Hz, 1H), 3.34 (dd, $J=12.4$, 6.4 Hz, 1H), 4.37–4.45 (m, 1H), 4.63 (t, $J=3.1$ Hz, 1H), 5.03 (dd, $J=11.4$, 3.3 Hz, 1H), 6.26 (dt, $J=10.2$, 4.5 Hz, 1H), 6.42 (d, $J=10.0$ Hz, 1H), 7.12–7.22 (m, 2H), 7.28–7.45 ppm (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=25.1$, 51.9, 54.6 (q, $^5J_{CF}=2.8$ Hz), 60.2, 64.9 (q, $^2J_{CF}=28.5$ Hz), 71.2 (q, $^5J_{CF}=3.2$ Hz), 122.2, 124.1 (q, $^1J_{CF}=291.8$ Hz), 127.2, 128.5, 129.0, 129.5, 138.5, 165.0 ppm (q, $^3J_{CF}=1.1$ Hz); ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-73.3$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{16}H_{16}F_3N_4O_2$: 353.1225 $[M+H^+]$; found: 353.1232.

(−)-(4*R*,6*S*,9a*S*)-6-(Acetoxymethyl)-4-phenyl-9a-(trifluoromethyl)-3,4,6,7-tetrahydropyrido[2,1-c][1,4]oxazin-1(9a*H*)-one (24): AgOAc (178 mg, 1.068 mmol) was added to a solution of **13** (47 mg, 0.107 mmol) in toluene (1.6 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through celite with EtOAc as the eluent, concentrated under reduced pressure, and purified by column chromatography on silica gel to afford **24** (35 mg, 89%) as a white solid. $R_f=0.19$ (hexane/EtOAc, 7:1); m.p. 55–57 °C; $[\alpha]^{25}_D=-134.8$ ($c=0.7$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.04$ (s, 3H), 2.14–2.22 (m, 2H), 3.05–3.18 (m, 1H), 3.90 (dd, $J=11.4$, 4.6 Hz, 1H), 4.23 (dd, $J=11.3$, 6.6 Hz, 1H), 4.35–4.42 (m, 1H), 4.67–4.72 (m, 1H), 4.99 (dd, $J=11.4$, 3.4 Hz, 1H), 6.29 (dt, $J=10.2$, 4.5 Hz, 1H), 6.49 (d, $J=10.2$ Hz, 1H), 7.13–7.17 (m, 2H), 7.29–7.40 ppm (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=20.8$, 25.0 (q, $^5J_{CF}=0.9$ Hz), 51.2, 59.2, 64.9 (q, $^5J_{CF}=2.4$ Hz), 65.0 (q, $^2J_{CF}=28.2$ Hz), 71.4 (q, $^5J_{CF}=3.3$ Hz), 123.0, 124.5 (q, $^1J_{CF}=289.4$ Hz), 127.3, 128.2, 129.0, 130.1, 138.6, 165.3, 170.8 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-73.6$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{18}H_{18}F_3NO_4$: 369.1188 $[M^+]$; found 369.1196.

(−)-(2*S*,6*S*)-6-(Azidomethyl)-2-(hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine (25): General procedure A and **23** (100 mg, 0.28 mmol) were employed with stirring for 4 h to obtain **25** (87 mg, 86%) as a white solid. $R_f=0.18$ (hexane/EtOAc, 3:1); m.p. 169–170 °C; $[\alpha]^{25}_D=-15.5$ ($c=1.2$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.21$–2.42 (m, 3H), 2.92 (td, $J=11.9$, 1.0 Hz, 1H), 3.48–3.54 (m, 1H), 3.57 (d, $J=12.1$ Hz, 1H), 3.69 (dd, $J=11.1$, 3.7 Hz, 1H), 4.15 (d, $J=12.0$ Hz, 1H), 4.26 (t, $J=10.9$ Hz, 1H), 4.54 (dd, $J=10.4$, 3.3 Hz, 1H), 4.84 (br, 1H), 5.67 (dd, $J=10.2$, 2.5 Hz, 1H), 6.16–6.25 (m, 1H), 7.28–7.46 ppm (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta=27.3$, 47.7, 53.2 (q, $^5J_{CF}=4.1$ Hz), 60.2 (q, $^5J_{CF}=1.3$ Hz), 60.3, 62.3, 65.0 (q, $^2J_{CF}=23.4$ Hz), 123.7 (q, $^4J_{CF}=2.6$ Hz), 125.7 (q, $^1J_{CF}=290.3$ Hz), 128.2 (q, $^6J_{CF}=1.3$ Hz), 128.2, 128.8, 130.5, 138.4 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-72.7$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{16}H_{19}F_3N_4O_2$: 357.1538 $[M+H^+]$; found: 357.1533.

(−)-(2*S*,6*S*)-6-(Acetoxymethyl)-2-(hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine (26): General procedure A and **24** (116 mg, 0.32 mmol) were employed with stirring for 3 h to obtain **26** (96 mg, 82%) as a colorless oil. $R_f=0.29$ (hexane/EtOAc, 1:1); $[\alpha]^{25}_D=-21.8$ ($c=0.6$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.95$ (s, 3H), 2.17 (ddd, $J=16.7$, 6.9, 1.3 Hz, 1H), 2.31–2.42 (m, 1H), 3.00 (d, $J=10.5$ Hz, 1H), 3.48 (br, 2H), 3.58 (d, $J=12.0$ Hz, 1H), 3.68 (dd, $J=11.2$, 3.7 Hz, 1H), 3.70–3.76 (m, 1H), 3.84 (td, $J=10.6$, 1.0 Hz, 1H), 4.19 (d, $J=12.0$ Hz, 1H), 4.25 (t, $J=10.8$, 1H), 4.52 (dd, $J=10.4$, 3.6 Hz, 1H), 5.69 (dd, $J=10.2$, 2.8 Hz, 1H), 6.17–6.26 (m, 1H), 7.28–7.38 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=20.9$, 27.1, 46.4, 60.1, 60.6, 62.3, 64.8 (q, $^5J_{CF}=4.1$ Hz),, 65.0 (q, $^2J_{CF}=23.6$ Hz), 123.8, 125.6 (q, $^1J_{CF}=290.0$ Hz), 128.1, 128.2, 128.6, 130.7, 138.6, 170.4 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta=-73.2$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{18}H_{22}F_3NO_4$ $[M]^+$: 373.1501; found: 373.1503.

(+)-(2*S*,6*S*)-6-(*tert*-Butoxycarbonylaminomethyl)-2-(hydroxymethyl)-2-(trifluoromethyl)piperidine (27): General procedure B and **25** (69 mg, 0.193 mmol) in the presence of Boc_2O (1.5 equiv) were employed with stirring for 6 h to obtain **27** (46 mg, 76%) as a colorless oil. $R_f=0.18$ (hexane/EtOAc, 3:1); $[\alpha]^{25}_D=+17.8$ ($c=1.2$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.09$ (qd, $J=12.5$, 4.0 Hz, 1H), 1.42 (s, 9H), 1.44–1.54 (m, 2H), 1.57–1.66 (m, 2H), 1.66–1.80 (m, 1H), 2.38 (br, 1H), 2.82–2.93 (m, 1H), 2.98–3.17 (m, 2H), 3.70 (d, $J=12.5$ Hz, 1H), 3.86 (d, $J=12.5$ Hz, 1H), 5.04 ppm (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=19.3$, 24.2 (q, $^3J_{CF}=1.9$ Hz), 28.2, 28.3, 46.5, 49.5, 58.2, 59.5 (q, $^2J_{CF}=23.9$ Hz), 79.6, 127.0 (q, $^1J_{CF}=282.6$ Hz), 156.5 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$):

$\delta = -80.4$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{13}H_{24}F_3N_2O_3$: 313.1739 $[M+H^+]$; found: 313.1738.

(+)-(2*S*,6*S*)-6-(Acetoxymethyl)-2-(hydroxymethyl)-2-(trifluoromethyl)piperidine (28): General procedure B and **26** (91 mg, 0.24 mmol) were employed with stirring for 6 h to obtain **28** (56 mg, 90%) as a white solid. $R_f = 0.25$ (hexane/EtOAc, 1:1); m.p. 57–59 °C; $[\alpha]^{25}_D = +32.8$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$ (qd, $J = 12.3$, 4.1 Hz, 1H), 1.41–1.70 (m, 4H), 1.75–1.85 (m, 1H), 1.99 (br, 1H), 2.07 (s, 3H), 2.33 (br, 1H), 2.94–3.05 (m, 1H), 3.76 (d, $J = 12.5$ Hz, 1H), 3.81–3.87 (m, 1H), 3.85 (dd, $J = 10.9$, 7.9 Hz, 1H), 4.12 ppm (dd, $J = 10.9$, 4.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 19.1$, 20.8, 24.2 (q, $^3J_{CF} = 2.0$ Hz), 27.1, 48.9, 58.5, 59.3 (q, $^2J_{CF} = 24.0$ Hz), 68.6, 127.1 (q, $^1J_{CF} = 282.6$ Hz), 170.9 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -80.5$ ppm (s, 3F); HRMS (FAB): m/z calcd $C_{10}H_{17}F_3NO_3$: 256.1161 $[M+H^+]$; found: 256.1164.

(+)-(2*S*,6*S*)-6-(*tert*-Butoxycarbonylaminomethyl)-2-(methoxycarbonyl)-2-(trifluoromethyl)piperidine (29): General procedure C and **27** (25 mg, 0.08 mmol) were employed to obtain **29** (14 mg, 51%) as a white solid. $R_f = 0.21$ (hexane/EtOAc, 5:1); m.p. 52–54 °C; $[\alpha]^{25}_D = +6.9$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$–1.36 (m, 2H), 1.45 (s, 9H), 1.51–1.61 (m, 1H), 1.66 (dd, $J = 13.0$, 4.0 Hz, 1H), 1.75–1.87 (m, 1H), 2.11 (br, 1H), 2.34 (dtd, $J = 12.9$, 3.5, 1.7 Hz, 1H), 2.64–2.84 (m, 1H), 3.00–3.22 (m, 2H), 3.81 (s, 3H), 4.81 ppm (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.4$, 25.9, 27.6, 28.3, 46.2, 52.0, 53.2, 66.7 (q, $^2J_{CF} = 26.5$ Hz), 79.4, 124.2 (q, $^1J_{CF} = 282.6$ Hz), 156.1, 169.5 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -78.3$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{14}H_{23}F_3N_2O_4$: 341.1688 $[M+H^+]$; found: 341.1695.

(+)-(2*S*,6*S*)-6-(Acetoxymethyl)-2-(methoxycarbonyl)-2-(trifluoromethyl)-piperidine (30): General procedure C and **28** (41 mg, 0.505 mmol) were employed to obtain **30** (21 mg, 47%) as a colorless oil. $R_f = 0.26$ (hexane/EtOAc, 4:1); $[\alpha]^{25}_D = +7.1$ ($c = 0.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.04$–1.38 (m, 2H), 1.52–1.62 (m, 1H), 1.69 (td, $J = 13.0$, 4.2 Hz, 1H), 1.77–1.89 (m, 1H), 2.10 (s, 3H), 2.32–2.42 (m, 1H), 2.76 (br, 1H), 2.79–2.91 (m, 1H), 3.77 (dd, $J = 10.9$, 8.7 Hz, 1H), 3.83 (s, 3H), 4.17 ppm (dd, $J = 10.9$, 3.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.2$, 20.8, 26.0 (q, $^3J_{CF} = 1.6$ Hz), 26.6, 51.3, 53.2, 66.3 (q, $^2J_{CF} = 26.4$ Hz), 68.4, 124.1 (q, $^1J_{CF} = 282.0$ Hz), 169.5, 170.8 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -78.8$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{11}H_{17}F_3NO_4$: 284.1110 $[M+H^+]$; found: 284.1111.

(−)-(4*R*,6*S*,8*R*,9*S*,9a*S*)-6-(Acetoxymethyl)-8,9-dihydroxy-4-phenyl-9a-(trifluoromethyl)hexahydropyrido[2,1-*c*][1,4]oxazin-1(6*H*)-one (31): NMO (43 mg, 0.362 mmol) and OsO_4 (2.5% wt in 2-methylpropanol; 0.284 mL, 0.018 mmol) were added to a solution of **24** (67 mg, 0.181 mmol) in acetone/H_2O (8:1, 1.8 mL). The reaction mixture was stirred for 48 h at room temperature. The reaction was quenched with some drops of 10% aqueous $NaHSO_3$, filtered through a short pad of silica with EtOAc as the eluent, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel to afford **31** (65 mg, 89%) as a white solid. $R_f = 0.20$ (hexane/EtOAc, 2:1); m.p. 51–53 °C; $[\alpha]^{25}_D = -153.0$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.74$ (dd, $J = 12.9$, 4.8 Hz, 1H), 1.84–1.95 (m, 1H), 2.01 (s, 3H), 2.64 (d, $J = 10.4$ Hz, 1H), 3.14–3.25 (m, 1H), 3.57 (d, $J = 4.5$ Hz, 1H), 3.98 (td, $J = 10.1$, 1.1 Hz, 1H), 4.11–4.24 (m, 1H), 4.24–4.34 (m, 2H), 4.59 (m, 2H), 4.90 (dd, $J = 13.0$, 4.8 Hz, 1H), 7.27–7.39 (m, 3H), 7.50–7.56 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.8$, 27.4, 53.8, 57.4, 63.3 (q, $^3J_{CF} = 3.5$ Hz), 63.9 (q, $^5J_{CF} = 5.4$ Hz), 68.2, 70.6 (q, $^5J_{CF} = 3.7$ Hz), 71.3 (q, $^2J_{CF} = 25.6$ Hz), 124.2 (q, $^1J_{CF} = 293.9$ Hz), 126.8, 128.3, 128.9, 140.8, 166.1 (q, $^3J_{CF} = 2.2$ Hz), 170.7 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -67.8$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{18}H_{21}F_3NO_6$: 404.1321 $[M+H^+]$; found: 404.1324.

(−)-(4*R*,6*S*,8*R*,9*S*,9a*S*)-6-(Acetoxymethyl)-8,9-(diacetoxy)-4-phenyl-9a-(trifluoromethyl)hexahydropyrido[2,1-*c*][1,4]oxazin-1(6*H*)-one (32): 4-Dimethylaminopyridine (DMAP; 11 mg, 0.086 mmol), pyridine (0.035 mL, 0.430 mmol), and Ac_2O (0.041 mL, 0.430 mmol) were added to a solution of **31** (35 mg, 0.086 mmol) in CH_2Cl_2 (1.8 mL). The reaction mixture was stirred at room temperature for 16 h and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated under reduced pressure concentrated and purified by column chromatography on silica gel to afford **32** (39 mg, 93%) as a white solid. $R_f = 0.24$ (hexane/EtOAc, 5:1); m.p. 48–50 °C; $[\alpha]^{25}_D = -81.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.68$–1.76 (m, 1H), 1.92–2.00 (m, 1H), 2.00 (s, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 3.24–3.33 (m, 1H), 3.97–4.05 (m, 1H), 4.31 (dt, $J = 12.1$, 1.1 Hz, 1H), 4.38 (dd, $J = 11.2$, 4.2 Hz, 1H), 4.58 (d, $J = 4.2$ Hz, 1H), 4.86 (dd, $J = 12.1$, 4.5 Hz, 1H), 5.37–5.46 (m, 1H), 5.99 (dd, $J = 2.6$, 0.9 Hz, 1H), 7.41–7.43 (m, 3H), 7.49–7.58 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.7$, 20.8, 20.8, 24.5, 53.4, 57.2, 63.8, (c, $^5J_{CF} = 5.9$ Hz), 64.8 (q, $^3J_{CF} = 3.4$ Hz), 66.7 (q, $^4J_{CF} = 1.0$ Hz), 69.9 (q, $^2J_{CF} = 27.2$ Hz), 70.0 (q, $^5J_{CF} = 3.5$ Hz), 123.6 (q, $^1J_{CF} = 295.4$ Hz), 126.9, 128.5, 128.9, 140.7, 163.3 (q, $^3J_{CF} = 2.1$ Hz), 168.6, 169.9, 170.5 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -67.4$ ppm (s, 3F); HRMS (FAB): m/z calcd for $C_{22}H_{24}F_3NO_8Na$: 510.1352 $[M+Na^+]$; found: 510.1347.

(−)-(2*S*,6*S*)-2,6-Bis(hydroxymethyl)-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (33): A solution of **26** (33 mg, 0.088 mmol) in HCl (1.25 M in MeOH, 0.71 mL, 0.88 mmol) was heated under microwave irradiation at 100 °C for 10 min. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel to afford **33** (15 mg, 80%) as a white solid. $R_f = 0.26$ (hexane/EtOAc, 1:2); m.p. 74–76 °C; $[\alpha]^{25}_D = -50.5$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.85$–1.90 (m, 2H), 3.02–3.10 (m, 1H), 3.23 (br, 3H), 3.46 (dd, $J = 10.7$, 8.2 Hz, 1H), 3.62–3.67 (m, 2H), 3.77 (d, $J = 12.4$ Hz, 1H), 5.44 (ddd, $J = 10.2$, 2.4, 1.7 Hz, 1H), 6.04 ppm (ddd, $J = 10.2$, 5.0, 3.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 27.0$, 48.9, 61.6 (q, $^2J_{CF} = 25.1$ Hz), 61.6, 65.8, 121.1 (q, $^4J_{CF} = 1.9$ Hz), 125.9 (q, $^1J_{CF} = 284.5$ Hz), 131.2 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -77.0$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_8H_{13}F_3NO_2$: 212.0898 $[M+H^+]$; found: 212.0896.

(−)-(2*S*,6*S*)-2,6-Bis(acetoxymethyl)-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (34): Ac_2O (0.01 mL, 0.106 mmol), pyridine (0.085 mL, 0.106 mmol), and DMAP (0.5 mg, 0.003 mmol) were added to a solution of **33** (7.5 mg, 0.035 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature for 6 h. Saturated aqueous NH_4Cl was added was added to the reaction mixture, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel to afford **34** (10 mg, 95%) as a colorless oil. $R_f = 0.52$ (hexane/EtOAc, 2:1); $[\alpha]^{25}_D = -56.1$ ($c = 1.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.80$–2.00 (m, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 3.12–3.21 (m, 1H), 3.78 (dd, $J = 10.9$, 8.6 Hz, 1H), 4.17 (d, $J = 12.1$ Hz, 1H), 4.19 (dd, $J = 10.9$, 3.5 Hz, 1H), 4.30 (dq, $J = 12.1$, 1.6 Hz, 1H), 5.50 (ddd, $J = 10.2$, 2.8, 1.3 Hz, 1H), 6.10 ppm (ddd, $J = 10.1$, 5.7, 2.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.6$, 20.7, 27.4, 46.8, 60.2 (q, $^2J_{CF} = 26.7$ Hz), 62.5, 67.6, 120.5 (q, $^4J_{CF} = 1.7$ Hz), 125.2 (q, $^1J_{CF} = 283.3$ Hz), 131.5, 170.2, 170.6 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -78.0$ ppm (s, 3F); HRMS (EI): m/z calcd for $C_{12}H_{17}F_3NO_4$: 296.1110 $[M+H^+]$; 296.1117.

(−)-(2*R*,3*S*,4*R*,6*S*)-3,4-Bis(acetoxy)-2,6-bis(acetoxymethyl)-2-(trifluoromethyl)piperidine (36): NMO (21 mg, 0.176 mmol) and OsO_4 (2.5% wt in 2-methylpropanol, 0.11 mL, 0.009 mmol) was added to a solution of **34** (26 mg, 0.088 mmol) in acetone/H_2O (8:1,1.3 mL). The reaction mixture was stirred for 48 h at room temperature and then quenched with some drops of 10% aqueous $NaHSO_3$, filtered through a short pad of silica with EtOAc, and concentrated under reduced pressure. Ac_2O (0.033 mL, 0.352 mmol) and DMAP (1 mg, 0.009 mmol) were added to the residue dissolved in CH_2Cl_2 (1.5 mL) and pyridine (0.028 mL, 0.352 mmol). The reaction mixture was stirred for 24 h at room temperature. Saturated aqueous NH_4Cl was added to the reaction mixture, the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4. The filtrates were concentrated and purified by column chromatography on silica gel to afford **44** (26 mg, 71%) as a colorless oil. $R_f = 0.34$ (hexane/EtOAc, 2:1); $[\alpha]^{25}_D = -60.8$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.55$ (ddd, $J = 14.1$, 11.9, 3.0 Hz, 1H), 1.75 (ddd, $J = 14.2$, 3.4, 2.6 Hz, 1H), 1.96 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 3.22–3.31 (m, 1H), 3.73 (dd, $J = 11.0$, 8.4 Hz, 1H), 4.15 (dd, $J = 11.0$, 3.4 Hz, 1H), 4.29 (d, $J = 12.8$ Hz, 1H), 5.12 (dq, $J =$

12.7, 2.1 Hz, 1H), 5.27 (d, J=3.9 Hz, 1H), 5.41 ppm (q, J=3.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=20.4, 20.6, 20.7, 21.0, 31.1, 44.1, 58.3, 61.5 (q, $^2J_{CF}$=24.5 Hz), 66.8, 67.3, 68.1 (q, $^3J_{CF}$=2.2 Hz), 125.1 (q, $^1J_{CF}$=286.4 Hz), 168.8, 169.6, 170.2, 170.4 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ=−76.4 ppm (s, 3F); HRMS (EI): m/z calcd for $C_{16}H_{23}F_3NO_8$: 414.1376 [M+H$^+$]; found: 414.1370.

(−)-(3*S*,5*R*)-3-Methyl-3-(pent-4-enyl)-5-phenylmorpholin-2-one (37): $BF_3{\cdot}OEt_2$ (0.21 mL, 1.64 mmol) was added to a solution of **1**[13] (200 mg, 0.82 mmol) in toluene (8.2 mL) at −78 °C. After stirring for 2 h, MeMgBr (3 M in Et_2O, 0.55 mL, 1.64 mmol) was added dropwise to the reaction mixture over 15 min. The reaction mixture was stirred at −78 °C for 4 h, and then saturated aqueous NH_4Cl was added. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel to afford **37** (137 mg, 65%) as a white solid. R_f=0.16 (hexane/EtOAc, 15:1); m.p. 67–69 °C; $[\alpha]^{25}_D$=−12.0 (c=0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.38–1.52 (m, 2H), 1.52–1.61 (m, 1H), 1.54 (s, 3H), 1.80–1.93 (m, 1H), 2.01 (dd, J=11.9, 3.2 Hz, 1H), 2.06–2.16 (m, 2H), 4.23 (t, J=10.6 Hz, 1H), 4.31 (dd, J=10.4, 3.2 Hz, 1H), 4.38 (dd, J=10.5, 3.2 Hz, 1H), 4.98 (d, J=10.2 Hz, 1H), 5.04 (dq, J=17.6, 1.8 Hz, 1H), 5.83 (ddt, J=16.9, 10.2, 6.6 Hz, 1H), 7.32–7.48 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=23.5, 27.3, 33.7, 42.0, 53.2, 60.9, 75.4, 114.8, 127.1, 128.6, 128.8, 138.0, 138.4, 173.2 ppm; HRMS (EI): m/z calcd for $C_{16}H_{22}NO_2$: 260.1651 [M+H$^+$]; found 260.1645.

(−)-(3*R*,5*R*)-3-Isobutyl-3-(pent-4-enyl)-5-phenylmorpholin-2-one (38): $BF_3{\cdot}OEt_2$ (0.21 mL, 1.64 mmol) was added to a solution of **1**[13] (200 mg, 0.82 mmol) in THF (8.2 mL) at −78 °C. After stirring for 2 h, *i*BuMgBr (2 M in THF, 0.82 mL, 1.64 mmol) was added dropwise to the reaction mixture over 15 min. The reaction mixture was stirred at −78 °C for 4 h, and then saturated aqueous NH_4Cl was added. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel to afford **38** (119 mg, 48%) as a colorless oil. R_f=0.20 (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$= −2.1 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (d, J= 6.5 Hz, 3H), 1.00 (d, J=6.4 Hz, 3H), 1.41–1.67 (m, 4H), 1.81–1.94 (m, 3H), 1.98–2.16 (m, 3H), 4.24 (t, J=10.5 Hz, 1H), 4.31 (dd, J=10.4, 3.3 Hz, 1H), 4.39 (dd, J=10.5, 3.3 Hz, 1H), 4.98 (d, J=10.2 Hz, 1H), 5.04 (dq, J=17.3, 2.0 Hz, 1H), 5.83 (ddt, J=17.0, 10.6, 6.8 Hz, 1H), 7.30–7.47 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=23.7, 24.1,24.2, 25.1, 33.8, 41.4, 48.8, 53.6, 63.6, 75.0, 114.8, 127.2, 128.6, 128.8, 138.2, 138.4, 173.2 ppm; HRMS (EI): m/z calcd for $C_{19}H_{28}NO_2$: 302.2120 [M+H$^+$]; found. 302.2115.

(+)-(*S*)-2-Amino-2-methylhept-6-enoic acid (39): $LiOH{\cdot}H_2O$ (582 mg, 13.88 mmol) was added to a solution of **37** (1.8 g, 6.94 mmol) in THF/H_2O (5:1, 69 mL). The reaction mixture was stirred for 3 h and the organic solvents were removed under reduced pressure. The aqueous phase was washed with Et_2O and concentrated under reduced pressure. Pb(OAc)$_4$ (4.62 g, 10.41 mmol) was added to the residue dissolved in CH_2Cl_2/MeOH (2:1, 69 mL) at 0 °C. The reaction mixture was vigorously stirred for 1 h at 0 °C, H_2O (69 mL) was added, and the temperature was allowed to warm to room temperature. After 4 h of additional stirring, the reaction mixture was filtered through celite with CH_2Cl_2 and H_2O as the eluents. The organic solvents were removed under reduced pressure, the aqueous residue was washed with CH_2Cl_2, and the mixture concentrated under reduced pressure. The product was purified by DOWEX 50WX8-100 to afford **39** (900 mg, 82%) as a white solid, the NMR spectroscopic data of which matched those previously reported.[26a] M.p. 300–301 °C; $[\alpha]^{25}_D$=+12.0 (c=1.0 in MeOH) (lit. data: m.p.>200 °C (decomp.); $[\alpha]^{25}_D$=+10.8 (c=0.83 in MeOH));[26a] HRMS (EI): m/z calcd for $C_8H_{16}NO_2$: 158.1181 [M+H$^+$]; found 158.1176.

(−)-(*R*)-2-Amino-2-isobutylhept-6-enoic acid (40): $LiOH{\cdot}H_2O$ (36 mg, 0.86 mmol) was added to a solution of **38** (130 mg, 0.43 mmol) in THF/H_2O (5:1, 4.3 mL). The reaction mixture was stirred for 3 h and the organic solvents were removed under reduced pressure. The aqueous phase was washed with Et_2O and concentrated under reduced pressure. Pb(OAc)$_4$ (286 mg, 0.645 mmol) was added to the residue dissolved in CH_2Cl_2/MeOH (2:1, 4.3 mL) at 0 °C. The reaction mixture was vigorously stirred for 1 h at 0 °C, H_2O (4.3 mL) was added, and the temperature was allowed to warm to room temperature. After 4 h of additional stirring, the reaction mixture was filtered through celite with CH_2Cl_2 and H_2O as the eluents. The organic solvents were removed under reduced pressure, the aqueous residue was washed with CH_2Cl_2, and the mixture concentrated under reduced pressure. The product was purified by DOWEX 50WX8-100 to afford **40** (50 mg, 60%) as a white solid. M.p. 269–271 °C; $[\alpha]^{25}_D$=−8.7 (c=1.1 in MeOH); ^{1}H NMR (300 MHz, MeOD): δ=0.97 (d, J=6.3 Hz, 6H), 1.33–1.48 (m, 1H), 1.48–1.60 (m, 1H), 1.60–1.73 (m, 2H), 1.74–1.92 (m, 3H), 2.07 (q, J=6.9 Hz, 2H), 4.95 (d, J=10.2 Hz, 1H), 5.02 (dq, J=17.2, 1.9 Hz, 1H), 5.80 ppm (ddt, J=17.0, 10.4, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, MeOD): δ=23.3, 23.8,25.0, 25.2, 34.8, 38.7, 46.5, 65.5, 115.5, 139.2, 175.0 ppm; HRMS (EI): m/z calcd for $C_{11}H_{22}NO_2$: 200.1651 [M+H$^+$]; found 200.1645.

Methyl (+)-(*R*)-2-(*tert*-butoxycarbonylamino)-2-methylhept-6-enoate (41): Boc_2O (3.27 g, 14.98 mmol) and NaOH (10% aq., 5 mL) were added to a solution of **39** (785 mg, 4.99 mmol) in THF/H_2O (2:1, 50 mL). The reaction mixture was stirred at room temperature for 12 h, and the organic solvents were removed under reduced pressure. The aqueous phase was washed with EtOAc and acidified with citric acid (10% aq.) until pH 3 was reached. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. $TMSCHN_2$ (2 M in hexane, 3.7 mL, 7.49 mmol) was added dropwise to the residue dissolved in PhMe/MeOH (2.5:1, 50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 12 h and quenched with some drops of AcOH. The organic solvents were removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel to afford **41** (880 mg, 65%) as a colorless oil. R_f=0.40 (hexane/EtOAc, 8:1); $[\alpha]^{25}_D$=+6.3 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.14–1.27 (m, 1H), 1.29–1.39 (m, 1H), 1.41 (s, 9H), 1.50 (s, 3H), 1.74 (ddd, J=13.4, 12.0, 4.8 Hz, 1H), 1.93–2.09 (m, 3H), 3.71 (s, 3H), 4.93 (d, J=9.2 Hz, 1H), 4.97 (dq, J= 16.9, 1.7 Hz, 1H), 5.21 (br, 1H), 5.73 ppm (ddt, J=16.9, 10.2, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.2, 23.3, 28.3, 33.4, 36.6, 52.4, 59.5, 79.4, 114.9, 138.1, 154.3, 175.0 ppm; HRMS (EI): m/z calcd for $C_{14}H_{26}NO_4$: 272.1862 [M+H$^+$]; found 272.1856.

Methyl (+)-(*S*)-2-(*tert*-Butoxycarbonylamino)-2-isobutylhept-6-enoate (42): Boc_2O (177 mg, 0.81 mmol) and NaOH (10% aq., 0.27 mL) were added to a solution of **40** (54 mg, 0.27 mmol) in THF/H_2O (2:1, 2.7 mL). The reaction mixture was stirred at room temperature for 12 h, and the organic solvents were removed under reduced pressure. The aqueous phase was washed with EtOAc and acidified with citric acid (10% aq.) until pH 3 was reached. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. $TMSCHN_2$ (2 M in hexane, 0.21 mL, 0.41 mmol) was added dropwise to the residue dissolved in PhMe/MeOH (2.5:1, 2.7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 12 h and quenched with some drops of AcOH. The organic solvents were removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel to afford **42** (60 mg, 70%) as a colorless oil. R_f=0.45 (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$=+2.7 (c=1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.76 (d, J=6.4 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 0.93–1.11 (m, 1H), 1.29–1.40 (m, 1H), 1.43 (s, 9H), 1.49–1.73 (m, 4H), 2.00 (q, J=6.9 Hz, 2H), 2.27–2.42 (m, 1H), 3.73 (s, 3H), 4.92 (d, J=10.1 Hz, 1H), 4.97 (dq, J=17.2, 1.6 Hz, 1H), 5.65 (br, 1H), 5.73 ppm (ddt, J=16.9, 10.2, 6.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=22.8, 23.2, 23.8, 24.6, 28.4, 33.3, 35.9, 44.0, 52.4, 63.3, 78.9, 114.7, 138.3, 153.6, 175.3 ppm; HRMS (EI): m/z calcd for $C_{17}H_{32}NO_4$: 314.2331 [M+H$^+$]; found 314.2326.

1-Ethyl 8-methyl (+)-(*S*,*E*)-7-(*tert*-butoxycarbonylamino)-7-methyloct-2-enedioate (43): The Grubbs second-generation catalyst (64 mg, 10 mol%) and ethyl acrylate (0.16 mL, 1.51 mmol) were added to a solution of **41** (205 mg, 0.755 mmol) in CH_2Cl_2 (3.8 mL). The reaction mixture was heated under reflux for 3 h, allowed to cool to room temperature, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel to afford **43** (243 mg, 93%) as a colorless oil. R_f=0.45 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$=+7.1 (c=1.1 in

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.20–1.30$ (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.32–1.42 (m, 1H), 1.36 (s, 9H), 1.45 (s, 3H), 1.75 (ddd, $J = 13.5$, 12.0, 4.8 Hz, 1H), 1.93–2.07 (m, 1H), 2.12 (q, $J = 7.0$ Hz, 2H), 3.68 (s, 3H), 4.11 (q, $J = 7.0$, 2H), 5.25 (br, 1H), 5.74 (dt, $J = 15.6$, 1.4, 1H) 6.84 ppm (dt, $J = 15.6$, 6.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 14.1, 22.4, 23.3, 28.2, 31.7, 36.2, 52.4, 59.3, 60.0, 79.4, 121.6, 148.1, 154.1, 166.4, 174.7 ppm; HRMS (EI): m/z calcd for $C_{17}H_{30}NO_6$: 344.2073 [$M+H^+$]; found 344.2068.

1-Ethyl 8-methyl (+)-(*R*,*E*)-7-(*tert*-butoxycarbonylamino)-7-isobutyloct-2-enedioate (44): The Grubbs second-generation catalyst (16 mg, 10 mol%) and ethyl acrylate (0.04 mL, 0.38 mmol) were added to a solution of **42** (60 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was heated under reflux for 3 h, allowed to cool to room temperature, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel to afford **44** (70 mg, 95%) as a colorless oil. $R_f = 0.40$ (hexane/EtOAc, 5:1); $[\alpha]^{25}_D = +3.0$ ($c = 0.9$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.75$ (d, $J = 6.4$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.99–1.17 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.42 (s, 9H), 1.46–1.54 (m, 1H), 1.54–1.59 (m, 1H), 1.59–1.65 (m, 1H), 1.65–1.75 (m, 1H), 2.07–2.23 (m, 2H), 2.23–2.42 (m, 2H), 3.74 (s, 3H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.65 (br, 1H), 5.77 (dt, $J = 15.7$, 1.6 Hz, 1H), 6.87 ppm (dt, $J = 15.7$, 6.8, Hz, 1H); ^{13}C NMR (75 -MHz, $CDCl_3$): $\delta = 14.2$, 22.4, 22.8, 23.7, 24.5, 28.3, 31.7, 35.8, 44.0, 52.5, 60.1, 63.2, 79.0, 121.5, 148.4, 153.6, 166.6, 175.0 ppm; HRMS (EI): m/z calcd for $C_{20}H_{36}NO_6$: 386.2543 [$M+H^+$]; found 386.2537.

(+)-(2*S*,6*S*)-6-(Ethoxycarbonylmethyl)-2-(methoxycarbonyl)-2-methylpiperidine (45): TFA (0.27 mL, 3.55 mmol) was added to a solution of **43** (243 mg, 0.71 mmol) in CH_2Cl_2 (7.1 mL). The reaction mixture was stirred overnight at room temperature. The solvents were evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (7.1 mL), and Et_3N (0.30 mL, 2.13 mmol) was added to the residue. The reaction mixture was heated under microwave irradiation at 100°C for 50 min. The organic solvents were removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel to afford **45** (96 mg, 56%) and the (2*S*,6*R*) diastereoisomer epi-**45** (24 mg, 14%) as colorless oils. **45**: $R_f = 0.29$ (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +7.1 ($c = 1.1$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (qd, $J = 11.7$, 3.4 Hz, 1H), 1.19–1.28 (m, 1H), 1.23 (s, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.27–1.40 (m, 1H), 1.55 (dd, $J = 13.4$, 1.9 Hz, 1H), 1.60–1.70 (m, 1H), 2.16 (d, $J = 10.6$ Hz, 1H), 2.30–2.36 (m, 2H), 2.68 (br, 1H), 2.87–2.98 (m, 1H), 3.70 (s, 3H), 4.12 ppm (q, $J = 7.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$, 22.0, 28.6, 31.2, 33.7, 41.7, 50.2, 51.9, 60.2, 60.3, 171.9, 176.9 ppm; HRMS (EI): m/z calcd for $C_{12}H_{22}NO_4$: 244.1549 [$M+H^+$]; found 244.1543.

(+)-(2*R*,6*S*)-6-(Ethoxycarbonylmethyl)-2-isobutyl-2-(methoxycarbonyl)-piperidine (46): TFA (0.07 mL, 0.90 mmol) was added to a solution of **44** (70 mg, 0.18 mmol) in CH_2Cl_2 (1.8 mL). The reaction mixture was stirred overnight at room temperature. The solvents were evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (1.8 mL), and Et_3N (0.07 mL, 0.54 mmol) was added to the residue. The reaction mixture was heated under microwave irradiation at 100°C for 50 min. The organic solvents were removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel to afford **46** (27 mg, 52%) and the (2*S*,6*R*) diastereoisomer epi-**46** (7 mg, 14%) as colorless oils. **46**: $R_f = 0.30$ (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +2.6 ($c = 1.1$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H), 1.10 (qd, $J = 12.1$, 3.7 Hz, 1H), 1.20–1.37 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.47–1.61 (m, 3H), 1.61–1.75 (m, 2H), 2.16–2.23 (m, 1H), 2.32–2.36 (m, 2H), 2.93–3.05 (m, 1H), 3.71 (s, 3H), 4.14 ppm (q, $J = 7.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$, 21.9, 23.6, 24.4, 24.4, 31.6, 33.3, 41.9, 49.8, 51.2, 51.6, 60.4, 63.1, 172.1, 176.4 ppm; HRMS (EI): m/z calcd for $C_{15}H_{28}NO_4$: 286.2018 [$M+H^+$]; found 286.2013.

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