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Synthetic Studies of Huperzine A and Its Fluorinated Analogues. 2. Synthesis and Acetylcholinesterase Inhibitory Activity of Novel Fluorinated Huperzine A Analogues[1]

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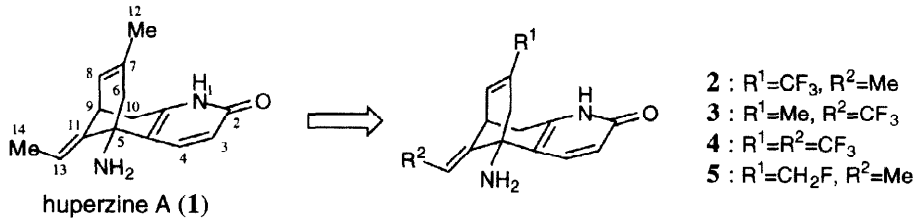
Abstract: *Four types of the novel fluorinated huperzine A analogues, (±)-12,12,12-trifluorohuperzine A (**2**), (±)-14,14,14-trifluorohuperzine A (**3**), (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**), and (±)-12-fluorohuperzine A (**5**), were synthesized; the methods feature introduction of a trifluoromethyl group with the Ruppert's reagent ($TMSCF_3$), construction of a trifluoroethylidene moiety by employing the Corey-Winter's reductive elimination, and fluorination of an allyl alcohol with diethylaminosulfur trifluoride (DAST) as the key steps. Among **2**-**5**, **2** and **5** were found to exhibit a fairly potent inhibitory activity against acetylcholinesterase (AChE) which, taking into account of their racemic forms, corresponds to one-fortieth and one-twentieth of that of natural (–)-huperzine A (**1**), respectively. These results obviously disclosed that both the C_{13}-methyl group and the $\Delta^{7,8}$-double bond play important roles for **1** to effectively bind with AChE.*

Introduction

(–)-Huperzine A (**1**) isolated from *Huperzia serrata* (Thunb.) Trev.=*Lycopodium serratum* Thunb., a Chinese folk medicine, has been shown to be a powerful selective inhibitor of acetylcholinesterase (AChE).[4-7] Since the use of **1** can induce a long term inhibition of AChE in brain and increase the level of the neurotransmitter acetylcholine (ACh), it is anticipated to be one of the most promising agents for the treatment of Alzheimer's disease (AD),[8] and is presently under clinical trials.[8,9]

Although a number of analogues of **1** have been synthesized and their inhibitory activity against AChE has been examined,[8,10] there have been no reports on the synthesis of the fluorinated analogues of **1**. It is well recognized that introduction of fluorine atom(s) into pharmacologically active compounds frequently improves and/or changes therapeutic profiles due to electronic and steric characteristics of a fluorine atom.[11] Therefore, we became very much interested in the novel fluorinated analogues of **1**, (±)-12,12,12-trifluorohuperzine A (**2**), (±)-14,14,14-trifluorohuperzine A (**3**), (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**), and (±)-12-fluoro-

Figure 1. Structures of huperzine A (**1**) and its fluorinated analogues **2-5**



huperzine A (**1**)

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huperzine A (**5**) (**Figure 1**). The latter analogue **5** was designed based upon the finding that **2** exhibits the most potent inhibitory activity against AChE among the analogues **2-4** (*vide infra*).

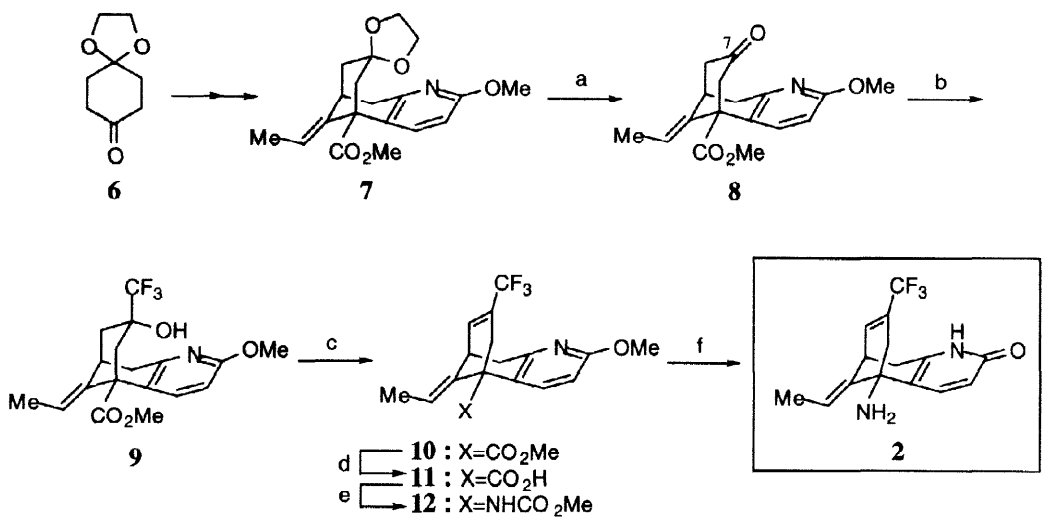
This report describes the synthesis of the novel fluorinated huperzine A analogues **2-5** as well as their AChE inhibitory activity.[1] The synthetic pathways to **2-5** were explored based on Kozikowski's methods employed for preparing **1** and its analogues.[5,10] The synthesis of **2-4** features the direct introduction of a trifluoromethyl group with the Ruppert's reagent [(trifluoromethyl)trimethylsilane ($TMSCF_3$)][12] as the key step (**8→9**, **Scheme 1** ; **18→19**, **Scheme 2**). The (*E*)-2,2,2-trifluoroethylidene moieties involved in **3** and **4** were also effectively constructed by employing the Corey-Winter's reductive elimination of 4-trifluoromethyl-1,3-dioxolane-2-thione system (**20→21**, **Scheme 2**).[13,14] In the synthesis of **5**, the C_{12}-fluorine atom was introduced by using diethylaminosulfur trifluoride (DAST)[15] at the last synthetic step (**48→5**, **Scheme 4**). Among the fluorinated analogues **2-5**, **2** and **5** carrying fluorine atom(s) only at their C_{12}-positions were found to show fairly potent inhibitory activity against AChE which, taking into account of their racemic forms, corresponds to one-fortieth and one-twentieth of that for **1**, respectively. These results obviously disclosed that both the C_{13}-methyl group and the $\Delta^{7,8}$-double bond play important roles for **1** to effectively bind with AChE.

Results and Discussion

1. Synthesis of (±)-12,12,12-Trifluorohuperzine A (2)

At first, we pursued the synthesis of (±)-12,12,12-trifluorohuperzine A (**2**) as shown in **Scheme 1**. This is because introduction of a trifluoromethyl group with $TMSCF_3$[12] can be examined at the early stage of the synthesis. Thus, the known ketal **7**, prepared from commercially available 1,4-cyclohexanedione monoethylene ketal (**6**) following the procedure reported by Kozikowski *et al.*,[5d] was hydrolyzed under acidic condition to afford the ketone **8** in 70% yield. The crucial introduction of a trifluoromethyl group to the C_7-position was effected by treating **8** with $TMSCF_3$ in the presence of tetra-*n*-butylammonium fluoride (TBAF),[12] giving rise to the trifluoromethyl carbinol **9** as the sole product in 50% yield after desilylation with TBAF. Since the addition reaction was found to accompany the formation of the trimethylsilyl enol ether of **8**, the desilylation was required to regenerate **8** prior to the work up. Highly stereoselective formation of **9** can be explained by the

Scheme 1. Synthesis of (±)-12,12,12-trifluorohuperzine A (**2**)



a) aq HCl, 2-propanol, 70% b) $TMSCF_3$, TBAF, THF ; TBAF, 50% c) $SOCl_2$, pyridine, 61% d) aq NaOH, THF-MeOH, 89% e) DPPA, Et_3N, toluene ; MeOH, 58% f) TMSI, $CHCl_3$; MeOH, 93%

addition of $TMSCF_3$ from the sterically less congested convex face. Dehydration of **9** with thionyl chloride in pyridine produced the olefin **10** as the single regioisomer in 61% yield. The reason why the highly regioselective dehydration took place is presently obscure. Hydrolysis of **10** gave an 89% yield of the corresponding carboxylic acid **11**, which was further transformed to the carbamate **12** in 58% yield by the modified Curtius rearrangement explored by Shioiri *et al.*[16] Finally, simultaneous cleavage of the methyl ether and the methyl carbamate functionalities present in **12** with iodotrimethylsilane (TMSI)[17] furnished the first target compound **2** in 93% yield.

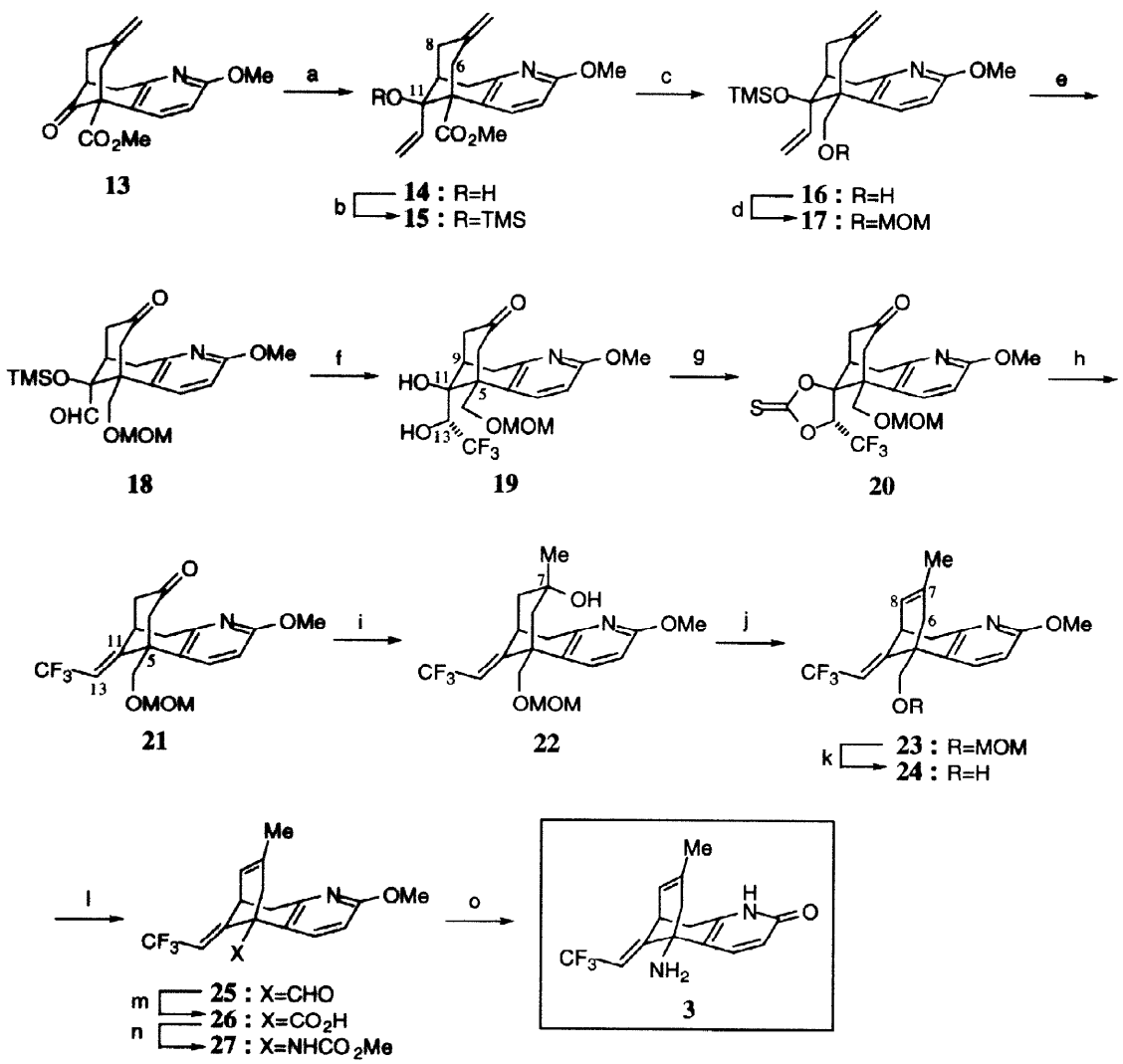
2. Synthesis of (±)-14,14,14-Trifluorohuperzine A (3)

With completion of the synthesis of (±)-12,12,12-trifluorohuperzine A (**2**), we selected (±)-14,14,14-trifluorohuperzine A (**3**) as the next synthetic target. Some preliminary attempts obviously disclosed that exploration of a general method for construction of a 2,2,2-trifluoroethylidene moiety from a ketonic function is necessary prior to commencing the synthesis of **3**.[18] After experimentation, we found that the requisite (*E*)-2,2,2-trifluoroethylidene group can be introduced to the C_{11}-position by employing the Corey-Winter's reductive elimination of 4-trifluoromethyl-1,3-dioxolane-2-thione system (**20**→**21**) (*vide infra*).[13] Generality and reliability of the developed synthetic method have already been presented in a separate paper.[14]

As shown in **Scheme 2**, treatment of the known β-keto ester **13**, prepared according to the reported procedure,[5d] with vinylmagnesium bromide gave the allyl alcohol **14**. This was immediately protected with a trimethylsilyl group, affording the trimethylsilyl ether **15** as the single stereoisomer in 51% overall yield. The stereochemistry at the C_{11}-position of **15** was assigned based on the NOESY experiments which show the interactions between the protons of the trimethylsilyl group and the C_6- and C_8-methylene protons. Accordingly, the relative configuration of **15** was determined as 5(*S**), 9(*S**), 11(*R**)-series (huperzine A numbering). Highly stereoselective formation of **14** may be explained by the addition of the Grignard reagent from the sterically less hindered direction which is opposite to the C_6-C_8 methylene bridge. Reduction of the methyl ester function in **15** with diisobutylaluminum hydride (DIBAL) provided a 68% yield of the alcohol **16**. Subsequent protection of the hydroxyl group in **16** with a methoxymethyl (MOM) group gave rise to the MOM ether **17** in 81% yield. Ozonolysis of the two terminal olefins present in **17** furnished the keto aldehyde **18** in 71% yield. Fortunately, the crucial trifluoromethylation of **18** took place in a highly chemo- and stereoselective manner, giving rise to the vicinal diol **19** as the single product in 81% yield after desilylation. Highly stereoselective addition of a trifluoromethyl group to the formyl group in **18** is remarkable and may be rationalized by the Felkin-Anh model shown in **Figure 2**,[19] wherein the C_9-position is assumed to be sterically less congested than the C_{11}-trimethylsilyloxy group.

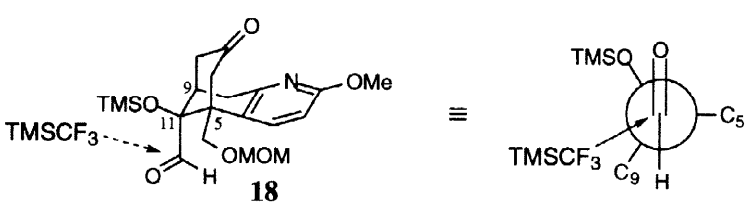
Formation of the desired thiocarbonate **20** (79%) was carried out by treating **19** with *N,N'*-thiocarbonyldiimidazole[13,14] in refluxing toluene. Treatment of **20** with trimethyl phosphite underwent the stereospecific olefin formation,[13,14] leading to the (*E*)-2,2,2-trifluoroethylidene derivatives **21** as the sole product in 92% yield. The (*E*)-configuration of **21** was rigorously assigned as depicted on the basis of the NOE experiments. Thus, when the C_{13}-vinyl proton in **21** was irradiated, an NOE of 16% was observed for the methylene protons adjacent to the MOM ether function, definitely establishing the srereochemistry of **21** as an (*E*)-form. Consequently, the relative configurations of **19** and **20** were definitely determined as a 5(*R**), 9(*R**), 11(*S**), 13(*R**)-series (huperzine A numbering) by considering the well-established *syn*-elimination mechanism for 1,3-dioxolane-2-thione systems.[13,14] Treatment of **21** with methyllithium provided the methyl carbinol **22** as the sole product in 51% yield. This result may be explained in a similar manner to that for the formation of **9** from **8**. Being different from the case for **9**, dehydration of **22** with thionyl chloride in pyridine gave a mixture of the desired $\Delta^{7,8}$-olefin **23** and its $\Delta^{6,7}$-isomer (*ca.* 1:1) in 96% yield. Without separation, direct treatment of this mixture with triflic acid simultaneously effected cleavage of the MOM ether and

Scheme 2. Synthesis of (±)-14,14,14-trifluorohuperzine A (**3**)



a) CH_2=CHMgBr, THF b) TMSOTf, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 51% (2 steps) c) DIBAL, CH_2Cl_2, 68% d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 81% e) O_3, MeOH-CH_2Cl_2 ; Me_2S, 71% f) $TMSCF_3$, TBAF, THF ; TBAF, 81% g) Im_2CS, toluene, 79% h) $P(OMe)_3$, 92% i) MeLi, Et_2O-THF, 51% j) $SOCl_2$, pyridine k) TfOH, 1,4-dioxane, 57% (2 steps) l) $(COCl)_2$, Me_2SO, CH_2Cl_2 ; Et_3N, 77% m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH-H_2O, 100% n) DPPA, Et_3N, toluene ; MeOH, 44% o) TMSI, $CHCl_3$; MeOH, 74%

Figure 2. The Felkin-Anh model for the reaction of the keto aldehyde **18** with $TMSCF_3$

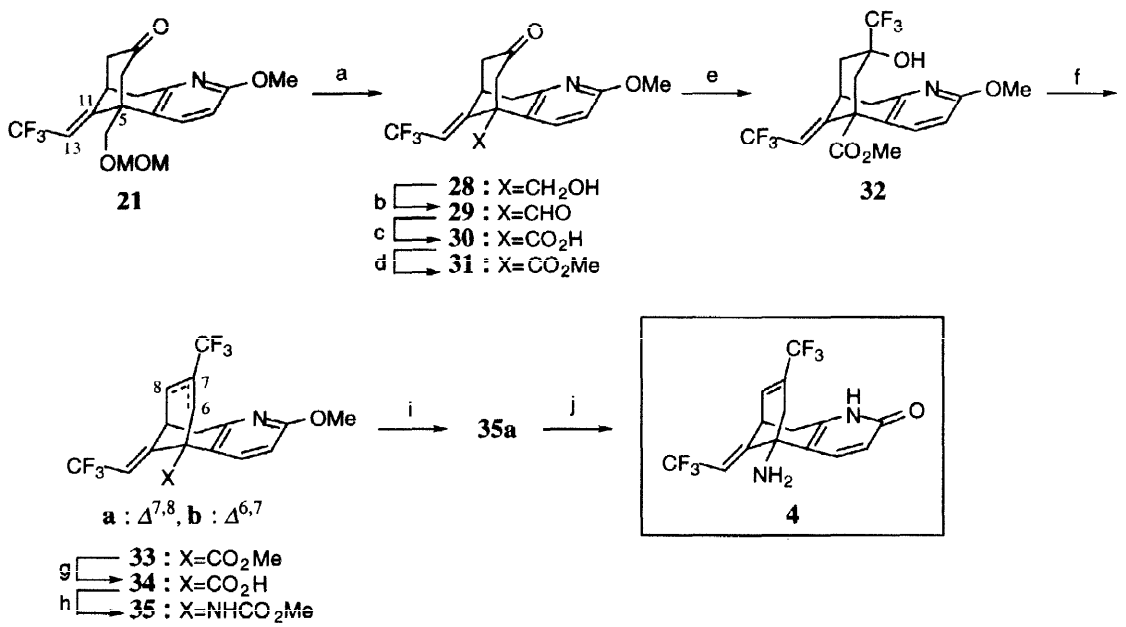


isomerization of the double bond, affording the alcohol **24** as the sole product in 57% yield. Swern oxidation[20] of **24** and subsequent sodium chlorite oxidation[21] of the resulting aldehyde **25** furnished the carboxylic acid **26** in 77% overall yield. Conversion of **26** to **3** was achieved in the same manner as described for the synthesis of **2**. Thus, the modified Curtius rearrangement[16] of **26** (44%) followed by deprotection of the resulting carbamate **27** with TMSI (74%)[17] gave rise to the second target compound **3**.

3. 12,12,12,14,14,14-Hexafluorohuperzine A (4)

Based upon the results accumulated by the two former syntheses, we next investigated the synthesis of (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**) starting with the (*E*)-2,2,2-trifluoroethylidene ketone **21** as shown in **Scheme 3**. Thus, cleavage of the MOM ether with bromotrimethylsilane (TMSBr) provided the alcohol **28** in 93% yield. This was sequentially treated under the conditions for Swern[20] and sodium chlorite[21] oxidation, affording the methyl ester **31** in 84% overall yield after esterification. Trifluoromethylation[12] of **31** gave the trifluoromethyl carbinol **32** as the sole product in 43% yield. This stereoselectivity may be explained by the same reason as proposed for the formation of **9** from **8**. Dehydration of **32** with thionyl chloride in pyridine gave an inseparable mixture of the desired $\Delta^{7,8}$-olefin **33a** and its $\Delta^{6,7}$-isomer **33b** (*ca.* 4:1) in 84% yield. Unfortunately, the undesired $\Delta^{6,7}$-isomer **33b** could not be transformed to the desired **33a** by acid-catalyzed isomerization. This phenomenon differs from that observed for the $\Delta^{6,7}$-isomer of **23** carrying a methyl group in place of a trifluoromethyl group. This result might be explained by prohibition of protonation of the $\Delta^{6,7}$-double bond due to strong electron-withdrawing effect of the C_7-trifluoromethyl group. Accordingly, the mixture of **33a** and **33b** was converted to a mixture of the carbamates **35a** and **35b** by way of the corresponding carboxylic acids **34a** and **34b** by sequential alkaline hydrolysis and the modified Curtius rearrangement.[16] At this stage, **35a** and **35b** were cleanly separated by column chromatography on silica gel,

Scheme 3. Synthesis of (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**)



a) TMSBr, MS 4Å, CH_2Cl_2, 93% b) $(COCl)_2$, Me_2SO, CH_2Cl_2 ; Et_3N c) $NaClO_2$,NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH-H_2O d) $TMSCHN_2$, MeOH, 84% (from **28**) e) $TMSCF_3$, TBAF, THF ; TBAF, 43% f) $SOCl_2$, pyridine, 84% g) aq NaOH, THF-MeOH, 100% h) DPPA, Et_3N, toluene ; MeOH, 70% i) separation by silica gel chromatography, 54% (from **32**) j) TMSI, $CHCl_3$; MeOH, 80%

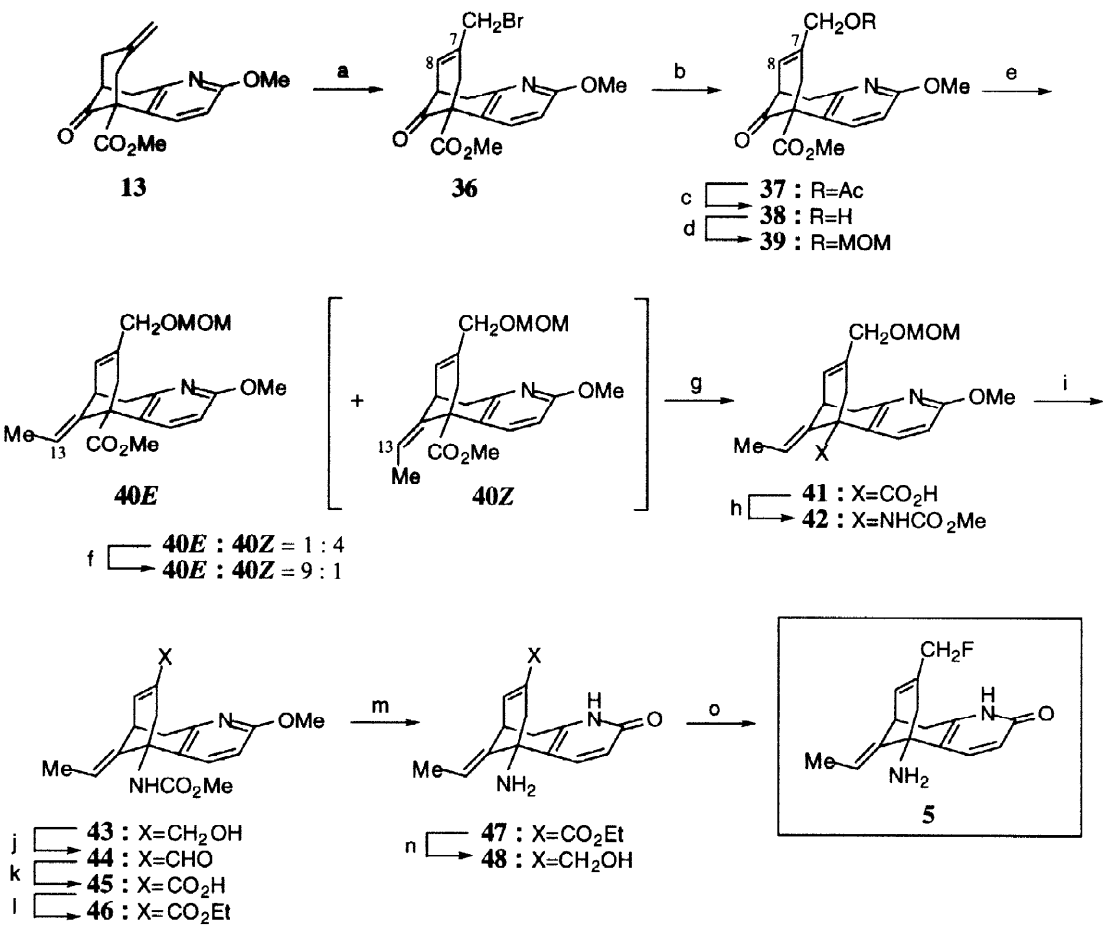
furnishing the desired $\Delta^{7,8}$-isomer **35a** in a pure form in 54% overall yield from **32**. Finally, the methyl carbamate **35a** was similarly deprotected with TMSI[17] to provide the third target compound **4** in 80% yield.

4. Synthesis of (±)-12-Fluorohuperzine A (5)

As detailed in the section for biological activity, (±)-12,12,12-trifluorohuperzine A (**2**) was found to exhibit the most potent inhibitory activity against AChE among the three types of trifluoromethylated analogues **2-4** so far prepared (*vide infra*). Taking into account of these results, we became interested in AChE inhibitory activity of the analogues modified solely at the C_7-position of **1**, and selected (±)-12-fluorohuperzine A (**5**) as the next synthetic target.

As shown in **Scheme 4**, the synthesis of **5** first commenced with the known β-keto ester **13** similarly to the preparation of (±)-14,14,14-trifluorohuperzine A (**3**). After several unsuccessful attempts to functionalize the *exo*-methylene moiety of **13**, treatment of **13** under the usual conditions for bromohydrin formation, for example, *N*-bromosuccinimide (NBS) in 1,4-dioxane-water, cleanly provided the allyl bromide **36** as the sole

Scheme 4. Synthesis of (±)-12-fluorohuperzine A (**5**)



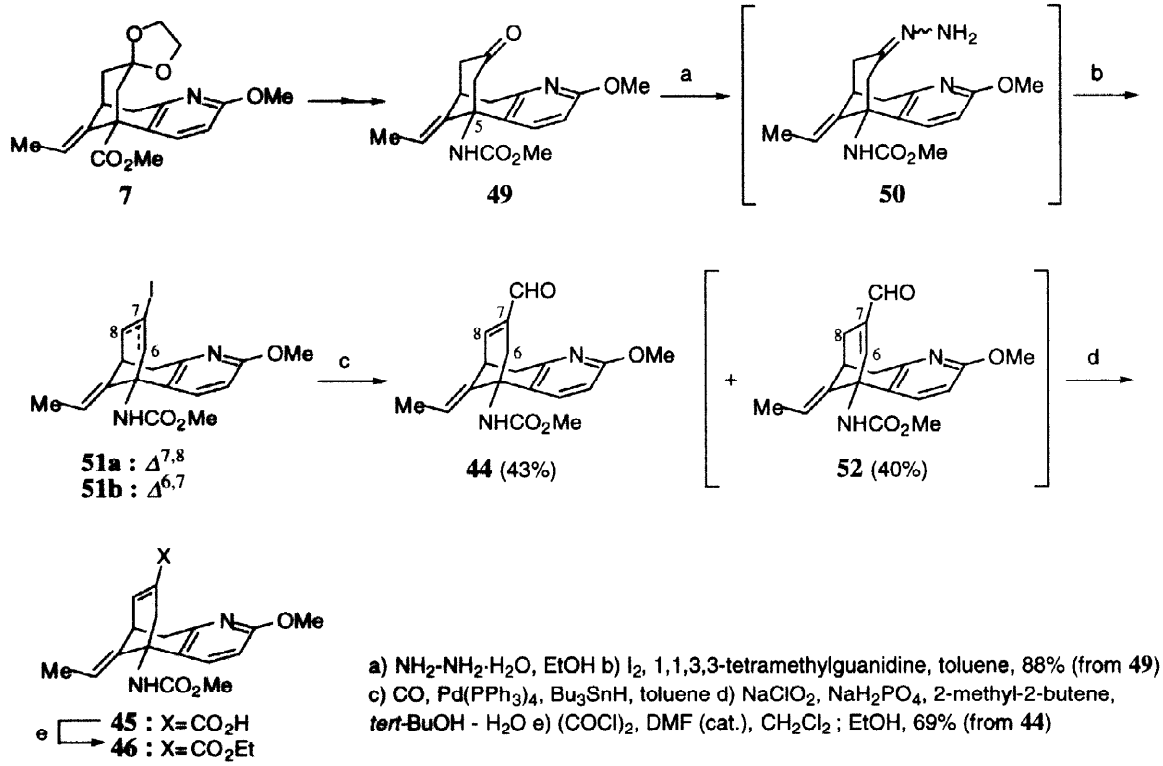
a) NBS, 1,4-dioxane-H_2O, 82% b) AgOAc, acetone, 81% c) K_2CO_3 (1 equiv), MeOH, 93% d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 93% e) $Ph_3P^+EtBr^-$, BuLi, THF, 75% f) PhSH, AIBN, toluene, 100% g) aq NaOH, THF - MeOH, 81% h) DPPA, Et_3N, toluene ; MeOH, 59% i) PPTS, *tert*-BuOH, 65% j) $(COCl)_2$, Me_2SO, CH_2Cl_2 ; Et_3N k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-butanol - H_2O l) $(COCl)_2$, DMF (cat.), CH_2Cl_2 ; EtOH, 78% (from **43**) m) TMSI, $CHCl_3$; MeOH, 78% n) DIBAL, CH_2Cl_2, 69% o) DAST, CH_2Cl_2, 17%

product in 82% yield. Highly regioselective introduction of the $\Delta^{7,8}$-double bond is remarkable, but has not been rationalized yet. Since the tricyclic β-keto ester system involved in **36** was susceptible to nucleophilic ring opening, attempted direct conversions of **36** to the allylic alcohol **38** under strongly basic conditions turned out to be fruitless. Consequently, **36** was first converted to the acetate **37** in 81% yield by treating with silver acetate in acetone. Deacetylation of **37** under the conditions for transesterification smoothly provided **38** in 93% yield. After protection of the hydroxyl group in **38** with a MOM group (93%), Wittig olefination of the resulting MOM ether **39** with ethylidenetriphenylphosphorane gave a mixture of (*E*)-olefin **40*E*** and (*Z*)-olefin **40*Z*** (1:4) in 75% yield. Treatment of the mixture with thiophenol and α,α'-azobis(isobutyronitrile) (AIBN) underwent isomerization of the ethylidene group,[5d] affording the sterically less hindered olefin **40*E*** as a major product (**40*E*:40*Z***=9:1). Without separation, the mixture was subjected to alkaline hydrolysis, giving rise to the carboxylic acid **41** in 81 % yield. The undesired (*Z*)-olefin **40*Z*** was not saponified and recovered unchanged probably due to the steric hindrance of the C_{13}-methyl group. The desired **41** was transformed to the carbamate **42** in 59% yield by the modified Curtius rearrangement[16] in the same manner as described for the synthesis of **2-4**. Removal of the MOM protecting group with pyridinium *p*-toluenesulfonate[22] gave a 65% yield of the allylic alcohol **43**. Although treatment of **43** with DAST[15] afforded the corresponding allyl fluoride, all the attempts to deprotect this allyl fluoride to obtain **5** met with failure. Deprotection of **43** to produce the deprotected allyl alcohol **48** was also unsuccessful. For example, the complete deprotections of these compounds with TMSI[17] provided complex mixtures of the reaction products which retain no allylic system by ^{1}H-NMR analysis. These unsuccessful results are probably due to increased chemical instability of the allyl fluoride and alcohol systems.

After consideration, we envisioned that the allyl alcohol system in **43** can be protected in the form of the more stable ethyl acrylate **46** during deprotection. Toward this end, **43** was sequentially treated under the conditions for Swern[20] and sodium chlorite[21] oxidation. Subsequent esterification of the formed carboxylic acid **45** by way of its acid chloride afforded **46** in 79% overall yield. As expected, simultaneous cleavage of the methyl ether and the methyl carbamate in **46** with TMSI[17] cleanly provided the pyridinone **47** in 79% yield. Regeneration of the allyl alcohol system was achieved by the reduction of **47** with DIBAL, affording a 69% yield of the corresponding alcohol **48**. Fluorination of **48** with DAST[15] gave rise to the final target compound **5** in 17% yield.

Although the synthesis of (±)-12-fluorohuperzine A (**5**) was achieved as described above, exploration of an alternative synthetic pathway to **46** was investigated because the former synthesis consists of a eleven-step sequence of reactions starting from **13** and the hydroxymethyl group at the C_7-position should be protected in the form of ethyl ester during deprotection. As shown in **Scheme 5**, the ketone **49** carrying a methyl carbamate group at the C_5-position was prepared from the ketal **7** in 3 steps according to the reported procedure.[5d] Treatment of **49** with hydrazine monohydrate followed by oxidative cleavage with iodine produced a mixture of the desired $\Delta^{7,8}$-iodide **51a** and its $\Delta^{6,7}$-isomer **51b** (*ca.* 1:1) in 88% combined yield by way of the hydrazone **50**.[23] Without separation, the mixture **51a** and **51b** was treated with tri-*n*-butyltin hydride in the presence of tetrakis(triphenylphosphine)palladium under carbon monoxide following the protocol reported by Stille *et al.*,[24] providing a mixture of the desired $\Delta^{7,8}$-aldehyde **44** and its $\Delta^{6,7}$-isomer **52** (*ca.* 1:1). This mixture was separated by column chromatography on silica gel to give **44** and **52** in 43% and 40% yields, respectively. Similarly to the case for the mixture of **33a** and **33b**, attempted isomerization of undesired **52** to desired **44** met with failure. Separated **44** was converted to **46** in 69% overall yield by the same two step sequence as described above. Taking into account of the number of steps, the latter method seems to be more efficient and practical than the former.

Scheme 5. Alternative synthesis of the ethyl acrylate **46** from **7**



5. Biological activity

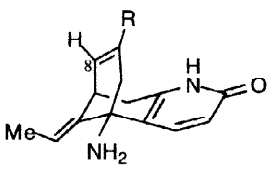
With completion of the synthesis of four types of the novel fluorinated huperzine A analogues, (±)-12,12,12-trifluorohuperzine A (**2**), (±)-14,14,14-trifluorohuperzine A (**3**), (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**), and (±)-12-fluorohuperzine A (**5**), their *in vitro* inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) was assessed by employing the modified protocol of Ellman *et al.*[25] The results are shown in **Table 1** along with those for natural huperzine A [(−)-**1**] and its unnatural enantiomer [(+)-**1**].[7] It appeared evident that all the fluorinated analogues **2**-**5** exhibit the AChE inhibitory activity inferior to that of **1**. Taking into account of their racemic forms, **2** was 40-fold less active than **1** while **3** and **4** were 200- and 300-fold less potent than **1**, respectively. While **5** possesses the stereostructure and electronic nature more closely related to those of **1**, it showed even 20-fold weaker activity than **1** when corrected for its racemic form. All the fluorinated analogues **2**-**5** exhibited no inhibitory activity against BuChE. Inhibition of BuChE has been thought to bring about the peripheral side effects in patients. From the results delineated above, it appeared that, among the C_7- and C_{13}-methyl groups, the C_{13}-methyl group plays a more important role for **1** to exhibit significant AChE inhibitory activity due to its steric, electronic, and/or hydrophobic effect(s). Comparing the results for **2** and **5** with that for **1**, it is also apparent that the electron density of $\Delta^{7,8}$-double bond strongly affects the AChE inhibitory activity. Thus, the chemical shifts of C_8-proton shown in **Table 2**, definitely shows that the electron density of $\Delta^{7,8}$-double bond decreases in the order of **2**, **5**, and **1**. This order agrees well with that of the AChE inhibitory activity summarized in **Table 1**.

Table 1. Inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)

Compound	IC_{50} value (μM)	
	AChE	BuChE
natural huperzine A [(–)-1]	0.005	> 50
unnatural huperzine A [(+)-1]	10	
(±)-12-fluorohuperzine A (**5**)	0.2	> 50
(±)-12,12,12,-trifluorohuperzine A (**2**)	0.4	> 50
(±)-14,14,14,-trifluorohuperzine A (**3**)	2	> 50
(±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**)	3	> 50

Table 2. Comparison of the ^{1}H-NMR chemical shifts of C_8-H

Compound	R	Chemical shift of C_8-H (ppm)
huperzine A (**1**)	Me	δ 5.41
(±)-12-fluorohuperzine A (**5**)	CH_2F	δ 5.80
(±)-12,12,12,-trifluorohuperzine A (**2**)	CF_3	δ 6.33



Conclusion

We have succeeded in developing the synthetic pathways to four types of the novel fluorinated huperzine A analogues, (±)-12,12,12-trifluorohuperzine A (**2**), (±)-14,14,14-trifluorohuperzine A (**3**), (±)-12,12,12,14,14,14-hexafluorohuperzine A (**4**), and (±)-12-fluorohuperzine A (**5**). The key feature of the syntheses consists of introduction of a trifluoromethyl group with the Ruppert's reagent ($TMSCF_3$), construction of a trifluoroethylidene moiety by employing the Corey-Winter's reductive elimination, and fluorination of an allyl alcohol with diethylaminosulfur trifluoride (DAST). From the results of *in vitro* acetylcholinesterase (AChE) inhibitory activity assay for **2-5**, it appears evident that **2** and **5** exhibit a fairly potent AChE inhibitory activity. Taking into account of their racemic forms, **2** and **5** were 40- and 20-fold less active than natural (–)-huperzine A (**1**), respectively. These results obviously disclosed that both the C_{13}-methyl group and the $\Delta^{7,8}$-double bond play important roles for **1** to effectively bind with AChE. It is expected that our findings hold promise for designing novel huperzine A analogues which may show characteristics being more prominent than those of **1**.

Experimental

General : All melting points were determined with a Yanaco MP-3 micro melting point apparatus and are uncorrected. Measurements of ^{1}H-NMR spectra were performed using a Brucker AM-400 (400 MHz) and a Brucker AM-200 (200 MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br). ^{19}F-NMR spectra were recorded with a Brucker AM-200 (188 MHz) spectrometer. The chemical shifts were expressed in ppm using trichlorofluoromethane (δ=0) as a internal standard. Measurements of infrared (IR) spectra were carried out using a JASCO FT/IR-5300 Fourier transform spectrometer. Low resolution mass (EIMS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high

resolution mass (HREIMS) spectra were obtained using a Hitachi M-80A spectrometer. Routine monitorings of reactions were carried out using glass-supported Merck Silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Merck Silica gel 60 F_{254} (230-400 mesh) with indicated solvents. Solvents and commercial reagents were dried and purified before use. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon. All the combined organic extracts were dried over anhyd. Na_2SO_4 and filtered before concentration *in vacuo* with a rotary evaporator. Following abbreviations are used for reagents and solvents: Me_2CO (acetone), AIBN [α,α-azobis(isobutyronitrile)], NBS (*N*-bromosuccinimide), C_6H_6 (benzene), *tert*-BuOH (*tert*-butyl alcohol), $CHCl_3$ (chloroform), CH_2Cl_2 (dichloromethane), Et_2O (diethyl ether), DAST (diethylaminosulfur trifluoride), DMF (*N,N*-dimethylformamide), DMSO (dimethyl sulfoxide), EtOH (ethanol), EtOAc (ethyl acetate), C_6H_{14} (hexane), MeOH (methanol), Me_2CHOH (2-propanol), C_5H_5N (pyridine), TBAF (tetra-*n*-butylammonium fluoride), THF (tetrahydrofuran), C_6H_5Me (toluene), Et_3N (triethylamine), CF_3TMS [(trifluoromethyl)trimethylsilane].

(5*R,9*R**,11*E*)-Methyl 11-ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-oxo-5,9-methanocycloocta[*b*]-pyridine-5(6*H*)-carboxylate (8)**

A solution of **7**[5d] (72.0 mg, 0.21 mmol) in Me_2CHOH (2.0 mL) and 5% HCl (0.5 mL) was heated at 70 °C for 2 h. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc. The combined organic extracts were washed with brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 5:1) to give **8** as a colorless oil (56.0 mg, 90%). IR (neat): 2965 (m), 1740 (s), 1720 (s), 1610 (m), 1585 (m), 1485 (s), 1435 (m), 1330 (m), 1260 (s), 1120 (m), 1070 (m), 1040 (m), 1015 (m), 805 (m), 740 (m), 650 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.01 (1H, d, J=8.6 Hz, C4-H), 6.55 (1H, d, J=8.6 Hz, C3-H), 5.37 (1H, q, J=6.8 Hz, C12-H), 3.86 (3H, s, OCH3), 3.80 (3H, s, CO2CH3), 3.73 (1H, m, C9-H), 3.21 (1H, dd, J=17.7, 6.0 Hz, C10-H), 3.13 (1H, d, J=14.5 Hz, C6-H), 2.88 (1H, dd, J=17.7, 0.9 Hz, C10-H), 2.69 (1H, dd, J=14.5, 2.2 Hz, C6-H), 2.65 (1H, dd, J=16.0, 7.1 Hz, C8-H), 2.47 (1H, dt, J=16.0, 2.2 Hz, C8-H), 1.82 (3H, d, J=6.7 Hz, CH3). EIMS (m/z): 302 ($M+1^+$, 19), 301 (M^+, 100), 286 (12), 269 (7), 258 (7), 244 (38), 242 (23), 231 (65), 212 (28), 200 (27), 184 (22), 172 (38), 154 (9), 141 (5), 128 (8), 115 (8). HREIMS (m/z): Calcd. for $C_{17}H_{19}NO_4$ (M^+): 301.1312. Found: 301.1293.

(5*R, 7*S**, 9*R**, 11*E*)-Methyl 11-ethylidene-7-trifluoromethyl-7,8,9,10-tetrahydro-7-hydroxy-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (9)**

A solution of TBAF in THF (1.0M solution, 64 μL, 64 μmol) was added to a solution of **8** (193 mg, 0.64 mmol) and CF_3TMS (0.20 mL, 1.3 mmol) in THF (0.5 mL) under argon.[12] The reaction mixture was stirred at room temperature for 30 min. After **8** was consumed, another solution of TBAF in THF (1.0M solution, 1.3 mL, 1.3 mmol) was added to the reaction mixture. After 15 min, the mixture was poured into H_2O and extracted with Et_2O. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* followed by purification by flash column chromatography (C_6H_{14}/EtOAc, 3:1) gave **9** as a colorless oil (120 mg, 50%). IR (neat): 3480 (m), 2960 (m), 1740 (s), 1605 (m), 1585 (m), 1480 (s), 1435 (m), 1380 (w), 1320 (m), 1250 (s), 1160 (s), 1125 (m), 1035 (m), 955 (w), 920 (w), 825 (w), 740 (w), 660 (w) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.02 (1H, d, J=8.5 Hz, C4-H), 6.53 (1H, d, J=8.5, C3-H), 5.20 (1H, q, J=6.7 Hz, C13-H), 3.87 (3H, s, OCH3), 3.80 (3H, s, CO2CH3), 3.60-3.50 (1H, m, C9-H), 3.26 (1H, dd, J=18.1, 7.4 Hz, C10-H), 3.02 (1H, d, J=18.1 Hz, C10-H), 2.63 (1H, d, J=14.3 Hz, C6-H), 2.15-2.06 (3H, m, C6-H, C8-H x 2), 1.73 (3H, d, J=6.7 Hz, CH3), 1.13 (1H, s, OH). ^{19}F-NMR (188 MHz, CDCl3) δ: -85.6 (s). EIMS (m/z): 372 ($M+1^+$, 21), 371 (M^+, 100), 370 (15), 356 (11), 339 (79), 312 (25), 294 (31), 258 (31), 258 (12), 244 (46), 230 (36), 212 (27), 200 (24), 184 (25), 172 (22), 154 (12), 141 (7), 128 (12), 115 (14), 84 (17).

(5*R,9*R**,11*E*)-Methyl 11-ethylidene-7-trifluoromethyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (10)**

Thionyl chloride (47 μL, 0.65 mmol) was added to a solution of **9** (120 mg, 0.32 mmol) in C_5H_5N (0.5 mL) at room temperature under argon. After stirring for 2 h, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with Et_2O. The combined organic extracts were washed with brine. Concentration *in vacuo* followed by purification by flash column chromatography (C_6H_{14}/EtOAc, 5:1) gave **10** as a colorless oil (65.0 mg, 61%). IR (neat): 2950 (m), 2860 (m), 1735 (s), 1680 (m), 1600 (s), 1580 (m), 1470 (s), 1425 (s), 1380 (m), 1325 (s), 1250 (s), 1160 (s), 1115 (s), 1080 (m), 1030 (s), 890 (m), 830 (m), 740 (m), 645 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.11 (1H, d, J=8.6 Hz, C4-H), 6.57 (1H, d, J=8.6 Hz, C3-H), 6.37-6.32 (1H, m, C8-H), 5.17 (1H, q, J=6.7 Hz, C13-H), 3.99 (3H, s, OCH3), 3.82-3.76 (1H, m, C9-H), 3.77 (3H, s, CO2CH3), 3.17 (1H, d, J=17.2 Hz, C6-H), 3.16 (1H, dd, J=17.0, 7.3 Hz, C10-H), 2.92 (1H, dd, J=17.0, 1.7 Hz, C10-H), 2.46 (1H, dd, J=17.2, 2.5 Hz, C6-H), 1.73 (3H, d, J=6.7 Hz, CH3). ^{19}F-NMR (188 MHz, CDCl3) δ: -69.6 (s). EIMS (m/z): 354 ($M+1^+$, 8), 353 (M^+, 49), 338 (9), 294 (100), 278 (11), 264 (7), 244 (9), 224 (5), 210 (8), 196 (4), 184 (5), 167 (4), 59 (10). HREIMS (m/z): Calcd. for $C_{18}H_{18}F_3NO_3$ (M^+): 353.1237. Found: 353.1214.

(5*R,9*R**,11*E*)-11-Ethylidene-7-trifluoromethyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]-pyridine-5(6*H*)-carboxylic acid (11)**

A solution of 20% aqueous NaOH (0.2 mL) was added to a solution of **10** (65.0 mg, 0.18 mmol) in MeOH-THF (2:1) (0.6 mL). The reaction mixture was heated at reflux for 20.5 h under argon. After cooling, the mixture was adjusted to pH 5-6 with 1N-HCl, and MeOH and THF were removed *in vacuo*. The residual aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine. Concentration *in vacuo* followed by purification by flash column chromatography (EtOAc) gave **11** as a colorless oil (55.4 mg, 89%). IR (neat): 3450 (w), 2940 (m), 1730 (s), 1605 (s), 1580 (m), 1480 (s), 1430 (m), 1380 (m),

1330 (s), 1285 (s), 1255 (s), 1170 (s), 1115 (s), 1030 (m), 900 (m), 830 (m), 650 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (1H, d, J = 8.6 Hz, C4-H), 6.60 (1H, d, J=8.6 Hz, C3-H), 6.36-6.31 (1H, m, C8-H), 5.42 (1H, q, J=6.8 Hz, C13-H), 3.89 (3H, s, OCH_3), 3.84-3.79 (1H, m, C9-H), 3.18 (1H, dd, J=17.1, 5.6 Hz, C10-H), 3.14 (1H, dd, J=17.1, 1.0 Hz, C6-H), 2.95 (1H, dd, J=17.1, 1.4 Hz, C10-H), 2.49 (1H, d, J=17.1 Hz, C6-H), 1.76 (3H, d, J=6.8 Hz, CH_3). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: -69.6 (s). EIMS (m/z): 340 ($M+1^+$, 14), 339 (M^+, 70), 338 (15), 324 (8), 310 (6), 294 (100), 278 (9), 266 (11), 250 (4), 230 (9), 216 (4), 202 (11), 186 (10), 167 (5), 154 (6), 140 (4), 128 (5), 115 (8), 86 (6), 69 (6), 57 (31). HREIMS (m/z): Calcd. for $C_{17}H_{16}F_3NO_3$ (M^+): 339.1080. Found: 339.1074.

(5*R,9*R**,11*E*)-Methyl [11-ethylidene-7-trifluoromethyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (12)**

A solution of **11** (55.0 mg, 0.16 mmol), Et_3N (21 μL, 0.15 mmol), and diphenylphosphoryl azide (33 μL, 0.15 mmol) in C_6H_5Me (0.7 mL) was heated at 85 °C for 3 h.[16] After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH (0.7 mL). The methanolic solution was heated at 75 °C for 17 h. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (C_6H_{14}/EtOAc, 3:1) to give **12** as colorless prisms (32.0 mg, 58%), mp 197.5-198 °C (from C_6H_{14}-EtOAc). IR (KBr): 3300 (m), 2950 (m), 1710 (s), 1600 (m), 1550 (s), 1480 (s), 1425 (m), 1330 (s), 1285 (m), 1260 (s), 1175 (s), 1120 (s), 1020 (m), 900 (m), 835 (m), 650 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.58 (1H, d, J=8.6 Hz, C4-H), 6.58 (1H, d, J=8.6 Hz, C3-H), 6.39-6.34 (1H, m, C8-H), 5.47 (1H, q, J=6.8 Hz, C13-H), 5.07 (1H, br s, NH), 3.88 (3H, s, OCH_3), 3.90-3.83 (1H, m, C9-H), 3.63 (3H, br s, $NHCO_2CH_3$), 3.17 (1H, dd, J=17.1, 4.9 Hz, C10-H), 2.92 (1H, dd, J=17.1, 1.8 Hz, C10-H), 2.80 (1H, d, J=15.8 Hz, C6-H), 2.51 (1H, d, J=15.8 Hz, C6-H), 1.74 (3H, d, J=6.8 Hz, CH_3). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: -69.5 (s). EIMS (m/z): 369 ($M+1^+$, 18), 368 (M^+, 84), 367 (7), 353 (29), 336 (15), 321 (21), 309 (25), 293 (89), 278 (100), 259 (14), 246 (19), 224 (44), 199 (12), 184 (11), 167 (7), 123 (9), 109 (6), 91 (12), 76 (20), 59 (70). HREIMS (m/z): Calcd. for $C_{18}H_{19}F_3N_2O_3$ (M^+): 368.1346. Found: 368.1337. Anal. Calcd. for $C_{18}H_{19}F_3N_2O_3$: C, 58.69; H, 5.20; N, 7.60. Found: C, 58.44; H, 5.13; N, 7.50.

(5*R,9*R**,11*E*)-5-Amino-11-ethylidene-7-trifluoromethyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]-pyridin-2(1*H*)-one [(±)-12,12,12-trifluorohuperzine A] (2)**

Iodotrimethylsilane (136 μL, 0.95 mmol) was added dropwise to a solution of **12** (25.0 mg, 68 μmol) in $CHCl_3$ (2.5 mL) at room temperature under argon, and the reaction mixture was heated at reflux for 5.5 h.[17] After concentration *in vacuo*, the residue was dissolved in MeOH (2.5 mL). The methanolic solution was heated at reflux for 4.5 h, stirred at room temperature for 12 h, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2. The dichloromethane solution was washed successively with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, H_2O, and brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (EtOAc/MeOH, 10:1) to give **2** as colorless prisms (18.6 mg, 93%), mp 264.5-266 °C (from C_6H_{14}-EtOAc). IR (KBr): 3450 (m), 2930 (w), 1665 (s), 1620 (m), 1550 (w), 1470 (w), 1380 (w), 1325 (m), 1280 (m), 1155 (m), 1115 (s), 1080 (w), 975 (w), 930 (w), 835 (w), 660 (w), 650 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.01(1H, br s, NH), 7.92 (1H, d, J=9.5 Hz, C4-H), 6.45 (1H, d, J=9.5 Hz, C3-H), 6.36-6.30 (1H, m, C8-H), 5.61 (1H, q, J=6.7 Hz, C13-H), 3.84-3.78 (1H, m, C9-H), 3.01 (1H, dd, J=17.2, 5.4 Hz, C10-H), 2.81 (1H, dd, J=17.1, 1.0 Hz, C10-H), 2.44 (1H, d, J=16.9 Hz, C6-H), 2.24 (1H, d, J=16.9 Hz, C6-H), 1.71 (3H, d, J=6.7 Hz, CH_3). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: -69.5 (s). EIMS (m/z): 297 ($M+1^+$, 17), 296 (M^+, 100), 295 (11), 281 (82), 267 (12), 241 (5), 227 (24), 211 (10), 199 (9), 187 (62), 174 (18), 160 (12), 147 (15), 130 (6), 106 (9), 91 (9). HREIMS (m/z): Calcd. for $C_{15}H_{15}F_3N_2O$ (M^+): 296.1133. Found: 296.1124. Anal. Calcd. for $C_{15}H_{15}F_3N_2O \cdot 1/3H_2O$: C, 59.60; H, 5.23; N, 9.27. Found: C, 59.45; H, 5.08; N, 9.14.

(5*S,9*S**,11*S**)-Methyl 11-ethenyl-7,8,9,10-tetrahydro-2-methoxy-7-methylene-11-trimethylsilyloxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (15)**

A solution of vinylmagnesium bromide in THF (1.06M solution, 25 mL, 27 mmol) was added to a solution of **13**[5d] (6.45 g, 23 mmol) in THF (150 mL) over 10 min at -78 °C under argon. After stirring for 1 h, the reaction mixture was poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue and 2,6-di-*tert*-butylpyridine (11.6 mL, 52 mmol) were dissolved in CH_2Cl_2 (150 mL). Trimethylsilyl triflate (9.4 mL, 52 mmol) was added to the dichloromethane solution at 0 °C under argon. After stirring overnight at room temperature, the reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 20:1) to give **15** as colorless prisms (4.47 g, 51%), mp 88-89 °C (from C_6H_{14}). IR (KBr): 3080 (w), 2970 (m), 2900 (w), 1740 (s), 1610 (s), 1585 (m), 1485 (s), 1435 (m), 1320 (s), 1280 (s), 1255 (s), 1110 (s), 1050 (m), 1015 (m), 910 (m), 850 (s), 760 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.00 (1H, d, J=8.6 Hz, C4-H), 6.48 (1H, d, J=8.6 Hz, C3-H), 6.38 (1H, dd, J=17.6, 11.2 Hz, C13-H), 5.43 (1H, dd, J=17.6, 1.0 Hz, C14-H), 5.20 (1H, dd, J=11.2, 1.0 Hz, C14-H), 4.59 (1H, q, J=1.9 Hz, C12-H), 4.24 (1H, q, J=1.9 Hz, C12-H), 3.85 (3H, s, OCH_3), 3.76 (3H, s, CO_2CH_3), 3.39 (1H, dd, J=13.6, 2.0 Hz, C6-H), 3.18 (1H, dd, J=18.5, 7.1 Hz, C10-H), 2.88 (1H, br d, J=13.3 Hz, C8-H), 2.69 (1H, d, J=18.5 Hz, C10-H), 2.50 (1H, br s, C9-H), 2.05 (1H, dt, J=13.3, 2.0 Hz, C8-H), 2.03 (1H, dd, J=13.6, 2.0 Hz, C6-H), 0.15 (9H, s, $(CH_3)_3Si$). EIMS (m/z): 388 ($M+1^+$, 7), 387 (M^+, 23), 372 (17), 328 (19), 312 (2), 297 (7), 286 (4), 272 (3), 258 (2), 238 (3), 212 (5), 200 (8), 184 (5), 167 (4), 155 (5), 129 (6), 115 (5), 89 (16), 73 (100), 59 (15). HREIMS (m/z): Calcd. for $C_{21}H_{29}NO_4Si$ (M^+): 387.1867. Found: 387.1874. Anal. Calcd. for $C_{21}H_{29}NO_4Si$: C, 65.08; H, 7.54; N, 3.61. Found: C, 65.05; H, 7.56; N, 3.50.

(5*R, 9*S**, 11*S**)-11-Ethenyl-5,6,7,8,9,10-hexahydro-5-hydroxymethyl-2-methoxy-7-methylene-11-trimethylsilyloxy-5,9-methanocycloocta[*b*]pyridine (16)**

A solution of diisobutylaluminum hydride in C_6H_{14} (0.93M solution, 26.1 mL, 24 mmol) was added to a solution of **15** (4.47 g, 12 mmol) in CH_2Cl_2 (70 mL) at -78 °C under argon. After stirring for 30 min, the reaction mixture was diluted successively with EtOAc and H_2O, filtered, then concentrated *in vacuo*. The residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 10:1) to give **16** as a colorless oil (2.80 g, 68%). IR (neat): 3450 (w), 3080 (w), 2950 (m), 1650 (w), 1600 (m), 1585 (w), 1480 (s), 1430 (m), 1320 (m), 1260 (s), 1175 (w), 1080 (m), 1050 (m), 910 (m), 895 (m), 850 (s), 760 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.37 (1H, d, J=8.7 Hz, C4-H), 6.53 (1H, d, J=8.7 Hz, C3-H), 6.13 (1H, dd, J=17.4, 10.1 Hz, C13-H), 5.50 (1H, dd, J=17.4, 1.2 Hz, C14-H), 5.21 (1H, dd, J=10.1, 1.2 Hz, C14-H), 4.62 (1H, q, J=2.0 Hz, C12-H), 4.32 (1H, q, J=2.0 Hz, C12-H), 4.11 (1H, dd, J=11.5, 6.8 Hz, C*H*2OH), 3.97 (1H, dd, J=11.5, 3.9 Hz, C*H*2OH), 3.86 (3H, s, OCH3), 3.18 (1H, dd, J=18.8, 7.3 Hz, C10-H), 3.00 (1H, br t, J=5.9 Hz, OH), 2.95 (1H, dd, J=13.0, 1.4 Hz, C6-H), 2.83 (1H, br d, J=13.5 Hz, C8-H), 2.79 (1H, d, J=11.2 Hz, C10-H), 2.40 (1H, br s, C9-H), 2.10 (1H, dt, J=13.5, 1.9 Hz, C8-H), 1.74 (1H, dd, J=13.0, 1.5 Hz, C6-H), 0.27 (9H, s, (CH3)3Si). EIMS (m/z): 359 (M^+, 68), 344 (49), 328 (100), 314 (3), 300 (7), 286 (6), 269 (30), 251 (9), 224 (9), 210 (9), 198 (8), 186 (13), 174 (12), 160 (3), 148 (5), 129 (10), 115 (7), 103 (4), 91 (5), 75 (40), 73 (73), 59 (9). HREIMS (m/z): Calcd. for C20H29NO3Si (M^+): 359.1914. Found: 359.1901.

(5*R, 9*S**, 11*S**)-11-Ethenyl-5,6,7,8,9,10-hexahydro-2-methoxy-5-(methoxymethoxy)methyl-7-methylene-11-trimethylsilyloxy-5,9-methanocycloocta[*b*]pyridine (17)**

Ethyldiisopropylamine (75 μL, 0.43 mmol) and chloromethyl methyl ether (32 μL, 0.43 mmol) were added to a solution of **16** (30.3 mg, 84 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C under argon. The reaction mixture was stirred overnight at room temperature, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 15:1) to give **17** as a colorless oil (27.6 mg, 81%). IR (neat): 2950 (m), 1605 (m), 1580 (w), 1480 (s), 1430 (m), 1320 (m), 1260 (s), 1135 (m), 1115 (s), 1050 (s), 1030 (s), 910 (m), 845 (s), 760 (w) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.62 (1H, d, J=8.6 Hz, C4-H), 6.49 (1H, d, J=8.6 Hz, C3-H), 6.12 (1H, dd, J=17.6, 11.2 Hz, C13-H), 5.37 (1H, dd, J=17.6, 1.1 Hz, C14-H), 5.10 (1H, dd, J=11.2, 1.0 Hz, C14-H), 4.71 (1H, d, J=6.5 Hz, OC*H*2OCH3), 4.66 (1H, d, J=6.5 Hz, OC*H*2OCH3), 4.60 (1H, q, J=2.0 Hz, C12-H), 4.27 (1H, q, J=2.0 Hz, C12-H), 4.01 (1H, d, J=10.1 Hz, C*H*2OMOM), 3.85 (3H, s, OCH3), 3.84 (1H, d, J=10.1 Hz, C*H*2OMOM), 3.42 (3H, s, OCH2OC*H*3), 3.18 (1H, dd, J=18.6, 7.4 Hz, C10-H), 2.84 (1H, br d, J=13.3 Hz, C8-H), 2.73 (1H, d, J=18.6 Hz, C10-H), 2.61 (1H, dd, J=12.9, 1.3 Hz, C6-H), 2.49 (1H, br s, C9-H), 2.07 (1H, d, J=13.3 Hz, C8-H), 1.91 (1H, dd, J=12.9, 1.4 Hz, C6-H), 0.21 (9H, s, (CH3)3Si). EIMS (m/z): 403 (M^+, 67), 388 (34), 372 (8), 358 (54), 342 (100), 328 (62), 313 (21), 300 (8), 286 (9), 268 (13), 251 (18), 238 (61), 226 (5), 214 (8), 198 (7), 186 (13), 172 (9), 160 (5), 148 (3), 129 (7), 103 (4), 89 (6), 73 (86), 59 (4), 45 (89). HREIMS (m/z): Calcd. for C22H33NO4Si (M^+): 403.2177. Found: 403.2165.

(5*R, 9*R**, 11*S**)-11-Formyl-5,6,7,8,9,10-hexahydro-2-methoxy-5-(methoxymethoxy)methyl-11-trimethylsilyloxy-7-oxo-5,9-methanocycloocta[*b*]pyridine (18)**

Ozone gas was bubbled through a solution of **17** (23.3 mg, 58 mmol) in CH_2Cl_2-MeOH (9:1) (2.0 mL) for 20 min at -78 °C. After stirring for 10 min, dimethyl sulfide (15 drops) was added at -78 °C, and the reaction mixture was warmed to room temperature overnight. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 5:1) to give **18** as a colorless oil (16.7 mg, 71%). IR (neat): 2960 (m), 2900 (m), 1725 (s), 1580 (m), 1485 (s), 1430 (m), 1330 (m), 1260 (m), 1215 (m), 1160 (m), 1120 (m), 1040 (s), 940 (m), 920 (m), 850 (s), 765 (m), 740 (m), 700 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 9.72 (1H, s, CHO), 7.45 (1H, d, J=8.8 Hz, C4-H), 6.64 (1H, d, J=8.8 Hz, C3-H), 4.47 (1H, d, J=6.6 Hz, OC*H*2OCH3), 4.44 (1H, d, J=6.6 Hz, OC*H*2OCH3), 3.88 (3H, s, OCH3), 3.87 (1H, d, J=10.1 Hz, C*H*2OMOM), 3.78 (1H, d, J=10.1 Hz, C*H*2OMOM), 3.27 (3H, s, OCH2OC*H*3), 3.27 (1H, dd, J=19.0, 6.8 Hz, C10-H), 2.98 (1H, d, J=19.0 Hz, C10-H), 2.95 (1H, ddd, J=15.3, 6.5, 1.1 Hz, C8-H), 2.76 (1H, d, J=14.1 Hz, C6-H), 2.72 (1H, br t, J=6.6 Hz, C9-H), 2.28 (1H, dt, J=15.3, 1.8 Hz, C8-H), 1.96 (1H, dd, J=14.1, 1.9 Hz, C6-H), 0.28 (9H, s, (CH3)3Si). EIMS (m/z): 407 (M^+, 8), 392 (9), 378 (42), 362 (3), 350 (8), 334 (23), 318 (21), 302 (3), 288 (3), 274 (6), 260 (8), 244 (17), 228 (8), 214 (8), 200 (7), 186 (11), 172 (6), 160 (9), 143 (3), 123 (14), 103 (7), 89 (6), 73 (46), 59 (4), 45 (100). HREIMS (m/z): Calcd. for C20H29NO6Si (M^+): 407.1763. Found: 407.1779.

(5*R, 9*R**, 11*S**, 1'*R**)-11-(2',2',2'-Trifluoro-1'-hydroxyethyl)-5,6,7,8,9,10-hexahydro-11-hydroxy-2-methoxy-5-(methoxymethoxy)methyl-11-trimethylsilyloxy-7-oxo-5,9-methanocycloocta[*b*]pyridine (19)**

A solution of TBAF in THF (1.0M solution, 40 μL, 40 μmol) was added to a solution of **18** (1.63 g, 4.0 mmol) and CF_3TMS (1.3 mL, 8.0 mmol) in THF (10 mL) under argon.[12] The reaction mixture was stirred at room temperature for 50 min. After **18** was consumed, a solution of TBAF in THF (1.0M solution, 8.0 mL, 8.0 mmol) was further added to the reaction mixture. After stirring for 15 min, the mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 1:1) to give **19** as colorless prisms (1.31 g, 81%), mp 153.5-154 °C (from C_6H_{14}-EtOAc). IR (KBr): 3470 (m), 2960 (m), 1720 (s), 1605 (s), 1580 (m), 1485 (s), 1435 (m), 1325 (m), 1310 (m), 1265 (s), 1160 (s), 1130 (s), 1110 (s), 1040 (s), 1020 (s), 920 (m), 835 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.38 (1H, d, J=8.7 Hz, C4-H), 6.57 (1H, d, J=8.7 Hz, C3-H), 5.20 (1H, br s, CF3CHO*H*), 4.75 (1H, d, J=6.5 Hz, OC*H*2OCH3), 4.71 (1H, d, J=6.5 Hz, OC*H*2OCH3), 4.40 (1H, s, OH), 4.19 (1H, quint, J=6.7 Hz, CF3C*H*OH), 4.17 (1H, d, J=10.9 Hz, C*H*2OMOM), 3.87 (3H, s, OCH3), 3.84 (1H, d, J=10.9 Hz, C*H*2OMOM), 3.43 (3H, s, OCH2OC*H*3), 3.36 (1H, dd, J=19.6, 6.8 Hz, C10-H), 3.23 (1H, dd, J=15.2, 6.0 Hz, C8-H), 3.07 (1H, d, J=14.1 Hz, C6-H), 2.88 (1H, br t, J=6.0 Hz, C9-H), 2.85 (1H, d, J=19.6 Hz, C10-H), 2.27 (1H, dt, J=15.2, 2.2 Hz, C8-H), 1.87 (1H, dd, J=14.1, 2.3 Hz, C6-

H). ^{19}F-NMR ($CDCl_3$) δ: -71.4 (d, J=6.5 Hz). EIMS (m/z): 405 (M^+, 21), 360 (4), 343 (81), 330 (14), 306 (5), 274 (12), 244 (33), 231 (9), 216 (39), 202 (8), 188 (21), 174 (35), 160 (20), 148 (7), 130 (6), 84 (14). HREIMS (m/z): Calcd. for $C_{18}H_{22}F_3NO_6$ (M^+): 405.1397. Found: 405.1387. Anal. Calcd. for $C_{18}H_{22}F_3NO_6$: C, 53.33; H, 5.47; N, 3.45. Found: C, 53.35; H, 5.51; N, 3.32.

(5*R, 9*R**, 11*S**, 4'*R**)-5,6,7,8,9,10-Hexahydro-2-methoxy-5-(methoxymethoxy)methyl-7-oxo-5,9-methanocycloocta[*b*]pyridine-11-spiro-5'- (4'-trifluoromethyl-1',3'-dioxolane-2'-thione) (20)**

A solution of **19** (1.31 g, 3.2 mmol) and *N,N'*-thiocarbonyldiimidazole (1.44 g, 8.1 mmol) in C_6H_5Me(25 mL) was heated at 110 °C for 5 h under argon.[13,14] The reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **20** as a colorless amorphous solid (1.14 g, 79%). IR (KBr): 2950 (m), 2900 (w), 1730 (s), 1605 (s), 1580 (m), 1485 (s), 1435 (m), 1380 (m), 1335 (s), 1280 (s), 1205 (s), 1185 (m), 1130 (s), 1040 (s), 1020 (s), 980 (m), 920 (m), 840 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38 (1H, d, J=8.8 Hz, C4-H), 6.65 (1H, d, J=8.8 Hz, C3-H), 5.53 (1H, q, J=6.7 Hz, CF_3CH), 4.69 (1H, d, J=6.8 Hz, OCH_2OCH_3), 4.63 (1H, d, J=6.8 Hz, OCH_2OCH_3), 3.88 (3H, s, OCH_3), 3.88 (1H, d, J=12.0 Hz, CH_2OMOM), 3.85 (1H, d, J=12.0 Hz, CH_2OMOM), 3.51 (1H, dd, J=19.7, 9.5 Hz, C10-H), 3.44 (3H, s, OCH_2OCH_3), 3.23 (1H, br t, J=6.0 Hz, C9-H), 3.21 (1H, ddd, J=15.0, 5.6, 1.6 Hz, C8-H), 2.93 (1H, d, J=19.7 Hz, C10-H), 2.83 (1H, d, J=14.7 Hz, C6-H), 2.51 (1H, ddd, J=16.9, 4.0, 2.4 Hz, C8-H), 2.11 (1H, dd, J=14.7, 2.4 Hz, C6-H). ^{19}F-NMR ($CDCl_3$) δ: -72.8 (d, J = 6.0 Hz). EIMS (m/z): 447 (M^+, 14), 386 (11), 358 (2), 342 (16), 326 (3), 310 (3), 289 (12), 260 (52), 244 (15), 228 (24), 216 (6), 200 (8), 186 (7), 172 (10), 160 (12), 115 (4), 77 (3), 45 (100). HREIMS (m/z): Calcd. for $C_{19}H_{20}F_3NO_6S$ (M^+): 447.0961. Found: 447.0942.

(5*R,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-5,6,7,8,9,10-hexahydro-2-methoxy-5-(methoxymethoxy)methyl-7-oxo-5,9-methanocycloocta[*b*]pyridine (21)**

A solution of **20** (1.14 g, 2.6 mmol) in trimethyl phosphite (1.0 mL) was heated at 130 °C for 15 h under argon.[13,14] After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **21** as colorless prisms (669 mg, 92%), mp 103-104 °C (from C_6H_{14}-Et_2O). IR (KBr): 2950 (m), 2900 (m), 1725 (s), 1680 (m), 1600 (s), 1580 (m), 1480 (s), 1430 (m), 1380 (m), 1345 (m), 1325 (m), 1280 (s), 1120 (s), 1050 (s), 960 (w), 920 (w), 875 (w), 830 (w), 740 (w) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44 (1H, d, J=8.6 Hz, C4-H), 6.85 (1H, d, J=8.6 Hz, C3-H), 6.05 (1H, q, J=8.2 Hz, C12-H), 4.69 (1H, d, J=6.9 Hz, OCH_2OCH_3), 4.67 (1H, d, J=6.9 Hz, OCH_2OCH_3), 4.05 (1H, d, J=10.7 Hz, CH_2OMOM), 3.98 (1H, d, J=10.7 Hz, CH_2OMOM), 3.89 (1H, br t, J=6.4 Hz, C9-H), 3.86 (3H, s, OCH_3), 3.38 (3H, s, OCH_2OCH_3), 3.32 (1H, dd, J=18.0, 6.3 Hz, C10-H), 2.95 (1H, d, J=17.3 Hz, C10-H), 2.76 (1H, dd, J=16.1, 7.0 Hz, C8-H), 2.69 (1H, d, J=14.2 Hz, C6-H), 2.55 (1H, dt, J=16.0, 2.1 Hz, C8-H), 2.42 (1H, dd, J=14.2, 2.4 Hz, C6-H). ^{19}F-NMR ($CDCl_3$) δ: -56.3 (d, J=7.2 Hz). EIMS (m/z): 371 (M^+, 52), 340 (4), 326 (6), 311 (18), 296 (17), 282 (8), 268 (30), 254 (14), 240 (11), 198 (6), 186 (9), 172 (7), 160 (4), 123 (9), 45 (100). HREIMS (m/z): Calcd. for $C_{18}H_{20}F_3NO_4$ (M^+): 371.1343. Found: 371.1324. Anal. Calcd. for $C_{18}H_{20}F_3NO_4$: C, 58.22; H, 5.43; N, 3.77. Found: C, 58.10; H, 5.46; N, 3.71.

(5*R,7*S**,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-5,6,7,8,9,10-hexahydro-7-hydroxy-2-methoxy-5-(methoxymethoxy)methyl-7-methyl-5,9-methanocycloocta[*b*]pyridine (22)**

A solution of methyllithium in Et_2O (1.16M solution, 4.8 mL, 5.6 mmol) was added to a solution of **21** (415 mg, 1.1 mmol) in THF (8.0 mL) at -78 °C under argon. After stirring for 1 h and 40 min, the reaction mixture was poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 2:1) to give **22** as colorless prisms (219 mg, 51%), mp 113-114 °C (from C_6H_{14}). IR (KBr): 3480 (m), 2950 (s), 2850 (m), 1680 (s), 1600 (s), 1480 (s), 1430 (s), 1380 (s), 1320 (s), 1280 (s), 1220 (m), 1120 (s), 1040 (s), 980 (m), 920 (s), 865 (m), 825 (m), 740 (s) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (1H, d, J=8.7 Hz, C4-H), 6.56 (1H, d, J=8.7 Hz, C3-H), 5.80 (1H, q, J=8.3 Hz, C13-H), 4.69 (1H, d, J=6.8 Hz, OCH_2OCH_3), 4.67 (1H, d, J=6.8 Hz, OCH_2OCH_3), 3.96 (1H, d, J=10.5 Hz, CH_2OMOM), 3.90 (1H, d, J=10.5 Hz, CH_2OMOM), 3.87 (3H, s, OCH_3), 3.57 (1H, br t, J=5.5 Hz, C9-H), 3.40 (3H, s, OCH_2OCH_3), 3.30 (1H, dd, J=18.2, 7.7 Hz, C10-H), 3.14 (1H, d, J=18.2 Hz, C10-H), 2.09 (1H, d, J=14.5 Hz, C6-H), 1.97 (1H, dd, J=14.5, 5.2 Hz, C6-H), 1.78 (2H, s, C8-H x 2), 1.14 (3H, s, CH_3), 0.89 (1H, br s, OH). ^{19}F-NMR ($CDCl_3$) δ: -56.1 (d, J = 10.0 Hz). EIMS (m/z): 387 (M^+, 18), 339 (31), 324 (11), 307 (10), 294 (60), 282 (4), 270 (12), 254 (43), 240 (7), 224 (5), 211 (4), 186 (7), 172 (5), 160 (3), 45 (100). HREIMS (m/z): Calcd. for $C_{19}H_{24}F_3NO_4$ (M^+): 387.1656. Found: 387.1664. Anal. Calcd. for $C_{19}H_{24}F_3NO_4$: C, 58.91; H, 6.24; N, 3.62. Found: C, 58.76; H, 6.21; N, 3.57.

(5*R,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-5,6,9,10-tetrahydro-5-hydroxymethyl-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine (24)**

Thionyl chloride (0.32 mL, 4.4 mmol) was added to a solution of **22** (341 mg, 0.88 mmol) in C_6H_5N (2.0 mL) at room temperature under argon. After stirring for 2 h, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in 1,4-dioxane (6.5 mL), and triflic acid (82 μL, 0.94 mmol) was added. After heating at 95 °C for 5 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 4:1) to give **24** as colorless prisms (157 mg, 57%), mp 145-147 °C (from C_6H_{14}-Et_2O). IR (KBr): 3380 (m), 2950 (m), 2900 (m), 1680 (m), 1600 (s), 1580 (m), 1480 (s), 1425 (m), 1385 (m), 1315 (m), 1275 (s), 1175 (m), 1120 (s), 1070 (m), 1040 (m), 915 (w), 875 (w),

830 (m), 740 (m), 705 (w) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53 (1H, d, J=8.7 Hz, C4-H), 6.63 (1H, d, J=8.7 Hz, C3-H), 5.82 (1H, q, J=8.3 Hz, C13-H), 5.42 (1H, br d, J=5.2 Hz, C8-H), 4.15-4.05 (3H, m, C*H*2O*H*), 3.89 (3H, s, OCH_3), 3.81 (1H, br s, C9-H), 3.16 (1H, dd, J=17.3, 5.3 Hz, C10-H), 2.95 (1H, dd, J=17.3, 1.8 Hz, C10-H), 2.26 (1H, dd, J=16.7, 1.0 Hz, C6-H), 1.92 (1H, d, J=16.7 Hz, C6-H), 1.54 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ: -56.3 (d, J=9.8 Hz). EIMS (m/z): 325 (M^+, 79), 306 (14), 294 (100), 280 (13), 268 (4), 256 (11), 242 (10), 222 (8), 210 (12), 196 (5), 172 (6), 160 (6), 148 (8), 128 (4), 115 (5), 84 (43). HREIMS (m/z): Calcd. for $C_{17}H_{18}F_3NO_2$ (M^+): 325.1287. Found: 325.1268. Anal. Calcd. for $C_{17}H_{18}F_3NO_2$: C, 62.76; H, 5.58; N, 4.31. Found: C, 62.84; H, 5.45; N, 4.26.

(5*R,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carbaldehyde (25)**

Dimethyl sulfoxide (105 μL, 1.5 mmol) was added to a solution of oxalyl chloride (100 μL, 1.1 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C under argon.[20] After stirring for 10 min, a solution of **24** (124 mg, 0.38 mmol) in CH_2Cl_2 (2.0 mL) was added at the same temperature. After stirring for 70 min, Et_3N (0.53 mL, 3.8 mmol) was added. After stirring was continued at 0 °C for 20 min, the reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 20:1) to give **25** as colorless prisms (92.4 mg, 77%), mp 133-134 °C (from C_6H_{14}). IR (KBr): 2950 (m), 2930 (m), 2840 (m), 2730 (w), 1730 (s), 1680 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1385 (s), 1330 (s), 1320 (s), 1275 (s), 1170 (s), 1120 (s), 1035 (s), 875 (m), 835 (m), 700 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.66 (1H, s, CHO), 7.02 (1H, d, J=8.5 Hz, C4-H), 6.62 (1H, d, J=8.5 Hz, C3-H), 5.41 (1H, br d, J=5.2 Hz, C8-H), 5.31 (1H, q, J=7.7 Hz, C13-H), 3.91 (3H, s, OCH_3), 3.84 (1H, br s, C9-H), 3.21 (1H, dd, J=17.6, 5.2 Hz, C10-H), 3.02 (1H, dd, J=17.6, 1.7 Hz, C10-H), 2.94 (1H, dd, J=17.3, 1.0 Hz, C6-H), 2.10 (1H, d, J=17.3 Hz, C6-H), 1.59 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ: -56.9 (d, J=9.5 Hz). EIMS (m/z): 323 (M^+, 100), 308 (8), 294 (73), 280 (20), 268 (14), 254 (10), 240 (16), 210 (14), 190 (11), 167 (6), 152 (5), 140 (4), 115 (5). HREIMS (m/z): Calcd. for $C_{17}H_{16}F_3NO_2$ (M^+): 323.1131. Found: 323.1120.

(5*R,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic acid (26)**

Sodium chlorite (85% purity) (60.0 mg, 0.57 mmol) was added to a solution of **25** (91.3 mg, 0.28 mmol), 2-methyl-2-butene (996 mg, 14 mmol), and NaH_2PO_4 (679 mg, 5.7 mmol) in *tert*-BuOH (15 mL) and H_2O (2.0 mL).[21] The reaction mixture was stirred for 1.5 h, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* gave crude **26** as a colorless solid (104 mg, quantitative yield), which was recrystallized from C_6H_{14}-Et_2O to provide **26** as colorless prisms (48.6 mg, 51%), mp 194-195 °C (from C_6H_{14}-Et_2O). IR (KBr): 3440 (w), 2930 (m), 1720 (s), 1685 (m), 1615 (m), 1580 (m), 1495 (s), 1440 (m), 1430 (m), 1360 (s), 1280 (s), 1240 (s), 1180 (m), 1130 (s), 1030 (m), 840 (m), 720 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27 (1H, d, J=8.6 Hz, C4-H), 6.62 (1H, d, J=8.6 Hz, C3-H), 5.54 (1H, q, J=7.9 Hz, C13-H), 5.39 (1H, br d, J=5.1 Hz, C8-H), 3.90 (3H, s, OCH_3), 3.63 (1H, br s, C9-H), 3.19 (1H, dd, J=17.3, 5.0 Hz, C10-H), 3.09 (1H, d, J=17.1 Hz, C6-H), 2.98 (1H, dd, J=17.3, 1.8 Hz, C10-H), 2.32 (1H, d, J=17.1 Hz, C6-H), 1.57 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ: -56.7 (d, J = 9.9 Hz). EIMS (m/z): 339 (M^+, 100), 324 (5), 310 (6), 294 (100), 284 (19), 270 (14), 256 (7), 240 (9), 224 (7), 210 (14), 196 (7), 182 (6), 167 (8), 151 (5), 128 (4), 115 (4). HREIMS (m/z): Calcd. for $C_{17}H_{16}F_3NO_3$ (M^+): 339.1080. Found: 339.1058. Anal. Calcd. for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 60.03; H, 4.80; N, 4.00.

(5*R,9*R**,11*E*)-Methyl [11-(2,2,2-Trifluoroethylidene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (27)**

A solution of **26** (81.7 mg, 0.24 mmol), Et_3N (50 μL, 0.36 mmol), and diphenylphosphoryl azide (57 μL, 0.27 mmol) in C_6H_5Me (2.0 mL) was heated at 85 °C for 4 h.[16] After MeOH (1.0 mL) was added, the reaction mixture was heated at 75 °C for 17 h. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 4:1) to give **27** as colorless prisms (25.8 mg, 44%), mp 184-185 °C (from C_6H_{14}-Et_2O). IR (KBr): 3330 (m), 2960 (m), 2920 (m), 1715 (s), 1600 (s), 1585 (m), 1540 (m), 1480 (s), 1430 (m), 1375 (m), 1315 (m), 1265 (s), 1120 (s), 1070 (m), 1050 (m), 1030 (m), 920 (m), 840 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.51 (1H, d, J=8.6 Hz, C4-H), 6.59 (1H, d, J=8.6 Hz, C3-H), 5.61 (1H, q, J=8.0 Hz, C13-H), 5.44 (1H, br d, J=5.0 Hz, C8-H), 5.09 (1H, br s, NH), 3.91 (1H, br s, C9-H), 3.89 (3H, s, OCH_3), 3.64 (3H, br s, CO_2CH_3), 3.20 (1H, dd, J=17.0, 2.5 Hz, C10-H), 2.92 (1H, dd, J=17.0, 2.0 Hz, C10-H), 2.66 (1H, br s, C6-H), 2.28 (1H, d, J=15.8 Hz, C6-H), 1.54 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ: -56.3 (d, J=7.1 Hz). EIMS (m/z): 368 (M^+, 100), 353 (26), 336 (6), 321 (15), 309 (16), 293 (35), 278 (16), 264 (5), 253 (6), 239 (8), 224 (29), 210 (8), 174 (5), 147 (8), 131 (3), 119 (5). HREIMS (m/z): Calcd. for $C_{18}H_{19}F_3N_2O_3$ (M^+): 368.1347. Found: 368.1359. Anal. Calcd. for $C_{18}H_{19}F_3N_2O_3$: C, 58.69; H, 5.20; N, 7.61. Found: C, 58.59; H, 5.12; N, 7.34.

(5*R,9*R**,11*E*)-5-Amino-11-(2,2,2-trifluoroethylidene)-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one [(±)-14,14,14-trifluorohuperzine A] (3)**

Iodotrimethylsilane (0.12 mL, 0.84 mmol) was added dropwise to a solution of **27** (20.9 mg, 57 μmol) in $CHCl_3$ (1.0 mL) at room temperature under argon, and the reaction mixture was heated at reflux for 10 h.[17] After MeOH (0.5 mL) was added to the solution, and the mixture was heated at reflux for 6 h. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2. The dichloromethane solution was washed successively with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, H_2O, and brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (EtOAc/MeOH, 10:1) to give **3** as

colorless prisms (12.5 mg, 74%), mp 234-235 °C (from C_6H_{14}-EtOAc). IR (KBr): 3380 (w), 3300 (w), 3130 (w), 3100 (w), 2920 (m), 2240 (m), 1660 (s), 1620 (s), 1560 (m), 1460 (m), 1430 (w), 1410 (w), 1385 (w), 1360 (m), 1305 (m), 1270 (s), 1175 (m), 1120 (s), 910 (m), 840 (m), 740 (m), 700 (w), 670 (w) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.76 (1H, br s, CONH), 7.85 (1H, d, J=9.5 Hz, C4-H), 6.47 (1H, d, J=9.5 Hz, C3-H), 5.85 (1H, q, J=8.3 Hz, C13-H), 5.39 (1H, br d, J=5.0 Hz, C8-H), 3.87 (1H, br s, C9-H), 3.04 (1H, dd, J=17.1, 5.1 Hz, C10-H), 2.80 (1H, dd, J=17.1, 1.7 Hz, C10-H), 2.27 (1H, d, J=17.6 Hz, C6-H), 2.22 (1H, d, J=17.6 Hz, C6-H), 1.58 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ: -56.6 (d, J=6.5 Hz). EIMS (m/z): 296 (M^+, 100), 281 (62), 261 (5), 241 (5), 227 (41), 213 (30), 197 (11), 185 (6), 173 (8), 160 (6), 147 (15), 130 (4), 119 (5), 106 (7), 91 (8). HREIMS (m/z): Calcd. for $C_{15}H_{15}F_3N_2O$ (M^+): 296.1135. Found: 296.1135. Anal. Calcd. for $C_{15}H_{15}F_3N_2O$: C, 60.81; H, 5.10; N, 9.45. Found: C, 60.66; H, 5.27; N, 9.25.

(5*R,9*R**,11*E*)-11-(2,2,2-Trifluoroethylidene)-5,6,7,8,9,10-hexahydro-5-hydroxymethyl-2-methoxy-7-oxo-5,9-methanocycloocta[*b*]pyridine (28)**

Bromotrimethylsilane (0.54 mL, 4.1 mmol) was added to a suspension of **21** (380 mg, 1.0 mmol) and molecular sieves 4Å (380 mg) in CH_2Cl_2 (6.0 mL) at -30 °C under argon. The reaction mixture was stirred overnight at room temperature, poured into saturated aqueous $NaHCO_3$, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 2:1) to give **28** as a colorless amorphous solid (312 mg, 93%). IR (KBr): 3450 (m), 2950 (m), 2900 (m), 1720 (s), 1680 (m), 1600 (s), 1580 (m), 1480 (s), 1430 (m), 1380 (m), 1350 (m), 1320 (m), 1280 (s), 1175 (m), 1120 (s), 1080 (m), 1050 (m), 875 (m), 830 (m), 740 (m), 715 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43 (1H, d, J=8.9 Hz, C4-H), 6.63 (1H, d, J=8.9 Hz, C3-H), 6.15 (1H, q, J=8.1 Hz, C12-H), 4.17 (1H, dd, J=12.0, 6.7 Hz, C*H*$_2$OH), 4.10 (1H, dd, J=12.0, 3.4 Hz, C*H*$_2$OH), 3.90 (1H, br t, J=6.6 Hz, C9-H), 3.87 (3H, s, OCH_3), 3.31 (1H, dd, J=18.1, 5.2 Hz, C10-H), 2.97 (1H, d, J=18.1 Hz, C10-H), 2.77 (1H, dd, J=16.0, 7.0 Hz, C8-H), 2.60 (1H, d, J=14.1 Hz, C6-H), 2.55 (1H, dt, J=16.0, 1.9 Hz, C8-H), 2.34 (1H, dd, J=14.1, 2.4 Hz, C6-H), 1.65 (1H, dd, J=6.7, 3.4 Hz, CH_2O*H*). ^{19}F-NMR ($CDCl_3$) δ: -56.3 (d, J=6.5 Hz). EIMS (m/z): 327 (M^+, 100), 308 (26), 296 (42), 280 (13), 268 (26), 256 (13), 240 (20), 222 (9), 210 (8), 198 (10), 186 (14), 172 (19), 160 (8), 142 (5), 128 (5), 115 (6), 84 (7). HREIMS (m/z): Calcd. for $C_{16}H_{16}F_3NO_3$ (M^+): 327.1081. Found: 327.1062.

(5*R,9*R**,11*E*)-Methyl 11-(2,2,2-trifluoroethylidene)-7,8,9,10-tetrahydro-2-methoxy-7-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (31)**

DMSO (0.46 mL, 6.4 mmol) was added to a solution of oxalyl chloride (0.40 mL, 4.6 mmol) in CH_2Cl_2 (2.0 mL) at -78 °C under argon.[20] After stirring for 10 min, a solution of **28** (300 mg, 0.92 mmol) in CH_2Cl_2 (4.0 mL) was added at the same temperature. After stirring was continued for 1 h, Et_3N (1.3 mL, 9.2 mmol) was added. The reaction mixture was stirred at 0 °C for 20 min, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* gave crude **29** (353 mg) as a colorless oil. This was subjected to the next oxidation without further purification. Sodium chlorite (85% purity) (195 mg, 1.8 mmol) was added to a solution of crude **29** (353 mg), 2-methyl-2-butene (3.22 g, 46 mmol), and NaH_2PO_4 (2.21 g, 18 mmol) in *tert*-BuOH (9.0 mL) and H_2O (3.0 mL).[21] The reaction mixture was stirred for 1 h, concentrated *in vacuo*, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* afforded crude **30** (419 mg) as a colorless oil. This was immediately subjected to the next esterification. A 10% solution of trimethylsilyldiazomethane in C_6H_{14} (0.5 mL) was added to a solution of crude **30** (419 mg) in MeOH (2.0 mL) and Et_2O (2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, and concentrated *in vacuo*. The residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 5:1) to give **31** as a colorless amorphous solid (273 mg, 84% from **28**). IR (KBr): 2960 (m), 2920 (m), 1740 (s), 1680 (m), 1605 (s), 1580 (m), 1480 (s), 1430 (m), 1380 (m), 1340 (m), 1325 (m), 1275 (s), 1170 (m), 1120 (s), 1080 (m), 1040 (m), 1020 (m), 900 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.01 (1H, d, J=8.6 Hz, C4-H), 6.60 (1H, d, J=8.6 Hz, C3-H), 5.57 (1H, q, J=7.7 Hz, C12-H), 3.91 (1H, br t, J=6.9 Hz, C9-H), 3.88 (3H, s, OCH_3), 3.85 (1H, s, CO_2CH_3), 3.32 (1H, dd, J=18.0, 5.9 Hz, C10-H), 3.20 (1H, d, J=14.1 Hz, C6-H), 2.97 (1H, dd, J=18.0, 1.2 Hz, C10-H), 2.81 (1H, dd, J=15.2, 2.3 Hz, C6-H), 2.78 (1H, dd, J=16.3, 7.1 Hz, C8-H), 2.56 (1H, dt, J=16.1, 1.8 Hz, C8-H). ^{19}F-NMR ($CDCl_3$) δ: -56.7 (d, J=8.1 Hz). EIMS (m/z): 355 (M^+, 100), 336 (4), 323 (15), 298 (35), 286 (7), 268 (16), 254 (10), 231 (12), 214 (6), 199 (16), 184 (7), 172 (17), 154 (4), 140 (3), 128 (3), 115 (4). HREIMS (m/z): Calcd. for $C_{17}H_{16}F_3NO_4$ (M^+): 355.1030. Found: 355.1010.

(5*R,7*S**,9*R**,11*E*)-Methyl 11-(2,2,2-trifluoroethylidene)-7-trifluoromethyl-7,8,9,10-tetrahydro-7-hydroxy-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (32)**

A solution of TBAF in THF (1.0M solution, 1 μL, 1 μmol) was added to a solution of **31** (180 mg, 0.51 mmol) and CF_3TMS (0.40 mL, 2.5 mmol) in THF (0.5 mL) under argon.[12] The reaction mixture was stirred at room temperature for 3 h. After **31** was consumed, a solution of TBAF in THF (1.0M solution, 0.5 mL, 0.5 mmol) was further added to the reaction mixture. After stirring for 15 min, the reaction mixture was poured into H_2O, and extracted with Et_2O. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* followed by purification by flash column chromatography (C_6H_6/EtOAc, 20:1) gave **32** as colorless prisms (93.3 mg, 43%), mp 166-168 °C (from C_6H_{14}-Et_2O). IR (KBr): 3480 (m), 2960 (m), 1740 (s), 1680 (m), 1605 (m), 1480 (s), 1440 (m), 1320 (m), 1275 (s), 1255 (s), 1180 (m), 1125 (s), 1030 (m), 915 (m), 890 (m), 825 (m), 740 (m), 660 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.00 (1H, d, J=8.6 Hz, C4-H), 6.56 (1H, d, J=8.6 Hz, C3-H), 5.43 (1H, q, J=7.7 Hz, C13-H), 3.88 (3H, s, OCH_3), 3.85 (1H, s, CO_2CH_3), 3.73 (1H, br t, J=5.6 Hz, C9-H), 3.35 (1H, dd, J=18.3, 7.5 Hz, C10-H), 3.10 (1H, d, J=18.3 Hz, C10-H), 2.67 (1H, d, J=14.7 Hz, C6-H), 2.23 (1H, dd, J=14.7, 2.2 Hz, C6-H), 2.21 (1H, dd, J=14.7, 5.0 Hz, C8-H), 2.14

(1H, dt, J=14.7, 2.3 Hz, C8-H), 1.27 (1H, br s, OH). ^{19}F-NMR ($CDCl_3$) δ: -85.5 (s), -56.8 (d, J=6.5 Hz). EIMS (m/z): 425 (M^+, 100), 406 (5), 396 (12), 366 (20), 348 (10), 328 (4), 313 (4), 298 (21), 278 (4), 254 (9), 230 (4), 218 (8), 184 (5), 170 (3). HREIMS (m/z): Calcd. for $C_{18}H_{17}F_6NO_4$ (M^+): 425.1060. Found: 425.1053. Anal. Calcd. for $C_{18}H_{17}F_6NO_4$: C, 50.83; H, 4.03; N, 3.29. Found: C, 50.70; H, 4.05; N, 3.12.

(5*R,9*R**,11*E*)-Methyl [11-(2,2,2-trifluoroethylidene)-7-trifluoromethyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (35a)**

Thionyl chloride (56 μL, 0.77 mmol) was added to a solution of **32** (109 mg, 0.26 mmol) in C_6H_5N (0.5 mL) at room temperature under argon. After stirring at 40 °C for 5 h, the reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 20:1) to give a mixture of **33a** and **33b** as a colorless oil (88.0 mg, 84%). The ratio of **33a** to **33b** was estimated as *ca.* 4:1 by the following ^{1}H-NMR spectrum. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.42 (0.8H, q, J=8.0 Hz, C_{13}-H), 5.53 (0.2H, q, J=8.0 Hz, C_{13}-H). This mixture was subjected to the next alkaline hydrolysis without separation. A solution of 3N-NaOH (0.4 mL) was added to a solution of the mixture of **33a** and **33b** (95.0 mg) in MeOH-THF (2:1) (0.6 mL). The reaction mixture was heated at reflux for 5 h under argon. After cooling, the reaction mixture was diluted with H_2O, adjusted to pH 4 with 1N-HCl, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* gave a mixture of **34a** and **34b** as a colorless oil (94.8 mg, quantitative yield). This mixture was immediately subjected to the next modified Curtius rearrangement. A solution of the mixture of **34a** and **34b** (92.0 mg), Et_3N (49 μL, 0.35 mmol), and diphenylphosphoryl azide (50 μL, 0.23 mmol) in C_6H_5Me (2.0 mL) was heated at 85 °C for 4 h.[16] After MeOH (1.0 mL) was added, the reaction mixture was heated at 85 °C for 4 h. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 5:1) to give **35a** as colorless prisms (63.3 mg, 64% from **33**) and **35b** as a colorless oil (5.7 mg, 6% from **33**). **35a**: mp 174-176 °C (from C_6H_{14}-Et_2O). IR (KBr): 3330 (m), 2960 (m), 2920 (w), 2850 (w), 2270 (w), 1720 (s), 1600 (s), 1580 (m), 1540 (s), 1480 (s), 1430 (s), 1375 (s), 1295 (s), 1270 (s), 1180 (s), 1120 (s), 1080 (s), 1030 (m), 915 (m), 835 (m), 740 (m), 650 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.54 (1H, d, J=8.7 Hz, C4-H), 6.63 (1H, d, J=8.7 Hz, C3-H), 6.36 (1H, br d, J=3.7 Hz, C8-H), 5.73 (1H, q, J=8.0 Hz, C13-H), 5.19 (1H, br s, NH), 4.13 (1H, br s, C9-H), 3.89 (3H, s, OCH_3), 3.66 (1H, br s, $NHCO_2CH_3$), 3.31 (1H, dd, J=17.4, 2.4 Hz, C10-H), 3.00 (1H, dd, J=17.4, 1.8 Hz, C10-H), 2.90-2.86 (1H, br s, C6-H), 2.58 (1H, dd, J=15.8 Hz, C6-H). ^{19}F-NMR ($CDCl_3$) δ: -69.5 (s), -56.6 (d, J=7.9 Hz). EIMS (m/z): 422 (M^+, 100), 402 (16), 389 (9), 363 (18), 353 (27), 347 (36), 321 (16), 307 (4), 293 (7), 278 (29), 264 (6), 219 (8), 122 (7), 83 (23). HREIMS (m/z): Calcd. for $C_{18}H_{16}F_6N_2O_3$ (M^+): 422.1064. Found: 422.1082. Anal. Calcd. for $C_{18}H_{16}F_6N_2O_3$: C, 51.19; H, 3.82; N, 6.63. Found: C, 51.15; H, 3.68; N, 6.56. **35b**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.54 (1H, d, J=8.6 Hz, C4-H), 6.59 (1H, d, J=8.6 Hz, C3-H), 6.42 (1H, br s, C8-H), 5.68 (1H, q, J=7.6 Hz, C13-H), 5.16 (1H, br s, NH), 3.95 (1H, br tr, J=7.1 Hz, C9-H), 3.89 (3H, s, OCH_3), 3.75 (1H, s, $NHCO_2CH_3$), 3.45 (1H, dd, J=18.7, 7.8 Hz, C10-H), 2.97 (1H, d, J=18.7 Hz, C10-H), 2.84 (1H, dd, J=17.4, 4.2 Hz, C6-H), 2.43 (1H, d, J=18.1 Hz, C8-H). EIMS (m/z): 422 (M^+, 100), 402 (16), 389 (6), 363 (31), 353 (63), 347 (13), 321 (20), 307 (3), 293 (5), 278 (20), 264 (3), 228 (10).

(5*R,9*R**,11*E*)-5-Amino-11-(2,2,2-trifluoroethylidene)-7-trifluoromethyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one [(±)-12,12,12,14,14,14-hexafluorohuperzine A] (4).**

Iodotrimethylsilane (0.11 mL, 0.76 mmol) was added dropwise to a solution of **35a** (31.9 mg, 76 μmol) in $CHCl_3$ (1.0 mL) at room temperature under argon, and the reaction mixture was heated at reflux for 10 h.[17] After MeOH (0.5 mL) was added, the mixture was further heated at reflux for 6 h. After concentration *in vacuo*, the residue was dissolved in EtOAc. The ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, H_2O, and brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (EtOAc/MeOH, 10:1) to give **4** as colorless prisms (21.0 mg, 80%), mp 249-250 °C (from C_6H_{14}-EtOAc). IR (KBr): 3400 (m), 3380 (m), 3300 (m), 3130 (m), 2950 (m), 1670 (s), 1625 (m), 1560 (m), 1460 (m), 1430 (m), 1415 (m), 1385 (m), 1365 (m), 1340 (m), 1285 (s), 1275 (s), 1180 (s), 1120 (s), 1040 (m), 940 (m), 915 (m), 835 (m), 780 (m), 720 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.42 (1H, br s, NH), 7.87 (1H, d, J=9.5 Hz, C4-H), 6.50 (1H, d, J=9.5 Hz, C3-H), 6.32 (1H, br d, J=5.0 Hz, C8-H), 5.99 (1H, q, J=8.1 Hz, C13-H), 4.08 (1H, br s, C9-H), 3.18 (1H, dd, J=17.5, 5.4 Hz, C10-H), 2.93 (1H, dd, J = 17.5, 1.5 Hz, C10-H), 2.53 (1H, d, J = 17.1 Hz, C6-H), 2.40 (1H, d, J=17.1 Hz, C6-H). ^{19}F-NMR ($CDCl_3$) δ: -69.5 (s), -56.8 (d, J=6.5 Hz). EIMS (m/z): 350 (M^+, 100), 331 (12), 281 (82), 267 (16), 241 (8), 211 (6), 197 (5), 185 (4), 173 (4), 160 (5), 147 (13), 106 (4), 84 (17). HREIMS (m/z): Calcd. for $C_{15}H_{12}F_6N_2O$ (M^+): 350.0852. Found: 350.0850. Anal. Calcd. for $C_{15}H_{12}F_6N_2O$: C, 51.44; H,3.45; N, 8.00. Found: C, 51.46; H, 3.43; N, 7.71.

(5*S,9*R**)-Methyl 7-bromomethyl-9,10-dihydro-2-methoxy-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (36)**

A solution of **13** (1.80 g, 6.3 mmol) and NBS (1.34 g, 7.5 mmol) in 1,4-dioxane (35 mL) and H_2O (3.5 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **36** as colorless prisms (1.87 g, 82%), mp 161-163 °C (from C_6H_{14}-EtOAc). IR (KBr): 2950 (m), 1750 (s), 1735 (s), 1605 (s), 1580 (m), 1480 (s), 1430 (m), 1330 (s), 1270 (s), 1220 (m), 1080 (m), 1030 (m), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.15 (1H, d, J=8.6 Hz, C4-H), 6.64 (1H, d, J=8.6 Hz, C3-H), 5.89-5.87 (1H, m, C8-H), 3.91 (3H, s, OCH_3), 3.83 (1H, d, J=10.4 Hz, CH_2Br), 3.79 (1H, d, J=10.4 Hz, CH_2Br), 3.78 (3H, s, CO_2CH_3), 3.53 (1H, d, J=17.4 Hz, C6-H), 3.44 (1H, dd, J=17.1, 4.8 Hz, C10-H), 3.25 (1H, br t, J=5.3 Hz, C9-H), 3.21 (1H, dd, J=17.1, 2.0 Hz, C10-H), 2.83 (1H,

d, J=17.4 Hz, C6-H). EIMS (m/z): 367 ($M+1^+$, 6), 365 ($M-1^+$,7), 287 (17), 286 (100), 258 (44), 230 (14), 226 (15), 199 (21), 198 (47), 184 (10), 170 (5), 154 (7), 128 (7), 115 (6), 84 (8). HREIMS (m/z): Calcd. for $C_{16}H_{16}{}^{79}BrNO_4$ (M^+): 365.0261. Found: 365.0252. Calcd. for $C_{16}H_{16}{}^{81}BrNO_4$ (M^+): 367.0242. Found: 367.0257. Anal. Calcd. for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82; Br, 21.82. Found: C, 52.20; H, 4.44; N, 3.71; Br, 22.04.

(5*S,9*R**)-Methyl 7-acetoxymethyl-9,10-dihydro-2-methoxy-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (37)**

A solution of **36** (1.87 g, 5.1 mmol) and AgOAc (2.14 g, 13 mmol) in Me_2CO (40 mL) was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo*, poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **37** as colorless prisms (1.43 g, 81%), mp 117-117.5 °C (from C_6H_{14}-Et_2O). IR (KBr): 2950 (m), 1750 (s), 1600 (s), 1580 (m), 1480 (m), 1430 (m), 1380 (m), 1330 (m), 1250 (s), 1080 (m), 1040 (m), 920 (m), 840 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.13 (1H, d, J=8.6 Hz, C4-H), 6.64 (1H, d, J=8.6 Hz, C3-H), 5.79-5.77 (1H, m, C8-H), 4.41 (1H, d, J=13.0 Hz, CH_2OAc), 4.35 (1H, d, J=13.0 Hz, CH_2OAc), 3.92 (3H, s, OCH_3), 3.78 (3H, s, CO_2CH_3), 3.44 (1H, dd, J=17.1, 4.8 Hz, C10-H), 3.43 (1H, d, J=17.5 Hz, C6-H), 3.25 (1H, br t, J=4.9 Hz, C9-H), 3.21 (1H, dd, J=17.1, 1.8 Hz, C10-H), 2.63 (1H, d, J=17.5 Hz, C6-H). EIMS (m/z): 345 (M^+, 49), 313 (35), 302 (10), 286 (21), 270 (5), 257 (35), 253 (45), 242 (9), 226 (57), 205 (14), 198 (100), 184 (13), 170 (9), 154 (12), 141 (6), 128 (9), 115 (8), 84 (14). HREIMS (m/z): Calcd. for $C_{18}H_{19}NO_6$ (M^+): 345.1211. Found: 345.1237. Anal. Calcd. for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.54; H, 5.59; N, 3.98.

(5*S,9*R**)-Methyl 9,10-dihydro-7-hydroxymethyl-2-methoxy-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (38)**

A solution of K_2CO_3 (300 mg, 2.2 mmol) in MeOH (3.0 mL) was added to a solution of **37** (1.43 g, 4.1 mmol) in MeOH (40 mL) over 10 min at 0 °C. The reaction mixture was stirred at the same temperature for 2 h, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, then dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 1:1) to give **38** as a colorless oil (1.17 g, 93%). IR (neat): 3450 (m), 2950 (m), 1750 (s), 1730 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1380 (s), 1260 (s), 1140 (m), 1080 (m), 1030 (m), 835 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.13 (1H, d, J=8.6 Hz, C4-H), 6.62 (1H, d, J=8.6 Hz, C3-H), 5.75-5.73 (1H, m, C8-H), 3.97 (1H, d, J=13.0 Hz, CH_2OH), 3.90 (3H, s, OCH_3), 3.89 (1H, d, J=13.0 Hz, CH_2OH), 3.77 (3H, s, CO_2CH_3), 3.43 (1H, dd, J=16.4, 4.8 Hz, C10-H), 3.39 (1H, d, J=17.4 Hz, C6-H), 3.24 (1H, br t, J=4.7 Hz, C9-H), 3.21 (1H, dd, J=16.4, 2.0 Hz, C10-H), 2.66 (1H, d, J=17.4 Hz, C6-H), 1.63 (1H, br s, OH). EIMS (m/z): 303 (M^+, 96), 285 (11), 271 (100), 258 (15), 244 (62), 240 (70), 226 (41), 216 (54), 205 (20), 198 (82), 186 (32), 172 (25), 154 (19), 142 (11), 128 (18), 115 (21), 102 (8), 89 (6), 77 (12). HREIMS (m/z): Calcd. for $C_{16}H_{17}NO_5$ (M^+): 303.1105. Found: 303.1123.

(5*S,9*R**)-Methyl 9,10-dihydro-2-methoxy-7-(methoxymethoxy)methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (39)**

Ethyldiisopropylamine (2.80 mL, 16 mmol) and chloromethyl methyl ether (1.21 mL, 16 mmol) were added to a solution of **38** (975 mg, 3.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon. The reaction mixture was stirred overnight at room temperature, poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **39** as a colorless oil (1.04 g, 93%). IR (neat): 2950 (m), 1750 (s), 1730 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1330 (s), 1260 (s), 1150 (s), 1110 (s), 1040 (s), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H -NMR (400 MHz, $CDCl_3$) δ: 7.13 (1H, d, J=8.6 Hz, C4-H), 6.62 (1H, d, J=8.6 Hz, C3-H), 5.76-5.74 (1H, m, C8-H), 4.44 (1H, d, J=6.6 Hz, OCH_2OCH_3), 4.38 (1H, d, J=6.6 Hz, OCH_2OCH_3), 3.91 (3H, s, OCH_3), 3.86 (2H, s, CH_2OMOM), 3.77 (3H, s, CO_2CH_3), 3.43 (1H, dd, J=17.0, 5.4 Hz, C10-H), 3.40 (1H, dt, J=17.5, 1.2 Hz, C6-H), 3.27 (3H, br s, OCH_2OCH_3), 3.25-3.23 (1H, m, C9-H), 3.21 (1H, dd, J=17.0, 1.9 Hz, C10-H), 2.68 (1H, d, J=17.5 Hz, C6-H). EIMS (m/z): 347 (M^+, 31), 315 (21), 302 (6), 285 (33), 270 (8), 257 (67), 244 (10), 244 (10), 226 (31), 214 (13), 205 (9), 198 (60), 186 (15), 170 (12), 154 (9), 143 (5), 128 (9), 115 (10), 84 (13), 69 (11), 45 (100). HREIMS (m/z): Calcd. for $C_{18}H_{21}NO_6$ (M^+): 347.1368. Found: 347.1377.

(5*R,9*R**,11*E*)-Methyl 11-ethylidene-9,10-dihydro-2-methoxy-7-(methoxymethoxy)methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (40*E*) and its (5*R**,9*R**,11*Z*)-isomer (40*Z*)**

A solution of butyllithium in C_6H_{14} (1.71M solution, 7.42 mL, 13 mmol) was added to a suspension of ethyltriphenylphosphonium bromide (5.29 g, 14 mmol) in THF (10 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. A solution of **39** (1.04 g, 3.0 mmol) in THF (10 mL) was added at 0 °C under argon. After stirring was continued overnight at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 5:1) to give a mixture of **40*E*** and **40*Z*** as a colorless oil (802 mg, 75%). The ratio of **40*E*** to **40*Z*** was estimated as *ca.* 1:4 by comparing the ^{1}H-NMR spectrum of this sample with those of pure **40*E*** and **40*Z*** described below. Thiophenol (0.47 mL, 4.6 mmol) and AIBN (382 mg, 2.3 mmol) was added to a solution of the mixture of **40*E*** and **40*Z*** (802 mg) in C_6H_5Me (10 mL), and the reaction mixture was heated at 85 °C for 43 h. After cooling, the mixture was concentrated *in vacuo*, poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14} /EtOAc, 5:1) to give a mixture of **40*E*** and **40*Z*** as a colorless oil (802 mg, quantitative recovery). The ratio of **40*E*** to **40*Z*** was similarly estimated as 9:1 based on the ^{1}H-

NMR spectrum. Treatment of the corresponding acid **41** obtained in the next step with trimethylsilyldiazomethane afforded an analytical sample of **40*E*** as a colorless oil. An analytical sample of **40*Z*** was recovered as a colorless oil in the next step without hydrolysis. **40*E***: IR (neat): 2950 (m), 1730 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1325 (m), 1250 (s), 1150 (s), 1105 (m), 1050 (s), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.10 (1H, d, J=8.5 Hz, C4-H), 6.53 (1H, d, J=8.5 Hz, C3-H), 5.72 (1H, br d, J=3.7 Hz, C8-H), 5.08 (1H, q, J=6.7 Hz, C13-H), 4.41 (1H, d, J=6.5 Hz, OCH_2OCH_3), 4.33 (1H, d, J=6.5 Hz, OCH_2OCH_3), 3.88 (3H, s, OCH_3), 3.80 (2H, s, CH_2OMOM), 3.75 (3H, s, CO_2CH_3), 3.68 (1H, br t, J=5.1 Hz, C9-H), 3.27 (3H, s, OCH_2OCH_3), 3.10 (1H, dd, J=17.1, 6.4 Hz, C10-H), 3.10 (1H, dd, J=17.1, 3.6 Hz, C6-H), 2.88 (1H, d, J=17.1, 1.7 Hz, C10-H), 2.31 (1H, d, J=17.1 Hz, C6-H), 1.70 (3H, d, J=6.7 Hz, C14-H). EIMS (m/z): 359 (M^+, 43), 327 (5), 314 (9), 297 (28), 282 (23), 268 (17), 254 (10), 238 (100), 224 (19), 210 (14), 198 (5), 186 (10), 167 (7), 154 (6), 115 (6), 84 (7), 69 (5), 45 (60). HREIMS (m/z): Calcd. for $C_{20}H_{25}NO_5$ (M^+): 359.1730. Found: 359.1738. **40*Z***: IR (neat): 2950 (m), 1730 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1320 (s), 1260 (s), 1150 (s), 1110 (m), 1040 (s), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.10 (1H, d, J=8.6 Hz, C4-H), 6.53 (1H, d, J=8.6 Hz, C3-H), 5.72-5.71 (1H, m, C8-H), 5.52 (1H, q, J=7.3 Hz, C13-H), 4.40 (1H, d, J=6.5 Hz, OCH_2OCH_3), 4.32 (1H, d, J=6.5 Hz, OCH_2OCH_3), 3.88 (3H, s, OCH_3), 3.80 (2H, s, CH_2OMOM), 3.71 (3H, s, CO_2CH_3), 3.26 (3H, s, OCH_2OCH_3), 3.19 (1H, dd, J=15.8, 5.2 Hz, C10-H), 3.14 (1H, m, C9-H), 3.04 (1H, d, J=17.0 Hz, C6-H), 2.84 (1H, d, J=15.8 Hz, C10-H), 2.37 (1H, d, J=17.0 Hz, C6-H), 1.51 (3H, d, J=7.3 Hz, C14-H). EIMS (m/z): 359 (M^+, 35), 297 (26), 282 (13), 268 (13), 250 (7), 238 (100), 224 (18), 210 (14), 196 (6), 180 (5), 167 (4), 115 (5), 84 (23). HREIMS (m/z): Calcd. for $C_{20}H_{25}NO_5$ (M^+): 359.1730. Found: 359.1730.

(5*R,9*R**,11*E*)-11-Ethylidene-9,10-dihydro-2-methoxy-7-(methoxymethoxy)methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic acid (41)**

A 9:1 mixture of **40*E*** and **40*Z*** (817 mg, 2.3 mmol) was dissolved in MeOH-THF (1:1) (10 mL), and 3N-NaOH (5.0 mL) was added. The reaction mixture was heated at reflux under argon for 24 h. After cooling, the mixture was adjusted to pH 4 with 1N-HCl, and MeOH and THF were removed *in vacuo*. The aqueous residue was extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 1:1) to give **41** (633 mg, 81%) and **40*Z*** (41.0 mg, 5% recovery) both as a colorless oil. **41**: IR (neat): 2950 (m), 1730 (s), 1600 (s), 1580 (m), 1480 (s), 1430 (s), 1330 (s), 1250 (s), 1250 (m), 1150 (m), 1110 (m), 1040 (s), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27 (1H, d, J=8.6 Hz, C4-H), 6.57 (1H, d, J=8.6 Hz, C3-H), 5.73 (1H, br d, J=3.6 Hz, C8-H), 5.34 (1H, q, J=6.7 Hz, C13-H), 4.41 (1H, d, J=6.5 Hz, OCH_2OCH_3), 4.34 (1H, d, J=6.5 Hz, OCH_2OCH_3), 3.88 (3H, s, OCH_3), 3.81 (2H, s, CH_2OMOM), 3.70 (1H, br t, J=4.4 Hz, C9-H), 3.26 (3H, s, OCH_2OCH_3), 3.12 (1H, dd, J=17.0, 5.1 Hz, C10-H), 3.05 (1H, d, J=17.2 Hz, C6-H), 2.90 (1H, dd, J=17.0, 3.3 Hz, C10-H), 2.34 (1H, d, J=17.2 Hz, C6-H), 1.74 (3H, d, J=6.7 Hz, C14-H). EIMS (m/z): 345 (M^+, 57), 313 (9), 300 (22), 283 (49), 268 (23), 254 (20), 238 (100), 224 (30), 210 (21), 198 (11), 186 (13), 172 (8), 154 (8), 128 (7), 115 (7), 84 (9), 45 (75). HREIMS (m/z): Calcd. for $C_{19}H_{23}NO_5$ (M^+): 345.1575. Found: 345.1590.

(5*R,9*R**,11*E*)-Methyl [11-ethylidene-9,10-dihydro-2-methoxy-7-(methoxymethoxy)-methyl-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (42)**

A solution of **41** (418 mg, 1.2 mmol), Et_3N (0.25 mL, 1.8 mmol) and diphenylphosphoryl azide (0.26 mL, 1.2 mmol) in C_6H_5Me (10 mL) was heated at 85 °C for 2.5 h.[16] After MeOH (2.0 mL) was added, the reaction mixture was heated at 85 °C for 4 h. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 2:1) to give **42** as a colorless oil (269 mg, 59%). IR (neat): 3330 (m), 2950 (m), 1730 (s), 1600 (s), 1580 (m), 1530 (s), 1480 (s), 1420 (s), 1320 (s), 1310 (m), 1260 (s), 1150 (s), 1100 (s), 1040 (s), 920 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.57 (1H, d, J=8.6 Hz, C4-H), 6.55 (1H, d, J=8.6 Hz, C3-H), 5.76 (1H, br d, J=4.4 Hz, C8-H), 5.39 (1H, q, J=6.8 Hz, C13-H), 5.04 (1H, br s, NH), 4.38 (1H, d, J=6.5 Hz, OCH_2OCH_3), 4.30 (1H, d, J=6.5 Hz, OCH_2OCH_3), 3.87 (3H, s, OCH_3), 3.78 (1H, s, CH_2OMOM), 3.78 (1H, s, CH_2OMOM), 3.75 (1H, br s, C9-H), 3.62 (3H, br s, $NHCO_2CH_3$), 3.25 (3H, s, OCH_2OCH_3), 3.12 (1H, dd, J=16.9, 4.0 Hz, C10-H), 2.85 (1H, dd, J=16.9, 1.8 Hz, C10-H), 2.59 (1H, d, J=15.2 Hz, C6-H), 2.37 (1H, d, J=15.2 Hz, C6-H), 1.72 (3H, d, J=6.8 Hz, C14-H). EIMS (m/z): 374 (M^+, 26), 342 (7), 329 (12), 312 (100), 297 (26), 283 (9), 267 (17), 224 (30), 253 (13), 237 (92), 224 (43), 210 (13), 199 (7), 184 (6), 166 (6), 148 (5), 130 (5), 97 (8), 77 (6), 59 (10), 45 (72). HREIMS (m/z): Calcd. for $C_{20}H_{26}N_2O_5$ (M^+): 374.1839. Found: 374.1813.

(5*R,9*R**,11*E*)-Methyl [11-ethylidene-9,10-dihydro-7-hydroxymethyl-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (43)**

A solution of **42** (260 mg, 0.70 mmol) and pyridinium *p*-toluenesulfonate (1.80 g, 7.2 mmol) in *tert*-BuOH (15 mL) was heated at reflux for 9 h.[22] The reaction mixture was poured into H_2O, adjusted to pH 7 with saturated aqueous $NaHCO_3$, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 1:1) to give **43** as a colorless oil (150 mg, 65%). IR (neat): 3330 (m), 2940 (m), 1720 (s), 1600 (s), 1580 (m), 1530 (m), 1480 (s), 1420 (s), 1320 (s), 1260 (s), 1070 (m), 1040 (s), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.57 (1H, d, J=8.6 Hz, C4-H), 6.55 (1H, d, J=8.6 Hz, C3-H), 5.73 (1H, d, J=4.8 Hz, C8-H), 5.39 (1H, q, J=6.8 Hz, C13-H), 5.10 (1H, br s, NH), 3.88 (1H, dd, J=13.3, 6.0 Hz, CH_2OH), 3.87 (3H, s, OCH_3), 3.81 (1H, dd, J=13.3, 6.0 Hz, CH_2OH), 3.74 (1H, br s, C9-H), 3.62 (3H, br s, $NHCO_2CH_3$), 3.12 (1H, dd, J=16.8, 4.0 Hz, C10-H), 2.84 (1H, dd, J=16.8, 1.8 Hz, C10-H), 2.61 (1H, br d, J=15.2 Hz, C6-H), 2.37 (1H, d, J=15.2 Hz, C6-H), 1.72 (3H, d, J = 6.8 Hz, C14-H), 1.39 (1H, br t, J=6.0 Hz, OH). EIMS (m/z): 330 (M^+, 37), 312 (26), 299 (25), 283 (8), 267 (19), 255 (32), 237 (39), 224 (100), 210 (25), 195 (8), 184 (6), 167 (7), 115 (5), 84 (12). HREIMS (m/z) : Calcd. for $C_{18}H_{22}N_2O_4$ (M^+): 330.1577. Found: 330.1567.

(5*R,9*R**,11*E*)-Methyl [7-ethoxycarbonyl-11-ethylidene-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamate (46)**

Dimethyl sulfoxide (0.19 mL, 2.7 mmol) was added to a solution of oxalyl chloride (0.17 mL, 1.9 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C under argon.[20] After stirring for 10 min, a solution of **43** (133 mg, 0.40 mmol) in CH_2Cl_2 (4.0 mL) was added at the same temperature. After stirring was continued for 1 h, Et_3N (0.55 mL, 3.9 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* afforded crude **44** (147 mg) as a colorless oil. The ^{1}H-NMR spectrum of this sample was identical to that of pure **44** independently prepared from **49** by way of **52**. Sodium chlorite (85% purity) (130 mg, 1.2 mmol) was added to a solution of crude **44** (147 mg), 2-methyl-2-butene (1.40 g, 20 mmol), and NaH_2PO_4 (960 mg, 8.0 mmol) in *tert*-BuOH (10 mL) and H_2O (3.0 mL) at room temperature.[21] The reaction mixture was stirred for 1 h, poured into H_2O, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* gave crude **45** (164 mg) as a colorless oil. This was immediately subjected to the next esterification. The spectral data of crude **45** was as follows: IR (neat): 3330 (m), 2940 (m), 1710 (s), 1600 (s), 1580 (m), 1530 (m), 1480 (s), 1430 (m), 1320 (s), 1260 (s), 1030 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.56 (1H, d, J=8.4 Hz, C4-H), 7.09 (1H, m, C8-H), 6.56 (1H, d, J=8.4 Hz, C3-H), 5.45 (1H, q, J=6.5 Hz, C13-H), 5.16 (1H, br s, NH), 3.86 (1H, br s, C9-H), 3.86 (3H, s, OCH3), 3.62 (3H, br s, NHCO2C*H*3), 3.20 (1H, br d, J=16.9 Hz, C10-H), 2.94 (1H, d, J=16.9 Hz, C10-H), 2.71 (1H, d, J=16.3 Hz, C6-H), 2.61 (1H, br d, J=16.3 Hz, C6-H), 1.72 (3H, d, J=6.5 Hz, C14-H). EIMS (m/z): 344 (M^+, 96), 329 (16), 312 (11), 299 (16), 285 (23), 269 (69), 254 (39), 239 (23), 224 (100), 210 (22), 199 (10), 184 (7), 167 (8), 154 (7), 142 (5), 128 (5), 115 (7), 91 (8), 77 (9), 59 (26). HREIMS (m/z): Calcd. for $C_{18}H_{20}N_2O_5$ (M^+): 344.1370. Found: 344.1364. Oxalyl chloride (0.18 mL, 2.0 mmol) and DMF (1 drop) were added to a solution of crude **45** (164 mg) in CH_2Cl_2 (5.0 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. The residue was dissolved in EtOH (5.0 mL). The ethanolic solution was stirred at room temperature for 1 h, poured into H_2O, neutralized with saturated aqueous $NaHCO_3$, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 3:1) to give **46** as colorless prisms (118 mg, 78% from **43**), mp 175-176 °C (from C_6H_{14}-EtOAc). IR (KBr): 3360 (m), 2980 (m), 2940 (m), 1710 (s), 1650 (m), 1600 (m), 1580 (m), 1530 (m), 1475 (s), 1420 (m), 1320 (s), 1260 (s), 1220 (m), 1090 (m), 1040 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 7.58 (1H, d, J=8.6 Hz, C4-H), 7.00 (1H, dd, J=5.4, 2.1 Hz, C8-H), 6.57 (1H, d, J=8.6 Hz, C3-H), 5.45 (1H, q, J=6.8 Hz, C13-H), 5.18 (1H, br s, NH), 4.16-4.04 (2H, m, CO2C*H*2CH3), 3.89-3.87 (1H, br s, C9-H), 3.87 (3H, s, OCH3), 3.62 (3H, br s, NHCO2C*H*3), 3.21 (1H, dd, J=16.9, 4.7 Hz, C10-H), 2.94 (1H, dd, J=16.9, 1.5 Hz, C10-H), 2.77 (1H, d, J=16.2 Hz, C6-H), 2.63 (1H, d, J=16.2 Hz, C6-H), 1.72 (3H, d, J=6.8 Hz, C14-H), 1.23 (3H, t, J=7.1 Hz, CO2CH2C*H*3). EIMS (m/z): 372 (M^+, 82), 357 (10), 343 (22), 327 (23), 313 (16), 297 (35), 282 (22), 268 (38), 251 (19), 239 (19), 224 (100), 210 (14), 199 (7), 180 (6), 167 (5), 84 (34). HREIMS (m/z): Calcd. for $C_{20}H_{24}N_2O_5$ (M^+): 372.1684. Found: 372.1697.

(5*R,9*R**,11*E*)-5-Amino-7-ethoxycarbonyl-11-ethylidene-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]-pyridin-2(1*H*)-one (47)**

Iodotrimethylsilane (0.34 mL, 2.4 mmol) was added dropwise to a solution of **46** (89.0 mg, 0.24 mmol) in $CHCl_3$ (3.0 mL) at room temperature under argon, and the reaction mixture was heated at reflux for 8 h.[17] After MeOH (1.0 mL) was added, the reflux was continued for 4 h. After concentration *in vacuo*, the residue was dissolved in EtOAc. After addition of 10% aqueous $Na_2S_2O_3$ until the yellow color disappeared, the aqueous mixture was washed successively with saturated aqueous $NaHCO_3$, H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (EtOAc/MeOH, 10:1) to give **47** as colorless prisms (55.8 mg, 78%), mp 244-245 °C (from EtOAc-MeOH). IR (KBr): 3380 (m), 3280(m), 2980 (m), 2940 (m), 1710 (s), 1660 (s), 1615 (s), 1560 (s), 1460 (s), 1430 (m), 1410 (m), 1380 (m), 1310 (m), 1250 (s), 1090 (m), 1140 (m), 1090 (s), 1050 (m), 840 (m), 740 (m), 660 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 13.24 (1H, br s, CONH), 7.92 (1H, d, J=9.5 Hz, C4-H), 6.93 (1H, dd, J=5.4, 2.2 Hz, C8-H), 6.43 (1H, d, J=9.5 Hz, C3-H), 5.59 (1H, q, J=6.8 Hz, C13-H), 4.12 (2H, q, J=7.2 Hz, CO2C*H*2CH3), 3.82 (1H, br t, J=5.3 Hz, C9-H), 3.02 (1H, dd, J=17.1, 5.5 Hz, C10-H), 2.86 (1H, dd, J=17.1, 1.3 Hz, C10-H), 2.71 (1H, d, J=17.3 Hz, C6-H), 2.26 (1H, d, J=17.3 Hz, C6-H), 1.69 (3H, d, J=6.8 Hz, C14-H), 1.50 (2H, br s, NH2), 1.24 (3H, t, J=7.2 Hz, CO2CH2C*H*3). EIMS (m/z): 300 (M^+, 100), 285 (40), 271 (28), 255 (20), 239 (12), 227 (90), 211 (47), 199 (12), 187 (70), 173 (19), 160 (12), 147 (9), 130 (5), 106 (7), 84 (22). HREIMS (m/z): Calcd. for $C_{17}H_{20}N_2O_3$ (M^+): 300.1472. Found: 300.1470. Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.80; H, 6.73; N, 9.24.

(5*R,9*R**,11*E*)-5-Amino-11-ethylidene-5,6,9,10-tetrahydro-7-hydroxymethyl-5,9-methanocycloocta[*b*]-pyridin-2(1*H*)-one (48)**

A solution of diisobutylaluminum hydride in C_6H_{14} (0.93M solution, 2.89 mL, 2.7 mmol) was added to a solution of **47** (80.7 mg, 0.27 mmol) in THF (2.0 mL) at -78 °C under argon.[15] After stirring was continued for 1 h, the reaction mixture was added to a solution of sodium potassium tartrate (0.2 mL). After dilution with EtOAc, the precipitates were filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (THF/MeOH, 10:1) to give **48** as colorless prisms (47.6 mg, 69%), mp 243-245 °C (from EtOAc-MeOH). IR (KBr): 3280 (m), 2930 (m), 1655 (s), 1610 (s), 1560 (m), 1460 (s), 1430 (m), 1300 (m), 1120 (m), 1070 (m), 930 (m), 840 (m), 730 (m) cm^{-1}. ^{1}H-NMR (400 MHz, CD3OD) δ: 7.94 (1H, d, J=9.5 Hz, C4-H), 6.38 (1H, d, J=9.5 Hz, C3-H), 5.72 (1H, d, J=5.0 Hz, C8-H), 5.61 (1H, q, J=6.8 Hz, C13-H), 3.84 (1H, d, J=13.5 Hz, CH2OH), 3.79 (1H, d, J=13.5 Hz, CH2OH), 3.75 (1H, br t, J=4.9 Hz, C9-H), 2.85 (1H, dd, J=17.1, 5.3 Hz, C10-H), 2.65 (1H, dd, J=17.1, 1.5 Hz, C10-H), 2.30 (1H, d, J=16.6 Hz, C6-H), 2.24 (1H, d, J=16.6 Hz, C6-H), 1.72 (3H, d, J=6.8 Hz, C14-H). EIMS (m/z): 358 (M^+, 90), 243 (40), 227 (100), 211 (32), 198 (16), 187 (72), 173 (27), 161 (23), 148 (11), 130 (8), 117 (6),

106 (7), 91 (10). HREIMS (m/z): Calcd. for $C_{15}H_{18}N_2O_2$ (M^+): 258.1366. Found: 258.1364. Anal. Calcd. for $C_{15}H_{18}N_2O_2 \cdot 1/2H_2O$: C, 67.39; H, 7.16; N, 10.48. Found: C, 67.37; H, 7.03; N, 10.29.

(5*R,9*R**,11*E*)-5-Amino-11-ethylidene-7-fluoromethyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]-pyridin-2(1*H*)-one [(±)-12-fluorohuperzine A] (5)**

A solution of DAST (66.0 mg, 0.41 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of **48** (10.6 mg, 41 μmol) in CH_2Cl_2 (40 mL) at -78 °C under argon.[23] After stirring for 2 h, the reaction mixture was concentrated *in vacuo*, neutralized with saturated aqueous $NaHCO_3$, then extracted with EtOAc. The combined organic extracts were washed with brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (EtOAc/MeOH 10:1) to give **5** as a colorless amorphous solid (1.8 mg, 17%). IR (KBr): 3380 (m), 3280 (m), 2930 (m), 1660 (s), 1610 (s), 1560 (m), 1460 (s), 1430 (m), 1310 (m), 1120 (m), 980 (m), 840 (m), 730 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.70 (1H, br s, CONH), 7.92 (1H, d, J=9.5 Hz, C4-H), 6.43 (1H, d, J=9.5 Hz, C3-H), 5.80 (1H, br s, C8-H), 5.56 (1H, q, J=6.8 Hz, C13-H), 4.61 (2H, d, JH-F=47.5 Hz, C12-H), 3.72 (1H, m, C9-H), 2.95 (1H, dd, J=17.1, 5.4 Hz, C10-H), 2.75 (1H, dd, J=17.1, 1.3 Hz, C10-H), 2.32 (1H, d, J=16.7 Hz, C6-H), 2.19 (1H, d, J=16.7 Hz, C6-H), 1.70 (3H, d, J=6.8 Hz, C14-H), 1.65 (2H, br s, NH2). ^{19}F-NMR ($CDCl_3$) δ: -215.0 (t, J=49 Hz). EIMS (m/z): 260 (M^+, 100), 245 (57), 227 (43), 211 (21), 198 (12), 187 (58), 173 (13), 160 (9), 147 (10), 130 (5), 106 (7), 106 (7), 84 (13). HREIMS (m/z): Calcd. for $C_{15}H_{17}FN_2O$ (M^+): 260.1324. Found: 260.1338.

(5*R,9*R**,11*E*)-Methyl [11-ethylidene-5,6,9,10-tetrahydro-7-iodo-2-methoxy-5,9-methanocycloocta[*b*]-pyridin-5(6*H*)-yl]carbamate (51a) and (5*R**,9*R**,11*E*)-Methyl [11-ethylidene-9,10-dihydro-7-iodo-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(8*H*)-yl]carbamate (51b)**

A solution of **49** (804 mg, 2.5 mmol), hydrazine monohydrate (0.77 mL, 13 mmol), and Et_3N (2.8 mL, 20 mmol) in EtOH (10 mL) was heated at 70 °C for 1.5 h under argon.[23] The reaction mixture was poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* gave crude hydrazone **50** as a colorless oil. This was immediately used for the next step without purification. A solution of 1,1,3,3-tetramethylguanidine (2.1 g, 13 mmol) and I_2 (1.94 g, 7.6 mmol) in C_6H_5Me (5.0 mL) was added to a solution of **50** in C_6H_5Me (10 mL) at 0 °C under argon. After stirring at 0 °C for 30 min, the reaction mixture was diluted with EtOAc, and washed successively with 10% aqueous $Na_2S_2O_3$, H_2O, and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 4:1) to give a mixture of **51a** and **51b** as a colorless amorphous solid (950 mg, 88%). The ratio of **51a** to **51b** was estimated as *ca.* 1:1 by comparing the ^{1}H-NMR spectrum with those of pure **51a** and **51b**. Analytical samples of **51a** and **51b** were obtained by preparative thin layer chromatography (C_6H_{14}/EtOAc, 4:1). **51a**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.57 (1H, d, J=8.6 Hz, C4-H), 6.59 (1H, d, J=8.6 Hz, C3-H), 6.35 (1H, br d, J=3.6 Hz, C8-H), 5.40 (1H, q, J=6.8 Hz, C12-H), 4.96 (1H, br s, NH), 3.89 (3H, s, OCH_3), 3.71 (1H, br s, C9-H), 3.62 (3H, s, $NHCO_2CH_3$), 3.28-2.88 (3H, m, C10-H x 2, C6-H), 2.80 (1H, d, J=16.0 Hz, C6-H), 1.73 (3H, d, J=6.8 Hz, C13-H). EIMS (m/z): 426 (M^+), 299, 239, 224, 213, 201, 174, 115, 84. **51b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.49 (1H, d, J=8.6 Hz, C4-H), 6.52 (1H, d, J=8.6 Hz, C3-H), 6.43 (1H, br s, C6-H), 5.41 (1H, q, J=6.8 Hz, C12-H), 4.98 (1H, br s, NH), 3.88 (3H, s, OCH_3), 3.71 (3H, s, $NHCO_2CH_3$), 3.51 (1H, t, J=6.0 Hz, C9-H), 3.38 (1H, dd, J=17.0, 5.0 Hz, C10-H), 3.06 (1H, dd, J=17.0 Hz, C8-H), 2.91 (1H, dd, J=17.0 Hz, C10-H), 2.66 (1H, d, J=17.0 Hz, C8-H), 1.75 (3H, d, J=6.8 Hz, C13-H). EIMS (m/z): 426 (M^+), 299, 239, 224, 213, 201, 174, 115, 84.

(5*R,9*R**,11*E*)-Methyl [11-ethylidene-7-formyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]-pyridin-5(6*H*)-yl]carbamate (44) and (5*R**,9*R**,11*E*)-Methyl [11-ethylidene-7-formyl-9,10-dihydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(8*H*)-yl]carbamate (52)**

A solution of the mixture of **51a** and **51b** (*ca.* 1:1) (950 mg, 2.2 mmol) and tetrakis(triphenylphosphine)palladium (130 mg, 0.11 mmol) in C_6H_5Me (10 mL) was stirred at 50 °C for 10 min under carbon monoxide. A solution of tri-*n*-butyltin hydride (714 mg, 2.5 mmol) in C_6H_5Me (20 mL) was slowly added over 4 h using a syringe pump. The mixture was stirred for another 2.5 h. After cooling, the mixture was poured into aqueous KF solution, stirred for 1 h, then extracted with Et_2O.[24] The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C_6H_{14}/EtOAc, 2:1) to give **44** (315 mg, 43%) and **52** (290 mg, 40%) both as a colorless amorphous solid. **44**: IR (KBr): 3340 (m), 2940 (m), 2840 (m), 1720 (s), 1680 (s), 1640 (m), 1600 (s), 1580 (m), 1520 (s), 1480 (s), 1420 (s), 1380 (m), 1320 (s), 1260 (s), 1185 (m), 1175 (m), 1140 (m), 1060 (m), 1040 (m), 840 (m), 730 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.35 (1H, s, CHO), 7.56 (1H, d, J=8.6 Hz, C4-H), 6.85 (1H, dd, J=5.2, 1.9 Hz, C8-H), 6.57 (1H, d, J=8.6 Hz, C3-H), 5.49 (1H, q, J6.8 Hz, C13-H), 5.18 (1H, br s, NH), 4.03 (1H, br t, J=4.9 Hz, C9-H), 3.86 (3H, s, OCH_3), 3.62 (3H, br s, $NHCO_2CH_3$), 3.31 (1H, dd, J=17.0, 4.7 Hz, C10-H), 2.98 (1H, dd, J=17.0, 1.8 Hz, C10-H), 2.73 (1H, d, J=16.2 Hz, C6-H), 2.50 (1H, d, J=16.2 Hz, C6-H), 1.75 (3H, d, J=6.8 Hz, C14-H). EIMS (m/z): 328 (M^+, 100), 313 (11), 299 (20), 285 (6), 267 (21), 253 (58), 238 (22), 224 (54), 210 (19), 195 (6), 167 (6), 84 (17). HREIMS (m/z): Calcd. for $C_{18}H_{20}N_2O_4$ (M^+): 328.1421. Found: 328.1406. **52**: IR (KBr): 3330 (m), 2950 (m), 2840 (m), 1730 (s), 1680 (s), 1640 (m), 1595 (s), 1520 (s), 1480 (s), 1430 (s), 1320 (s), 1250 (s), 1190 (m), 1160 (m), 1100 (m), 1080 (m), 1040 (m), 830 (m), 740 (m) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.36 (1H, s, CHO), 7.62 (1H, d, J=8.6 Hz, C4-H), 7.27 (1H, s, C6-H), 6.55 (1H, d, J=8.6 Hz, C3-H), 5.48 (1H, q, J=6.8 Hz, C13-H), 5.19 (1H, br s, NH), 3.87 (3H, s, OCH_3), 3.75 (3H, br s, $NHCO_2CH_3$), 3.72 (1H, t, J=7.3 Hz, C9-H), 3.30 (1H, dd, J=18.6, 7.6 Hz, C10-H), 2.85 (1H, d, J=18.6 Hz, C10-H), 2.67 (1H, dd, J=18.3, 6.5 Hz, C8-H), 2.48 (1H, d, J=18.3 Hz, C8-H), 1.77 (3H, d, J=6.8 Hz, C14-H). EIMS (m/z): 328 (M^+, 100), 313 (11), 299 (35), 285 (7), 269 (22), 253 (20), 239 (8), 224 (25), 210 (14), 188 (5), 174 (6), 160 (6), 148 (6), 123 (7), 84 (14). HREIMS (m/z): Calcd. for $C_{18}H_{20}N_2O_4$ (M^+): 328.1421. Found: 328.1404.

Biological activity

Inhibitory activity against AChE was evaluated according to the modified protocol of Ellman *et al.*[25] AChE sourced from rat cortex was used for the experiments and the results were expressed by the value of IC_{50}.

References and Notes

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