Ligands for Brain Cholinergic Channel Receptors: Synthesis and *in Vitro* Characterization of Novel Isoxazoles and Isothiazoles as Bioisosteric Replacements for the Pyridine Ring in Nicotine

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Ligands which activate neuronal nicotinic acetylcholine receptors (nAChRs) represent a potential approach for the palliative treatment for the symptoms of memory loss associated with Alzheimer's disease (AD). Based upon this approach, a series of novel 3,5-disubstituted isoxazoles and isothiazoles were prepared and evaluated *in vitro* as cholinergic channel activators (ChCAs) of neuronal nAChRs. Many of the 3-substituted 5-(2-pyrrolidinyl)isoxazoles were found to have nanomolar binding affinities comparable to (*S*)-nicotine (**2a**) in a preparation of whole rat brain. However, in a paradigm measuring the evoked release of [^{3}H]dopamine from a preparation of rat striatum, there were differences in the agonist potencies and efficacies of these analogues relative to **2a**. The differences in agonist potency observed between compounds of comparable binding potency may be due to differences in ligand interactions with various subtypes of neuronal nAChRs.

Introduction

Alzheimer's disease (AD) is a central nervous system neurodegenerative disorder affecting up to 10% of the population over the age of 65. Currently, it is the forth leading cause of death in the developed world and it is anticipated that as the size of the elderly population increases, so will the number of people afflicted with AD. Although the etiology of AD is not yet known, neurochemical studies performed on autopsied brain tissue have shown that the disease adversely affects a number of brain neurochemical systems. Of all the abnormalities noted, the most pronounced and consistent change is a deficiency in markers of cholinergic tone in the neocortex and hippocampus. The degree of cholinergic dysfunction has been correlated with the severity of dementia and these collective findings have led to the cholinergic hypothesis of AD-related memory loss.[1-3]

Pilot clinical studies have suggested that (*S*)-nicotine (**2a**) may be useful in the palliative treatment of deficits in attention and information processing associated with AD.[4,5] Since **2a** also produces a number of adverse side effects including irritations of the gastrointestinal tract[6,7] and negative effects upon the cardiovascular system,[8-12] it does not represent an optimal entity for the safe and effective treatment of the symptoms of memory loss associated with AD. The shortcomings of **2a**, coupled with the existence of a diversity of mRNAs which code for the component protein subunits which form nAChRs[13,14] prompted our efforts to prepare cholinergic channel activators (ChCAs) which might be differentiated from **2a**. By selectively interacting with the appropriate putative subtypes of neuronal nAChRs, it was felt that it might be possible to prepare ChCAs which retain the ability to produce the beneficial actions associated with neuronal nAChR stimulation by **2a** while also having a dramatically reduced propensity to elicit adverse side effects. Such ChCAs represent a potentially novel class of psychoactive drugs for the safe and effective treatment of AD.[15]

3b * = (R) R = H **1b** * = (R) R = H
4a * = (S) R = CH_3 **2a** * = (S) R = CH_3

Figure 1. The structures of **3b** and **4a** with the corresponding nornicotine (**1b**) and nicotine (**2a**) standards.

Recently, reports from these laboratories have described the synthesis, receptor binding properties, and rodent behavioral activities of **ABT-418 (4a)** and **A-82695 (3b)**, two novel ChCAs in which a substituted isoxazole ring has been incorporated as a bioisosteric replacement for the pyridine ring found in (*S*)-nicotine (**2a**) and (*R*)-nornicotine (**1b**), respectively (Figure **1**).[16-18] From receptor binding studies, it was found that both **4a** and **3b** have binding potencies comparable to **2a**; however, their abilities to elicit various behavioral effects differed significantly. Beneficial cognitive enhancing activity as well as anxiolytic effects were observed in mice at doses of **4a** and **3b** which were 10–30-fold lower than the doses of **2a** required to produce the same effects. Evaluation of these compounds for adverse effects showed that the doses of **3b** or **4a** required to produce negative effects were at dose levels 6–100-fold higher than those at which **2a** showed significant liabilities.

The variety of behavioral effects elicited by **2a** *in vivo* may be pharmacologically attributed to its ability to modulate the release of several neurotransmitters including noradrenaline, dopamine, acetylcholine, and 5-hydroxytryptamine from several different brain re-

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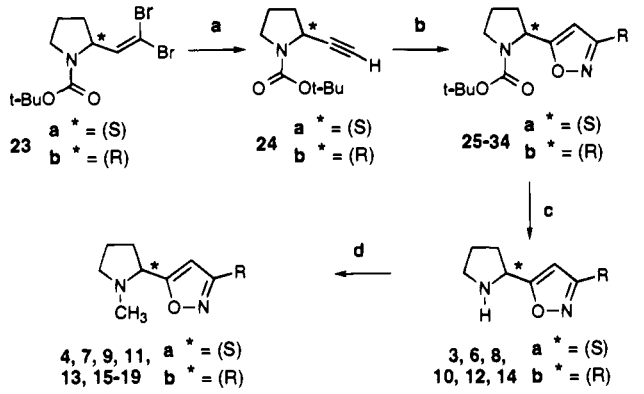
Scheme 1[a]



[a] Reagents: (a) *n*-BuLi, THF, −78 °C, then $NaHCO_3$ (aq); (b) PhNCO, Et_3N, RCH_2NO_2, benzene; or $RCH_2C(N{=}OH)Cl$, base (c) TFA–CH_2Cl_2; (d) 37% (CH_2O) (aq), 88% HCO_2H, reflux.

gions.[19] To develop a better understanding of the structure–activity relationships (SAR) associated with **4a** and **3b**, an expanded series of disubstituted isoxazoles and isothiazoles have been prepared and characterized *in vitro* with respect to their brain nAChR binding affinities at the sites labeled by [^{3}H]cytisine as well as in a functional assay measuring the evoked release of [^{3}H]dopamine.

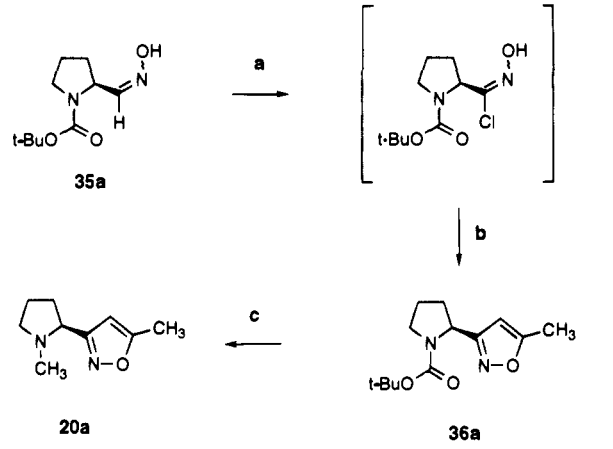
Chemistry

The nornicotine enantiomers **1a** and **1b** were resolved via HPLC on a chiral column.[16] The 3-substituted 5-(2-pyrrolidinyl)isoxazoles **3**–**19** were prepared as outlined in Scheme 1. The dibromovinyl derivative **23**[20] was converted to the terminal acetylene **24**. Reacting compound **24** with a nitrile oxide generated *in situ* from either a nitro or hydroximoyl chloride precursor afforded the protected isoxazole derivatives **25**–**34**. Nitrogen deprotection gave the product secondary amines **3, 6, 8, 10, 12,** and **14**. Deprotection and the N-methylation under Eschweiler–Clarke conditions afforded the tertiary amines **4, 7, 9, 11, 13, 15**–**19**. The *N*-ethylpyrrolidine **5a** was prepared by acetylation of **3a** followed by $LiAlH_4$ reduction. As evidence that racemization did not occur during the synthetic sequence, the enantiomeric purities of **4a** and **4b** were determined to be >99% ee by HPLC assay on a chiral column.[16]

The 3-methyl-5-(2-pyrrolidinyl)isoxazole **20a** was prepared as outlined in Scheme 2. The oxime **35a** prepared from the protected (*S*)-prolinal was converted to the chloro oxime by treatment with *N*-chlorosuccinimide. Generation of the corresponding nitrile oxide and reaction with 2-bromopropene in the presence of excess triethylamine afforded **36a**. Deprotection of the nitrogen followed by N-methylation gave the desired product **20a**.

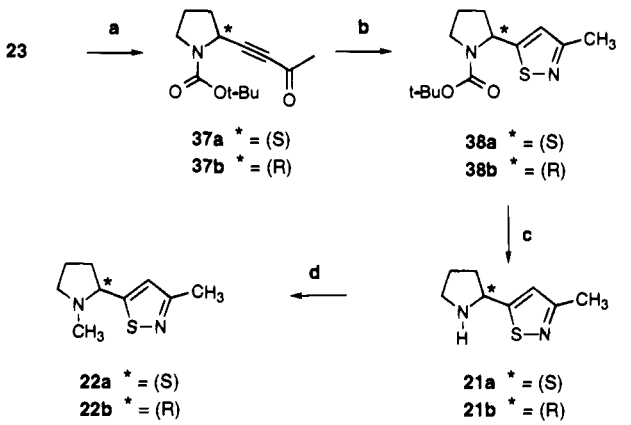
The isothiazoles **21** and **22** were prepared as outlined in Scheme 3. The (*S*)- and (*R*)-vinyl dibromides **23** were independently converted to the acetylide anions by the action of *n*-butyllithium and then quenched with acetaldehyde. Swern oxidation of the resulting alcohols produced the ketones **37**, which were then transformed into the protected isothiazoles **38** following the procedure of Lucchesini et al.[21] Deprotection of the pyrrolidine nitrogens gave the secondary amines **21**, which were N-methylated to afford **22**.

Scheme 2[a]



[a] Reagents: (a) NCS, $ClCH_2CH_2Cl$, 0 °C; (b) 2-Bromopropene, Et_3N, $ClCH_2CH_2Cl$; (c) TFA–CH_2Cl_2, then 37% (CH_2O) (aq), 88% HCO_2H, reflux.

Scheme 3[a]



[a] Reagents: (a) *n*-BuLi, THF, −78 °C, then CH_3CHO, then $(COCl)_2$, DMSO, −60 °C, Et_3N; (b) H_2NOSO_3H, CH_3OH–H_2O, then NaSH, $NaHCO_3$; (c) HCl–dioxane; (d) 37% (CH_2O) (aq), 88% HCO_2H, reflux.

Pharmacology

Compounds were evaluated for their binding affinities to neuronal nAChRs by measuring the displacement of [^{3}H]cytisine from a preparation of whole rat brain according to the procedure described by Arneric et al.[17] The binding results of the test compounds have been normalized to their equilibrium dissociation constants (K_i).

Ligand intrinsic activity responses were determined by measuring the magnitude of the neuronal nAChR-evoked [^{3}H]dopamine released from a prelabeled superfused preparation of rat striatial slices as described by Arneric et al.[17] Studies from our laboratories utilizing this assay have shown that the evoked release response produced by the ChCA standard **2a** reaches a maximum which begins to plateau at a concentration of approximately 0.1 μM. Thus, all of the test compounds were evaluated at a single high dose concentration of 10 μM, and the results are expressed as a percentage of the response evoked by the agonist standard **2a** which is defined as producing a 100% response at a concentration of 0.1 μM. Release responses were blocked by the competitive nAChR antagonist dihydro-β-erythroidine (10 μM). Abbreviated "three-point" dose–response curves

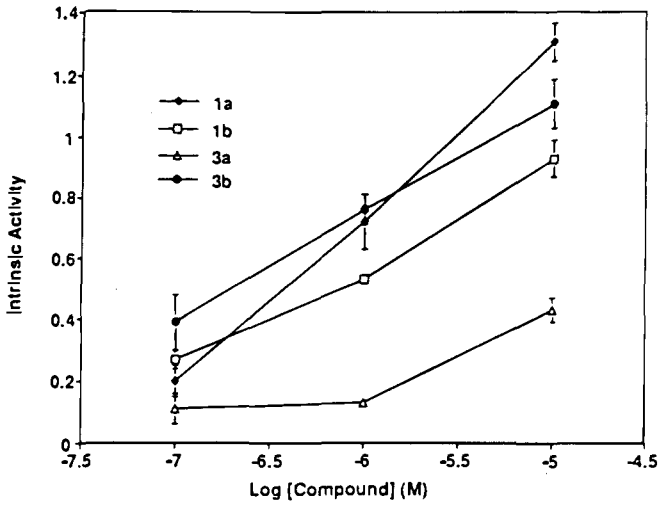


Figure 2. Abbreviated dose–response curves for the evoked release of [^{3}H]dopamine from rat striatum for the N-unsubstituted pyrrolidines **1a**, **1b**, **3a**, and **3b**. Intrinsic activities are normalized to the response produced by **2a** at a concentration of 10^{-7} M, which is defined as 1.

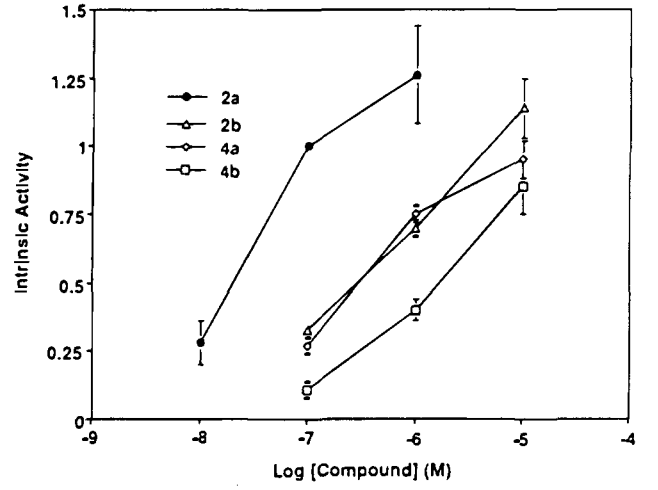


Figure 3. Abbreviated dose–response curves for the evoked release of [^{3}H]dopamine from rat striatum for the N-methylated pyrrolidines **2a**, **2b**, **4a**, and **4b**. Intrinsic activities are normalized to the response produced by **2a** at a concentration of 10^{-7} M, which is defined as 1.

were generated for the ChCA standards **1** and **2** as well as the isoxazoles **3** and **4** and are shown in Figures 2 and 3.

Results and Discussion

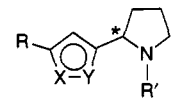
The binding and single concentration intrinsic activity profiles of the standards **1** and **2** along with the novel isoxazole and isothiazole analogues **3–22** are shown in Table 1. N-Methylation of **1** enhances the binding affinity of the compound in the (*S*)-enantiomeric series while for the (*R*)-enantiomeric form it has no effect. From the binding SAR of the 3-substituted 5-(2-pyrrolidinyl)isoxazoles (**3–19**), it is apparent that potent nanomolar affinity to brain nAChRs can be achieved with compounds having either the (*S*)- or the (*R*)-configuration. Interestingly, N-methylation of the pyrrolidine nitrogen produces divergent trends in binding potency between the enantiomeric series of isoxazole compounds. For the (*S*)-enantiomers, there is a consistent enhancement in the binding potency of at least 50-fold which appears to be independent of the substituent at the 3-position of the isoxazole. A methyl group on the pyrrolidine nitrogen is optimal, as there is a drop in the binding potency of the *N*-ethyl analogue **5a**. With the (*R*)-enantiomeric series, the unsubstituted pyrrolidines **3b** and **6b** have potencies which are approximately 7.5-fold higher than the corresponding *N*-methyl analogues **4b** and **7b**.

A variety of substituents have been incorporated at the 3-position of the isoxazole ring of compounds with the (*S*)-configuration. Lipophilic substituents of small to intermediate size are well-tolerated with respect to brain nAChR binding. Lower straight chain alkyls (**4a, 7a, 9a, 15a**), the benzyl derivative **13a**, the ether **18a**, and the trifluoromethyl derivative **19a** all bind with K_i values of less than 25 nM. More polar substituents such as the ester **16a** and the alcohol **17a** bind with significantly lower affinity. The low binding potency of the phenyl-substituted derivative **11a** suggests that branching at the position adjacent to the heteroaromatic ring is not tolerated.

Table 1. Neuronal nAChR *in Vitro* Profile

Standards

no.	conf	compd	binding affinity[a] (K_i, nM)	% dopamine release[a,d]
1a	*S*	nornicotine	22.0 ± 3.0	155 ± 2
1b	*R*	nornicotine	17.0 ± 2.0	93 ± 6
2a	*S*	nicotine	1.1 ± 0.4	126 ± 18[b]
2b	*R*	nicotine	16.0 ± 3.4	114 ± 11



Analogues

no.	conf	structure R	structure R'	binding affinity[a] (K_i nM)	% dopamine release[a,d]
			X = N, Y = O		
3a	*S*	CH_3	H	333 ± 35	43 ± 4
3b	*R*	CH_3	H	7.4 ± 0.7	111 ± 4
4a	*S*	CH_3	CH_3	4.2 ± 0.6	95 ± 7
4b	*R*	CH_3	CH_3	52.9 ± 12.4	85 ± 10
5a	*S*	CH_3	C_2H_5	34.3 ± 4.0	64 ± 11
6a	*S*	C_2H_5	H	552 ± 63	30 ± 5
6b	*R*	C_2H_5	H	11.7 ± 0.1	79 ± 21
7a	*S*	C_2H_5	CH_3	7.6 ± 0.3	78 ± 8
7b	*R*	C_2H_5	CH_3	71.0 ± 6.3	46 ± 6
8a	*S*	n-C_3H_7	H	>10000	
9a	*S*	n-C_3H_7	CH_3	14.0 ± 1.8	45 ± 4
10a	*S*	C_6H_5	H	>10000	
11a	*S*	C_6H_5	CH_3	788 ± 160	
12a	*S*	$CH_2C_6H_5$	H	3500[c]	
13a	*S*	$CH_2C_6H_5$	CH_3	7.4 ± 0.7	30 ± 6
14a	*S*	n-C_4H_9	H	5000[c]	
15a	*S*	n-C_4H_9	CH_3	24.2 ± 1.4	38 ± 8
16a	*S*	$CO_2C_2H_5$	CH_3	890 ± 84	
17a	*S*	CH_2OH	CH_3	126 ± 20	41 ± 10
18a	*S*	CH_2OCH_3	CH_3	21.9 ± 5.7	51 ± 4
19a	*S*	CF_3	CH_3	6.1 ± 2.0	92 ± 16
			X = O, Y = N		
20a	*S*	CH_3	CH_3	1333 ± 333	
			X = N, Y = S		
21a	*S*	CH_3	H	51 ± 5	61 ± 6
21b	*R*	CH_3	H	228 ± 23	56 ± 3
22a	*S*	CH_3	CH_3	222 ± 14	41 ± 5
22b	*R*	CH_3	CH_3	207 ± 30	22 ± 2

[a] Values are the means ±SEM. [b] Value was determined at the analogue concentration of 10^{-6} M. [c] Mean value of two determinations. [d] Percent relative to **2a** at 10^{-7} M.

The substitution pattern as well as the heteroatoms contained within the 5-membered aromatic ring both appear to be very important. Isoxazole **20a**, which has the position of the nitrogen and oxygen inverted relative to **4a**, has only micromolar binding affinity. Replacement of the oxygen atom in the aromatic heterocycle of compounds **3** and **4** with a sulfur yields the corresponding isothiazoles **21** and **22**. With the exception of the pyrrolidine unsubstituted (*S*)-enantiomer **21a**, this modification resulted in analogues which have lower neuronal nAChR binding potencies than their isoxazole counterparts.

In contrast to the lack of effects that relatively small changes in the steric size of the lipophilic substituent at 3-position of the isoxazole has upon binding affinity, these modifications were found to have a much greater modulatory effect upon the maximal agonist response in the dopamine release assay. Substituents with minimal steric requirements such as the methyl group found in **3b** and **4a**, the ethyl group in **6b** and **7a**, and trifluoromethyl functionality in **19a** afforded analogues which produced a robust agonist response. In contrast, larger lipophilic substituents at this position yielded compounds which were at best only partial agonists in the functional assay. The three-point dose–response curves for **1**–**4** shown in Figures 2 and 3 further illustrate the potency differences of the agonists which were evaluated. With the exception of **1a**, all of the other analogues included in the Figures appear as full agonists, however, the maximal response achieved with **2a** is at a concentration at least 1 order of magnitude lower than any of the other compounds tested.

[^{3}H]-(−)-Cytisine has been shown to bind with high affinity to the $\alpha4\beta2$ subtype of nAChR, the major subtype in rodent brain, accounting for greater than 90% of the (−)-nicotine binding sites.[22,23] On the other hand, the stimulated release of dopamine from rat striatial slices has been suggested to involve $\alpha3$ subunit activation.[24] Thus, the differences in the agonist potencies relative to the binding potencies upon comparison of the *in vitro* profiles of the standards with many of the isoxazole analogues may be the result of selective interactions of these ChCAs with different subtypes of neuronal nAChRs. Such a selective interaction of ChCAs with subtypes of nAChRs may also contribute to the potency differences observed *in vivo* with compounds which show a much greater therapeutic window with respect to the production of beneficial behavioral effects as opposed to the undesirable side effects also associated with nAChR activation.

In summary, a number of suitably substituted isoxazoles have been identified as potent bioisosteric replacements of the pyridine ring found in **2** when the ligands are evaluated at neuronal nAChRs. Many of the isoxazole ChCAs have binding potencies to the neuronal $\alpha4\beta2$ subtype which differ by less than 10-fold. In contrast, when their intrinsic activities are measured in a evoked dopamine release assay which is believed to involve the activation of a neuronal nAChR containing an $\alpha3$ subunit, the variation in potency for the same compounds is greater than 1 order of magnitude. Selective interaction of ChCAs with subtypes of neuronal nAChRs may explain the potency differences observed between these two *in vitro* assays and may also play a part in the explaining the potency variations with respect to positive as well as negative effects produced *in vivo*.

Experimental Section

Proton magnetic resonance spectra were obtained on a General Electric GN-300 (300 MHz) instrument or, where specified, a General Electric GN-500 (500 MHz) instrument. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Mass spectra were obtained with a Hewlett-Packard HP5965 spectrometer. These determinations were performed by the PPD Analytical Research Department, Abbott Laboratories. Elemental analyses were obtained from Robertson Microlit Laboratories, Inc. (Madison, NJ).

Flash chromatography was carried out using Merck silica gel 60 (200–400 mesh) and column chromatography was carried out using Merck silica gel 60 (70–230 mesh). Melting points are uncorrected and were determined on a Büchi melting point apparatus. Optical rotation data was obtained on a Perkin-Elmer Model 241 polarimeter. All reactions were performed under an inert atmosphere of nitrogen and with anhydrous solvents unless otherwise noted.

(2*S*)-2-Ethynyl-*N*-(*tert*-butyloxycarbonyl)pyrrolidine (24a). A solution of **23**a (27.1 g, 76.3 mmol) in THF (550 mL) was cooled to −75 °C using a dry ice bath, and then a 2.5 *M* solution of *n*-butyllithium in hexane (62.6 mL, 156.5 mmol) was added dropwise over a 15 min period. After stirring for 1 h, saturated aqueous sodium bicarbonate was added dropwise to the reaction flask. The dry ice bath was removed and an additional portion of saturated aqueous sodium bicarbonate was added. The mixture was extracted with EtOAc (3×), and the combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (diethyl ether/hexane 1:6 → 1:5) to give 11.5 g (77% yield) of the product as an oil: $[\alpha]^{23}_D = -92.1°$ (*c* 2.20, MeOH); MS (CI) *m/e* 196 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H) 1.85–2.25 (m, 5 H), 3.24–3.53 (m, 2 H), 4.45 (m, 1 H).

(2*R*)-2-Ethynyl-*N*-(*tert*-butyloxycarbonyl)pyrrolidine (24b): oil; $[\alpha]^{26}_D = +113.0°$ (*c* 0.94, MeOH).

Method A. 3-Methyl-5-(*N*-(*tert*-butyloxycarbonyl)-2-(*S*)-pyrrolidinyl)isoxazole (25a). To a stirred solution of **24a** (1.45 g, 7.43 mmol) and phenyl isocyanate (1.45 mL, 13.37 mmol) in benzene (3.5 mL) was added a benzene (2 mL) solution of triethylamine (10 drops) and nitroethane (535 μL, 7.43 mmol). A precipitate began to form about 2–3 min after addition was complete. The reaction mixture was stirred at ambient temperature for 2 h, heated at reflux for 1.5 h, and then allowed to cool to ambient temperature and stirred overnight. The reaction mixture was then filtered and the filter cake washed with benzene. The filtrate was concentrated *in vacuo* and the residue was purified using flash chromatography (EtOAc/hexane 1:8) to give, after concentration *in vacuo*, 1.02 g (55% yield) of the product as a viscous yellow oil: $[\alpha]^{23}_D = -104.4°$ (*c* 0.90, MeOH); MS (DCI/NH_3) *m/e* 253 $(M + H)^+$, 270 $(M + NH_4)^+$; ^{1}H NMR (DMSO-d_6; 100 °C) δ 1.32 (s, 9 H), 1.80–1.90 (m, 3 H), 2.16 (s, 3 H), 2.19 (m, 1 H), 3.31–3.42 (m, 2 H), 4.87 (dd, 1 H), 6.04 (s, 1 H).

3-Methyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*R*)-pyrrolidinyl)isoxazole (25b) was prepared from **24b** (1.96 g, 10 mmol) according to method A in 60% yield. $[\alpha]^{23}_D = +102.4°$ (*c* 0.70, MeOH).

Method B. 3-Methyl-5-(2(*S*)-pyrrolidinyl)isoxazole (3a). Compound **25a** (880 mg, 3.49 mmol) was dissolved in CH_2Cl_2 (7.5 mL) and cooled to 0 °C. Excess trifluoroacetic acid (7.5 mL) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was concentrated *in vacuo*, leaving an amber oil. The oil was dissolved in saturated aqueous sodium bicarbonate solution and continuously extracted with CH_2Cl_2 for approximately 16 h. The solvent was evaporated and the residue was purified by flash chromatography (5% MeOH/$CHCl_3$ → 10% MeOH/$CHCl_3$) to give 456 mg (86% yield) of the product: $[\alpha]^{23}_D = -13.1°$ (*c* 0.9, MeOH); MS (DCI/NH_3) *m/e* 153 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.80–2.00

(m, 3 H), 1.99 (br s, 1 H), 2.17 (m, 1 H), 2.28 (s, 3 H), 2.96–3.16 (m, 2 H), 4.32 (dd, 1 H), 5.95 (s, 1 H).

3-Methyl-5-(2(*R*)-pyrrolidinyl)isoxazole (3b) was prepared from **25b** (1.41 g, 5.6 mmol) according to method B in 78% yield: $[\alpha]^{23}_D = +11.6°$ (*c* 1.0, MeOH).

Method C. 3-Methyl-5-(2(*S*)-pyrrolidinyl)isoxazole Oxalate (3a·Ox). A solution of **3a** (20 mg, 0.188 mmol) in diethyl ether was prepared. To this solution was added a solution of oxalic acid (25 mg, 0.282 mmol) in diethyl ether in a dropwise fashion with rapid stirring. The resultant white precipitate was filtered and triturated with three portions of diethyl ether. The white solid was recrystallized from CH_3OH/Et_2O to give, after evaporating the residual solvent, 23.7 mg (52% yield) of the product: mp = 133–135 °C; MS (DCI/NH_3) *m/e* 253 $(M + H)^+$, 270 $(M + NH_4)^+$; ^1H NMR (D_2O) δ 2.11–2.33 (m, 3 H), 2.31 (s, 3 H), 2.55 (m, 1 H), 2.48 (dd, 2 H), 4.92 (t, 1 H), 6.52 (s, 1 H). Anal. ($C_8H_{12}N_2O·C_2H_2O_4$) C, H, N.

3-Methyl-5-(2(*R*)-pyrrolidinyl)isoxazole Benzoate (3b·Bz). To a stirred solution of **3b** (855 mg, 5.62 mmol) in diethyl ether was added benzoic acid (755 mg, 6.18 mmol). The reaction was allowed to stir for 1 h, after which time the ether was evaporated. The remaining solid was recrystallized from hot diethyl ether (2×) to give 601 mg (39% yield) of the product as pale-tan long needles: mp = 90.5–91.5 °C; $[\alpha]^{23}_D = +9.5°$ (*c* 0.58, MeOH); MS (DCI/NH_3) *m/e* 153 $(M + H)^+$, 170 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 1.95–2.23 (m, 3 H), 2.22 (s, 3 H), 2.31 (m, 1 H), 3.00–3.32 (m, 2 H), 4.62 (dd, *J* = 7.4 Hz, 5.9 Hz, 1 H), 6.12 (s, 1 H), 7.39–7.44 (m, 2 H), 7.51 (m, 1 H), 8.01–8.04 (m, 2 H), 8.14 (br s, 1 H). Anal. ($C_8H_{12}N_2O·C_7H_6O_2$) C, H, N.

Method D. 3-Methyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (4a). A solution of **3a** (93.5 mg, 0.61 mmol), in a mixture of 37% aqueous formaldehyde (1.5 mL) and 88% aqueous formic acid (1.5 mL), was heated at reflux for 1 h. The reaction mixture was allowed to cool to ambient temperature and was then extracted with diethyl ether. The aqueous layer was made basic (pH ~ 10–11) by sequential addition of saturated aqueous sodium bicarbonate solution and solid potassium carbonate. The basic, aqueous solution was then extracted with three portions of $CHCl_3$ and combined with the remaining organic phase. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1:1) to give 71 mg (70% yield) of the product as a colorless oil: $[\alpha]^{23}_D = -101°$ (*c* 0.68, MeOH); MS (FAB) *m/e* 167 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.78–2.03 (m, 3 H), 2.17–2.42 (m, 2 H), 2.29 (s, 3 H), 2.34 (s, 3 H), 3.17 (m, 1 H), 3.43 (dd, 1 H), 5.99 (s, 1 H).

Method E. 3-Methyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole Hydrochloride (4a·HCl). Compound **4a** (1.04 g, 6.26 mmol) was dissolved in diethyl ether (100 mL) and cooled to 0 °C. While the solution was being stirred, an ethereal solution of HCl was added to the reaction, resulting in the formation of a white precipitate. The solvent was evaporated *in vacuo* and the remaining solid was recrystallized from $MeOH/Et_2O$ to give 543 mg (86% yield) of the product as hygroscopic white needles: mp = 155–157 °C; $[\alpha]^{23}_D = -32.4°$ (*c* 0.58, MeOH); MS (DCI/NH_3) *m/e* 167 $(M + H)^+$, 184 $(M + NH_4)^+$; ^1H NMR (D_2O) δ 2.23–2.48 (m, 3 H), 2.34 (s, 3 H), 2.61 (m, 1 H), 2.92 (br s, 3 H), 3.38 (m, 1 H), 3.77 (m, 1 H), 4.74–4.84 (partly buried in H_2O peak, 1 H), 6.65 (s, 1 H). Anal. ($C_9H_{14}N_2O·HCl$) C, H, N.

3-Methyl-5-(1-methyl-2(*R*)-pyrrolidinyl)isoxazole (4b) was prepared from **3b** (370 mg, 2.23 mmol) according to method D in 64% yield: $[\alpha]^{23}_D = +101.0°$ (*c* 0.76, MeOH).

3-Methyl-5-(1-methyl-2(*R*)-pyrrolidinyl)isoxazole hydrochloride (4b·HCl) was prepared from **4b** (228 mg, 1.38 mmol) according to method E. The white solid obtained was recrystallized from $MeOH/Et_2O$ to give 248 mg (89% yield) of the the product as white needles: mp = 154–155 °C; $[\alpha]^{23}_D = +29.1°$ (*c* 0.80, MeOH). Anal. ($C_9H_{14}N_2O·HCl$) C, H, N.

3-Methyl-5-(1-ethyl-2(*S*)-pyrrolidinyl)isoxazole (5a). Compound **3a** (90 mg, 0.59 mmol) and acetic anhydride (120 mg, 1.2 mmol) were combined in a 1,4-dioxane (1.5 mL) and refluxed for 1 h. The reaction was allowed to cool to ambient temperature and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (2% $MeOH/CHCl_3$) to give 117 mg (100%) of the amide as a clear yellow oil: MS (DCI/NH_3) *m/e* 195 $(M + H)^+$, 212 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 1.86–2.45 (m, 10 H), 3.47–3.74 (m, 2 H), minor conformational isomer 5.00 (d, *J* = 7.0 Hz, 1 H), major isomer 5.30 (dd, *J* = 5.9 Hz, 2.6 Hz, 1 H), minor conformational isomer 5.91 (s, 1 H), major isomer 5.96 (s, 1 H).

The amide (108 mg, 0.56 mmol) in THF (1 mL) was treated with a 1.0 M THF solution of $LiAlH_4$ (506 mL, 0.56 mmol). The reaction was allowed to stir at ambient temperature for 2 h and then worked up under standard conditions. The crude product was then purified using flash chromatography (EtOAc/hexane 1:1) to give 63 mg (63% yield) of the product as a clear oil: MS (DCI/NH_3) *m/e* 181 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ: 1.07 (t, *J* = 7.2 Hz, 3 H), 1.82–2.00 (m, 3 H), 2.14–2.47 (m, 3 H), 2.28 (s, 3 H), 2.72 (dq, *J* = 12.1 Hz, 7.4 Hz, 1 H), 3.23 (m, 1 H), 3.60 (dd, *J* = 8.3 Hz, 6.4 Hz, 1 H), 5.97 (s, 1 H).

3-Methyl-5-(1-ethyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (5a·HCl) was prepared from **5a** (59 mg, 0.33 mmol) according to method E. The white solid obtained was recrystallized from CH_2Cl_2/hexane to give the product as fine white needles in 58% yield: mp = 166–168 °C; $[\alpha]^{23}_D = -33.3°$ (*c* 0.33, MeOH); MS (DCI/NH_3) *m/e* 181 $(M + H)^+$; ^1H NMR (D_2O) δ 1.27 (t, *J* = 7.4 Hz, 3 H), 2.18–2.41 (m, 4 H), 2.31 (s, 3 H), 2.56 (m, 1 H), 3.16 (m, 1 H), 3.28–3.33 (m, 2 H), 3.75 (m, 1 H), 6.61 (s, 1 H). Anal. ($C_{10}H_{16}N_2O·HCl$) C, H, N.

3-Ethyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (26a) was prepared from **24a** (885 mg, 4.45 mmol) and 1-nitropropane according to method A in 52% yield: MS (DCI/NH_3) *m/e* 267 $(M + H)^+$, 284 $(M + NH_4)^+$; ^1H NMR (DMSO-d_6, 100 °C) δ 1.19 (t, *J* = 7.5 Hz, 3 H), 1.34 (s, 9 H), 1.89–1.95 (m, 3 H), 2.25 (m, 1 H), 2.60 (q, *J* = 7.5 Hz, 2 H), 3.39–3.45 (m, 2 H), 4.91 (dd, *J* = 7.5 Hz, 2.5 Hz, 1 H), 6.10 (s, 1 H).

3-Ethyl-5-(2(*S*)-pyrrolidinyl)isoxazole (6a) was prepared from **26a** (610 mg, 2.29 mmol) according to method B in 64% yield: MS (DCI/NH_3) *m/e* 167 $(M + H)^+$, 184 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.80–1.95 (m, 3 H), 2.07 (br s, 1 H), 2.17 (m, 1 H), 2.66 (q, 2 H), 2.97–3.16 (m, 2 H), 4.32 (dd, 1 H), 5.99 (s, 1 H).

3-Ethyl-5-(2(*S*)-pyrrolidinyl)isoxazole oxalate (6a·Ox) was prepared from **6a** (51.2 mg, 0.35 mmol) according to method C. Recrystallization from $MeOH/Et_2O$ afforded the product as white crystals in 86% yield: mp = 131–133 °C; MS (DCI/NH_3) *m/e* 167 $(M + H)^+$, 184 $(M + NH_4)^+$; ^1H NMR (CD_3OD) δ 1.27 (t, *J* = 7.5 Hz, 3 H), 2.17–2.31 (m, 3 H), 2.50 (m, 1 H), 2.73 (q, *J* = 7.5 Hz, 2 H), 3.42–3.47 (m, 2 H), 4.91 (buried in H_2O peak, 1 H), 6.56 (s, 1 H). Anal. ($C_9H_{14}N_2O·C_2H_2O_4$), C, H, N.

3-Ethyl-5-(2(*R*)-pyrrolidinyl)isoxazole oxalate (6b·Ox) was prepared from **6b** (84 mg, 0.51 mmol) according to method C. Recrystallization from $MeOH/Et_2O$ afforded the product as white crystals in 67% yield: mp = 131–132 °C; $[\alpha]^{23}_D = +8.3°$ (*c* 0.46, MeOH). Anal. ($C_9H_{14}N_2O·C_2H_2O_4$) C, H, N.

3-Ethyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (7a) was prepared from **6a** (150 mg, 0.90 mmol) according to method D to afford the product as a clear colorless oil in 95% yield: ^1H NMR ($CDCl_3$) δ 1.26 (t, 3 H), 1.81–2.02 (m, 3 H), 2.23 (m, 1 H), 2.34 (s, 3 H), 2.67 (q, 2 H), 3.13–3.21 (m, 2 H), 3.43 (dd, 1 H), 6.03 (s, 1 H).

3-Ethyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (7a·HCl) was prepared from **7a** (72 mg, 0.42 mmol) according to method E. The resultant white precipitate was triturated (4×) with diethyl ether and then the solvent evaporated *in vacuo* to give 72 mg (80% yield) of a hygroscopic white solid: mp = 135–136 °C; $[\alpha]^{23}_D = -28.6°$ (*c* 0.42, MeOH); MS (DCI/NH_3) *m/e* 181 $(M + H)^+$, 198 $(M + NH_4)^+$; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.21 (t, *J* = 7.8 Hz, 3 H), 2.05–2.28 (m, 4 H), 2.67 (q, *J* = 7.8 Hz, 2 H), 2.81 (br s, 3 H), 3.20 (m, 1 H), 3.67 (m, 1 H), 4.72 (m, 1 H), 6.85 (br s, 1 H). Anal. ($C_{10}H_{16}N_2O·HCl$) C, H, N.

3-Ethyl-5-(1-methyl-2(*R*)-pyrrolidinyl)isoxazole hydrochloride (7b·HCl) was prepared from **7b** (130 mg, 0.72 mmol) according to method E. The white precipitate obtained was recrystallized from $MeOH/Et_2O$ to give the product as fine

white needles in 42% yield: mp = 134–135 °C; $[\alpha]^{23}_D$ = +33.2° (*c* 0.44, MeOH). Anal. ($C_{10}H_{16}N_2O$·HCl) C, H, N.

3-*n*-Propyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (27a) was prepared from **24a** (1.23 g, 6.30 mmol) and 1-nitrobutane according to method A in 61% yield: $[\alpha]^{23}_D$ = −51.4° (*c* 0.80, MeOH); MS (DCI/NH_3) *m/e* 281 (M + H)$^+$, 298 (M + NH_4)$^+$; ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 0.93 (t, *J* = 7.5 Hz, 3 H), 1.34 (s, 9 H), 1.64 (qt, *J* = 7.5 Hz, 7.3 Hz, 2 H), 1.88–1.95 (m, 3 H), 2.24(m, 1 H), 2.56 (t, *J* = 7.3 Hz, 2 H), 3.37–3.46 (m, 2 H), 4.92 (dd, *J* = 8.3 Hz, 2.6 Hz, 1 H), 6.08 (s, 1 H).

3-*n*-Propyl-5-(2(*S*)-pyrrolidinyl)isoxazole (8a) was prepared from **27a** (987 mg, 3.52 mmol) according to method B to afford a 92% yield of the product as an amber oil: $[\alpha]^{23}_D$ = −11.5° (*c* 1.2, MeOH); MS (DCI/NH_3) *m/e* 181 (M + H)$^+$, 198 (M + NH_4)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3 H), 1.68 (tq, *J* = 7.5 Hz, 7.4 Hz, 2 H), 1.80–1.97 (m, 3 H), 2.06 (br s, NH), 2.18 (m, 1 H), 2.61 (t, *J* = 7.5 Hz, 2 H), 2.98–3.16 (m, 2 H), 4.32 (dd, *J* = 7.7 Hz, 5.5 Hz, 1 H), 5.97 (s, 1 H).

3-*n*-Propyl-5-(2(*S*)-pyrrolidinyl)isoxazole hydrochloride (8a·HCl) was prepared from **8a** (174 mg, 0.97 mmol) according to method E. The white solid obtained was recrystallized from MeOH/Et_2O to give the product as fine white needles in 72% yield: $[\alpha]^{23}_D$ = −4.2° (*c* 0.5, MeOH); mp = 79–81 °C; MS (DCI/NH_3) *m/e* 181 (M + H)$^+$; ^{1}H NMR (D_2O) δ 0.92 (t, *J* = 7.5 Hz, 3 H), 1.63–1.75 (m, 2 H), 2.22–2.38 (m, 3 H), 2.55 (m, 1 H), 2.69 (t, *J* = 7.4 Hz, 2 H), 3.47–3.53 (m, 2 H), 4.95 (dd, *J* = 8.1 Hz, 7.4 Hz, 1 H), 6.59 (s, 1 H). Anal. ($C_{10}H_{16}N_2O$·HCl) C, H, N.

3-*n*-Propyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (9a) was prepared from **8a** (370 mg, 2.05 mmol) according to method D to afford the product as a clear yellow oil in 74% yield: $[\alpha]^{23}_D$ = −84.1° (*c* 1.2, MeOH); MS (DCI/NH_3) *m/e* 195 (M + H)$^+$, 212 (M + NH_4)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3 H), 1.69 (tq, *J* = 7.7 Hz, 7.4 Hz, 2 H), 1.80–2.20 (m, 3 H), 2.24 (m, 1 H), 2.37 (m, 1 H), 2.34 (br s, 3 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 3.17 (m, 1 H), 3.43 (dd, *J* = 8.1 Hz, 7.4 Hz, 1 H), 6.01 (s, 1 H).

3-*n*-Propyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (9a·HCl) was prepared from **9a** (250 mg, 1.29 mmol) according to method E. Evaporation of the solvent afforded the product as hygroscopic short white needles in 90% yield: mp = 112–114 °C; $[\alpha]^{23}_D$ = −27.2° (*c* 0.66, MeOH); MS (DCI/NH_3) *m/e* 195 (M + H)$^+$; ^{1}H NMR (D_2O) δ 0.92 (t, *J* = 7.4 Hz, 3 H), 1.70 (tq, *J* = 7.4 Hz, 7.4 Hz, 2 H), 2.22–2.48 (m, 3 H), 2.61 (m, 1 H), 2.70 (t, 7.4 Hz, 2 H), 2.93 (br s, 3 H), 3.42 (m, 1 H), 3.77 (m, 1 H), 4.77–4.87 (partly buried in H_2O peak, 1 H), 6.70 (s, 1 H). Anal. ($C_{10}H_{16}N_2O$·HCl) C, H, N.

3-Phenyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (28a). Benzohydroxamoyl chloride (1.10 g, 6.96 mmol) was treated with sodium hydroxide to generate the benzonitrile oxide. The nitrile oxide in diethyl ether was immediately added to a stirring solution of **24a** (680 mg, 3.48 mmol) in diethyl ether (1.75 mL). The reaction was stirred for 2 h, then refluxed for 2 h, and finally allowed to stir overnight at room temperature. The solvent was evaported *in vacuo* and the residue purified by flash chromatography (EtOAc/hexane 1:10) to give 579 mg (53% yield) of the the product as a white solid: $[\alpha]_D^{23}$ = −100° (*c* 0.7, MeOH); mp = 88–90 °C; MS (DCI/NH_3) *m/e* 315 (M + H)$^+$; ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 1.35 (s, 9 H), 1.93–2.01 (m, 3 H), 2.31 (m, 1 H), 3.44 (m, 1 H), 3.50 (m, 1 H), 5.00 (dd, *J* = 8.1 Hz, 2.5 Hz, 1 H), 6.71 (s, 1 H), 7.47–7.51 (m, 3 H), 7.81–7.83 (m, 2 H).

3-Phenyl-5-(2(*S*)-pyrrolidinyl)isoxazole (10a) was prepared from **28a** (547 mg, 1.74 mmol) according to method B to afford the product in 46% yield: $[\alpha]^{23}_D$ = −13.0° (*c* 0.7, MeOH); MS (DCI/NH_3) *m/e* 215 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 1.71–1.88 (m, 3 H), 2.14 (m, 1 H), 2.92 (t, *J* = 6.8 Hz, 2 H), 4.34 (dd, *J* = 7.35 Hz, 5.15 Hz, 1 H), 6.87 (s, 1 H), 7.47–7.54 (m, 3 H), 7.83–7.87 (m, 2 H).

3-Phenyl-5-(2(*S*)-pyrrolidinyl)isoxazole oxalate (10a·Ox) was prepared from **10a** (86.5 mg, 0.38 mmol) according to method C and recrystallized from MeOH/Et_2O to afford the product as a white solid in 71% yield: mp = 176–178 °C; MS (DCI/NH_3) *m/e* 215 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 2.17–2.43 (m, 3 H), 2.58 (m, 1 H), 3.50 (t, *J* = 7.0 Hz, 2 H), 5.00 (dd, *J* = 7.72 Hz, 7.72 Hz, 1 H), 7.11 (s, 1 H), 7.48–7.52 (m, 3 H), 7.85–7.89 (m, 2 H). Anal. ($C_{13}H_{14}N_2O$·$C_2H_2O_4$) C, H, N.

3-Phenyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (11a) was prepared from **10a** (99.2 mg, 0.46 mmol) according to method D to give the product as a viscous oil in 88% yield: MS (DCI/NH_3) *m/e* 229 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 1.78–1.96 (m, 3 H), 2.17–2.39 (m, 2 H), 2.27 (s, 3 H), 3.07 (m, 1 H), 3.52 (m, 1 H), 6.94 (s, 1 H), 7.46–7.54 (m, 3 H), 7.85–7.89 (m, 2 H).

3-Phenyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole oxalate (11a·Ox) was prepared from **11a** (86.5 mg, 0.38 mmol) according to method C to give the product as a white solid in 73% yield: mp = 106–108 °C; MS (DCI/NH_3) *m/e* 229 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 2.24–2.34 (m, 2 H), 2.48 (m, 1 H), 2.63 (m, 1 H), 2.93 (s, 3 H), 3.34–3.38 (m, partially buried in MeOH peak 1 H), 3.73 (m, 1 H), 4.76 (dd, *J* = 8.4 Hz, 8.4 Hz 1 H), 7.21 (s, 1 H), 7.48–7.55 (m, 3 H), 7.86–7.91 (m, 2 H). Anal. ($C_{14}H_{16}N_2O$·$C_2H_2O_4$) C, H, N.

3-Benzyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (29a) was prepared from **24a** and 2-phenyl-1-nitroethane[25] according to method A in 59% yield: MS (DCI/NH_3) *m/e* 329 (M + H)$^+$, 346 (M + NH_4)$^+$; ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.27 (s, 9 H), 1.84–1.97 (m, 3 H), 2.24 (m, 1 H), 3.33–3.46 (m, 2 H), 3.95 (s, 2 H), 4.90 (dd, *J* = 7.8 Hz, 2.7 Hz, 1 H), 6.02 (s, 1 H), 7.20–7.34 (m, 5 H).

3-Benzyl-5-(2(*S*)-pyrrolidinyl)isoxazole (12a) was prepared from **29a** (600 mg, 1.83 mmol) according to method B to afford the product as a pale yellow oil in 63% yield: MS (DCI/NH_3) *m/e* 229 (M + H)$^+$, 246 (M + NH_4)$^+$; ^{1}H NMR ($CDCl_3$/D_2O exchange) δ 1.88–1.92 (m, 3 H), 2.16 (m, 1 H), 2.93–3.10 (m, 2 H), 3.97 (s, 2 H), 4.27 (dd, *J* = 7.5 Hz, 5.3 Hz, 1 H), 5.88 (s, 1 H), 7.21–7.37 (m, 5 H).

3-Benzyl-5-(2(*S*)-pyrrolidinyl)isoxazole oxalate (12a·Ox) was prepared from **12a** (60.0 mg, 0.263 mmol) according to method C and recrystallized from MeOH/Et_2O to afford the product as a white solid in 90% yield: mp = 155–157 °C; $[\alpha]^{23}_D$ = −12.0° (*c* 0.7, MeOH), MS *m/e* 229 (M + H)$^+$, 246 (M + NH_4)$^+$; ^{1}H NMR (CD_3OD) δ 2.10–2.30 (m, 3 H), 2.47 (m, 1 H), 3.38–3.44 (m, 2 H), 4.03 (s, 2 H), 4.82–4.95 (partially buried under water peak (m, 1 H), 6.48 (s, 1 H), 7.20–7.34 (m, 5 H). Anal. ($C_{14}H_{16}N_2O$·$C_2H_2O_4$) C, H, N.

3-Benzyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (13a) was prepared from **12a** (191 mg, 0.84 mmol) according to method D to give the product as a colorless oil in 75% yield: MS (DCI/NH_3) *m/e* 243 (M + H)$^+$, 260 (M + NH_4)$^+$, ^{1}H NMR ($CDCl_3$) 1.79–2.00 (m, 3 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 2.30 (s, 3 H), 3.14 (m, 1 H), 3.40 (m, 1 H), 3.99 (s, 2 H), 5.92 (s, 1 H), 7.21–7.36 (m, 5 H).

3-Benzyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (13a·HCl) was prepared from **13a** (97 mg, 0.40 mmol) according to method E. Evaporation of the solvent gave the product as a clear colorless viscous oil in quantitative yield: $[\alpha]^{23}_D$ = −22.3° (*c* 0.26, MeOH); MS (DCI/NH_3) *m/e* 243 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 2.21–2.44 (m, 3 H), 2.57 (m, 1 H), 2.91 (br s, 3 H), 3.30–3.42 (partly buried in MeOH peak, 1 H), 3.78 (m, 1 H), 4.05 (s, 2 H), 4.76 (m, 1 H), 6.60 (s, 1 H), 7.21–7.32 (m, 5 H). Anal. ($C_{15}H_{16}N_2O$·HCl·0.8H_2O) C, H, N.

3-*n*-Butyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (30a) was prepared from **24a** and 1-nitropentane according to method A in 61% yield: $[\alpha]^{23}_D$ = −90.0° (*c* 0.60, MeOH); MS (DCI/NH_3) *m/e* 295 (M + H)$^+$, 312 (M + NH_4)$^+$; ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 0.90 (t, *J* = 7.7 Hz, 3 H), 1.12–1.40 (m, 2 H), 1.34 (s, 9 H), 1.60 (tt, *J* = 7.4 Hz, 2 H), 1.87–1.96 (m, 3 H), 2.25 (m, 1 H), 2.58 (t, *J* = 7.4 Hz, 2 H), 3.37–3.47 (m, 2 H), 4.91 (dd, *J* = 7.8, 2.9 Hz, 1 H), 6.08 (s, 1 H).

3-*n*-Butyl-5-(2(*S*)-pyrrolidinyl)isoxazole (14a) was prepared from **30a** (540 mg, 1.83 mmol) according to method B to afford the product as a pale yellow oil in 85% yield: MS (DCI/NH_3) *m/e* 195 (M + H)$^+$, 212 (M + NH_4)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3 H), 1.32–1.44 (m, 2 H), 1.58–1.68 (m, 2 H), 1.80–1.97 (m, 3 H), 2.13–2.23 (m, 1 H), 2.63 (t, *J* = 7.5 Hz, 2 H), 2.97–3.15 (m, 2 H), 4.31 (dd, *J* = 7.4 Hz, 5.5 Hz, 1 H), 5.97 (s, 1 H).

3-*n*-Butyl-5-(2(*S*)-pyrrolidinyl)isoxazole hydrochloride (14a·HCl) was prepared from **14a** (71.6 mg, 0.37 mmol) according to method E. Evaporation of the solvent afforded the product as a hygroscopic solid in 85% yield: $[\alpha]^{23}_D = -6.2°$ (*c* 0.38, MeOH); MS *m/e* 195 $(M + H)^+$, 212 $(M + NH_4)^+$; ^1H NMR (D_2O) 0.91 (t, $J = 7.4$ Hz, 3 H), 1.33 (qt, $J = 7.7, 7.4$ Hz, 2 H), 1.65 (tt, $J = 7.7, 7.4$ Hz, 2 H), 2.18–2.34 (m, 3 H), 2.55 (m, 1 H), 2.72 (t, $J = 7.4$ Hz, 2 H), 3.49 (t, $J = 7.0$ Hz, 2 H), 4.94 (dd, $J = 8.1, 7.7$ Hz, 1 H), 6.58 (s, 1 H). Anal. ($C_{11}H_{18}N_2O$·HCl·0.2H_2O) C, H, N.

3-*n*-Butyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (15a) was prepared from **14a** (219 mg, 1.1 mmol) according to method D to give the product as a colorless oil in 63% yield: $[\alpha]^{23}_D = -54.4°$ (*c* 0.59, MeOH); MS (DCI/NH_3) *m/e* 209 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (t, $J = 7.4$ Hz, 3 H), 1.38 (br tq, $J = 7.7$ Hz, 7.0 Hz, 2 H), 1.59–1.69 (m, 3 H), 1.80–2.02 (m, 2 H), 2.23 (m, 1 H), 2.36 (m, 1 H), 2.34 (s, 3 H), 2.65 (t, $J = 7.7$ Hz, 2 H), 3.17 (m, 1 H), 3.42 (br dd, $J = 7.0, 7.0$ Hz, 1 H), 6.00 (s, 1 H).

3-*n*-Butyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (15a·HCl) was prepared from **15a** (99.0 mg, 0.48 mmol) according to method E. Evaporation of the solvent afforded the product as hygroscopic solid in 61% yield: mp = 100–102 °C; $[\alpha]^{23}_D = -25.2°$ (*c* 0.40, MeOH); MS (DCI/NH_3) *m/e* 209 $(M + H)^+$; ^1H NMR (D_2O) δ 0.91 (t, $J = 7.4$ Hz, 3 H), 1.33 (br tq, $J = 7.7, 7.4$ Hz, 2 H), 1.66 (tt, $J = 7.7, 7.4$ Hz, 2 H), 2.22–2.48 (m, 3 H), 2.63 (m, 1 H), 2.74 (t, $J = 7.7$ Hz, 2 H), 2.91 (br s, 3 H), 3.37 (m, 1 H), 3.76 (m, 1 H), 4.74–4.82 (partly buried in H_2O peak, 1 H), 6.69 (s, 1 H). Anal. ($C_{12}H_{20}N_2O$·HCl·0.4H_2O) C, H, N.

3-(Ethoxycarbonyl)-5-(*N*-(tert-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (31a). Ethyl chlorooximidatoacetate (5.40 g, 35.4 mmol), **24a** (2.30 g, 11.8 mmol), and dried powdered 4A sieves (2.3 g) were combined in CH_2Cl_2 (8 mL) and allowed to stir at room temperature for 13 days.[26] The reaction was then filtered through Celite and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1:4) to give 4.88 g of a viscous yellow oil of ~85% purity: MS *m/e* 311 $(M + H)^+$, 328 $(M + NH_4)^+$; ^1H NMR (DMSO-d_6, 500 MHz, 100 °C) 1.30 (t, $J = 7.0$ Hz, 3 H) 1.34 (s, 9 H), 1.91–2.01 (m, 3 H), 2.30 (m, 1 H), 3.40–3.51 (m, 2 H), 4.32 (q, $J = 7.0$ Hz, 2 H), 5.02 (dd, $J = 8.2, 3.5$ Hz, 1 H), 6.60 (s, 1 H).

3-(Ethoxycarbonyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (16a). Compound **31a** (315 mg, 1.0 mmol) was deprotected according to method B to afford the secondary amine as an amber oil in 39% yield: MS (DCI/NH_3) *m/e* 211 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.41 (t, $J = 7.2$ Hz, 3 H), 1.84–2.01 (m, 3 H), 2.25 (m, 1 H), 3.05–3.17 (m, 2 H), 4.43 (q, $J = 7.2$ Hz, 2 H), 4.47 (m, 1 H), 6.57 (s, 1 H). The amine (75 mg, 0.36 mmol) was methylated according to method D to give the product as a colorless oil in 48% yield: MS (DCI/NH_3) *m/e* 225 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.41 (t, $J = 7.2$ Hz, 3 H), 1.85–2.03 (m, 3 H), 2.21–2.45 (m, 2 H), 2.34 (s, 3 H), 3.17 (m, 1 H), 3.54 (dd, $J = 8.1, 6.99$ Hz, 1 H), 4.43 (q, $J = 7.2$ Hz, 2 H), 6.59 (s, 1 H).

3-(Ethoxycarbonyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (16a·Ox) was prepared from **16a** (35.6 mg, 0.16 mmol) according to method C. Evaporation of the solvent gave the product as a semisolid in quantitative yield: MS (DCI/NH_3) *m/e* 225 $(M + H)^+$; ^1H NMR (D_2O, 500 MHz) δ 1.39 (t, $J = 7.3$ Hz, 3 H), 2.24–2.36 (m, 2 H), 2.48 (m, 1 H), 2.68 (m, 1 H), 2.98 (br s, 3 H), 3.39 (m, 1 H), 3.88 (m, 1 H), 4.47 (q, $J = 7.3$ Hz, 2 H), 4.88 (m, 1 H), 7.19 (s, 1 H). Anal. ($C_{11}H_{16}N_2O_3$·1.1$C_2H_2O_4$) C, H, N.

3-(Hydroxymethyl)-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (32a). To a solution of semipurified **31a** (4 g) in EtOH/H_2O (70 mL) was added KOH (1.35 g) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then acidified with 2 N HCl and extracted with $CHCl_3$ (3×). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by flash chromatography (10% MeOH/$CHCl_3$ → 0.5% HOAc/10% MeOH/$CHCl_3$) to afford, after evaporation of the solvent and azeotroping with toluene, the acid (3.09 g) as a yellow foam.

The acid (387 mg, 1.37 mmol) and 1.0 M borane–THF complex (4.80 mL, 4.80 mmol) were combined at room temperature in THF (4.5 mL) and then heated to reflux for 4 h. The reaction was cooled to room temperature and then saturated $NaHCO_3$ solution was added. The mixture was stirred for 1 h and then diluted with ethyl acetate. The two phases which formed were separated. The aqueous phase was extracted with $CHCl_3$ (1×) and the organic extract was combined with the original organic phase. The mixture was then dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (2% MeOH/$CHCl_3$) to give 266 mg (72% yield) of a clear viscous oil: MS (CI) *m/e* 269 $(M + H)^+$; ^1H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 1.35 (s, 9 H), 1.87–1.96 (m, 3 H), 2.25 (m, 1 H), 3.37–3.46 (m, 2 H), 4.47 (s, 2 H), 4.94 (dd, $J = 8.4, 2.8$ Hz, 1 H), 6.17 (s, 1 H).

3-(Hydroxymethyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (17a). Compound **32a** (266 mg, 1.0 mmol) was treated with 4 N HCl in 1,4-dioxane to give crude N-deprotected material. MS (DCI/NH_3) *m/e* 169 $(M+H)^+$. The crude secondary amine was then methylated according to method D and the resulting crude product was purified by flash chromatography (1% MeOH/$CHCl_3$ → 2% MeOH/$CHCl_3$) to give 104 mg (58% yield) of a clear oil: MS (DCI/NH_3) *m/e* 183 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.81–2.03 (m, 3 H), 2.25 (m, 1 H), 2.34 (s, 3 H), 2.39 (m, 1 H), 3.18 (m, 1 H), 3.49 (m, 1 H), 4.74 (s, 2 H), 6.24 (s, 1 H).

3-(Hydroxymethyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole hydrochloride (17a·HCl) was prepared from **17a** (97.5 mg, 0.54 mmol) according to method E. Evaporation of the solvent and trituration with Et_2O afforded the product as a solid in 85% yield: MS (DCI/NH_3) *m/e* 183 $(M + H)^+$; ^1H NMR (D_2O) δ 2.24–2.51 (m, 3 H), 2.65 (m, 1 H), 2.93 (s, 3 H), 3.39 (m, 1 H), 3.78 (m, 1 H), 4.76 (s, 2 H), 4.81 (m, 1 H), 6.80 (s, 1 H). Anal. ($C_9H_{14}N_2O_2$·HCl·0.2H_2O) C, H, N.

3-(Methoxymethyl)-5-(*N*-(tert-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (33a). Compound **32a** (274 mg, 1.02 mmol), in THF (1 mL), was added to a stirring slurry of 80% sodium hydride (31 mg, 1.02 mmol), in THF (1 mL). The reaction was stirred for 15 min at ambient temperature and then iodomethane (190 mL, 3.06 mmol) was added. After an additional 15 min of stirring, the reaction was poured over a two phase solution of EtOAc/saturated aqueous NH_4Cl. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*, and the residue was purified by flash chromatography (EtOAc/hexane 1:3) to afford 234 mg (81% yield) of a clear yellow oil: MS (CI) *m/e* $(M + H)^+$ 283; ^1H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 1.34 (s, 9 H), 1.87–1.96 (m, 3 H), 2.26 (m, 1 H), 3.32 (s, 3 H), 3.36–3.47 (m, 2 H), 4.43 (s, 2 H), 4.94 (dd, $J = 7.8, 2.6$ Hz, 1 H), 6.20 (s, 1 H).

3-(Methoxymethyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (18a). N-Deprotection of **33a** with 4 N HCl–dioxane followed by methylation according to method D afforded the product in 93% yield: MS (CI) *m/e* $(M + H)^+$ 197; ^1H NMR ($CDCl_3$) δ 1.80–2.03 (m, 3 H), 2.24 (m, 1 H), 2.34 (s, 3 H), 2.36 (m, 1 H), 3.17 (m, 1 H), 3.39 (s, 3 H), 3.47 (dd, $J = 8.1, 7.4$ Hz, 1 H), 4.51 (s, 2 H), 6.20 (s, 1 H).

3-(Methoxymethyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole Fumarate (18a·Fu). Compound **18a** (34 mg, 0.17 mmol) and fumaric acid (20 mg, 0.17 mmol) were combined in MeOH (1 mL) and stirred for 30 min. The solvent was evaporated *in vacuo* and the remaining viscous oil was left on the high-vacuum line overnight to give 37 mg of the product as a clear viscous oil (60% yield): MS (CI) *m/e* $(M + H)^+$ 197; ^1H NMR (MeOD) δ 2.24–2.03 (m, 3 H), 2.42 (m, 1 H), 2.58 (s, 3 H), 6.72 (s, 2 H), 2.82 (ddd, $J = 10.7, 10.3, 8.5$, 1 H), 3.39 (s, 3 H), 3.40 (m, 1 H), 4.08 (dd, $J = 8.1, 8.1$ Hz, 1 H), 4.52 (s, 2 H), 6.54 (s, 1 H). Anal. ($C_{10}H_{16}N_2O_2$·1.4$C_4H_4O_4$·0.2H_2O) C, H, N.

3-(Trifluoromethyl)-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (34a). To a solution of **24a** (200 mg, 1.02 mmol) in toluene (10 mL) was added solid K_2CO_3 (414 mg, 3.00 mmol) followed by freshly prepared (trifluoroacetyl)-hydroximoyl chloride[27] (295 mg, 2.00 mmol), and the reaction mixture brought to reflux. After refluxing the mixture for ~20 h second aliquots of K_2CO_3 (450 mg) and (trifluoroacetyl)-hydroximoyl chloride (592 mg, 4.01 mmol) were added, and

refluxing was continued for an additional 7 h. The reaction mixture was then diluted with Et_2O (50 mL) and washed with 20 mL portions of saturated aqueous $NaHCO_3$, 10% aqueous citric acid, and brine, dried ($MgSO_4$), and concentrated to afford the crude product as an oil. Flash chromatographic purification (EtOAc/hexane 1:6) afforded 130 mg (41% yield) of the pure product as a pale yellow oil: MS (CI) *m/e* 307 $(M + H)^+$, 324 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.94–2.43 (m, 4 H), 3.37–3.66 (m, 2), 4.99 (br s, 1 H) 5.11 (br s, 1 H), 6.29 (br s, 1 H), 6.35 (br s, 1 H).

3-(Trifluoromethyl)-5-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole Hydrochloride (19a·HCl). Nitrogen deprotection of **34a** (37 mg, 0,121 mmol) according to method B followed by methylation according to method D and salt formation according to method E gave, after evaporation of the solvent, the product as a hygroscopic solid in 73% yield: MS (CI) *m/e* 221 $(M + H)^+$, 238 $(M + NH_4)^+$; ^1H NMR (D_2O) δ 2.28–2.43 (m, 2 H), 2.53 (m, 1 H), 2.74 (m, 1 H), 3.02 (m, 4 H), 3.47 (br s, 1 H), 3.85 (br s, 1 H), 7.28 (s, 1 H). Anal. ($C_9H_{11}N_2OF_3$·HCl·0.3H_2O) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)pyrrolidine 2(*S*)-Aldoxime (35a).** To a stirred 0 °C solution of hydroxylamine hydrochloride (488 mg, 7.03 mmol) in pyridine (7 mL) was added *N*-(*tert*-butyloxycarbonyl)-(*S*)-prolinal (1.40 g, 7.03 mmol). The reaction mixture was stirred for 16 h while gradually warming to room temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between aqueous buffer (pH = 4) and EtOAc/diethyl ether (1:1). The organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo*, to give 1.40 g (93% crude yield) of a oil which was carried forward without purification: MS (DCI/NH_3) *m/e* 215 $(M + H)^+$.

5-Methyl-3-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isoxazole (36a). *N*-Chlorosuccinimide (1.23 g, 9.09 mmol) was added to an ice-cooled solution of **35a** (1.85 g, 8.65 mmol) in dichloroethane (20 mL). The reaction was stirred for 0.75 h at 0 °C, followed by 0.5 h at room temperature. The reaction mixture was then cooled to −5 °C and an excess of 2-bromopropene was added, followed by the gradual addition of triethylamine (1.19 mL, 8.56 mmol). After stirring at 0 °C for an additional 2.5 h, excess triethylamine was added to the mixture and stirring was continued for 16 h. The reaction mixture was concentrated *in vacuo* and the solid residue dissolved in $CHCl_3$ (40 mL). The organic phase was washed with 10% $KHSO_4$, followed by saturated $NaHCO_3$ and brine. The organic phase was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane 1:1) to yield 607.2 mg (27%) of the pure product: MS (DCI/NH_3) *m/e* 253 $(M + H)^+$, 270 $(M + NH_4)^+$; ^1H NMR (DMSO-d_6, 100 °C) δ 1.34 (s, 9 H), 1.86–1.97 (m, 3 H), 2.22 (m, 1 H), 2.98 (s, 3 H), 3.32–3.47 (m, 2 H), 4.84 (dd, J = 8.0 Hz, J = 3.0 Hz, 1 H), 6.03 (s, 1 H).

5-Methyl-3-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole (20a). Deprotection of **36a** (607.2 mg, 2.41 mmol) according to method B followed by N-methylation according to method D and chromatographic purification (5% MeOH/CH_2Cl_2) afforded 108 mg (27% yield) of the product as a colorless oil: MS (DCI/NH_3) *m/e* 167 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.80–2.04 (m, 3 H), 2.15–2.37 (m, 2 H), 2.27 (s, 3 H), 2.40 (s, 3 H), 3.20 (t, J = 8.5 Hz, 1 H), 3.35 (t, J = 8.0 Hz, 1 H), 6.00 (d, J = 0.7 Hz, 1 H).

5-Methyl-3-(1-methyl-2(*S*)-pyrrolidinyl)isoxazole oxalate (20a·Ox) was prepared from **20a** (31.3 mg, 0.19 mmol) according to method C. Evaporation of the solvent afforded 24 mg (50% yield) of an oil: MS (DCI/NH_3) *m/e* 167 $(M + H)^+$; ^1H NMR (D_2O) δ 2.18–2.34 (m, 3 H), 2.47 (s, 3 H), 2.65 (m, 1 H), 2.96 (s, 3 H), 3.33 (m, 1 H), 3.89 (m, 1 H), 4.60 (m 1 H), 6.36 (s, 1 H). Anal. ($C_9H_{14}N_2O$·1.3$C_2H_2O_4$) C, H, N.

3-Keto-1-[*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl]-1-butyne (37a). To a solution of **23a** (2.0 g, 5.63 mmol) in THF (10 mL) cooled to −75 °C was added *n*-BuLi (4.6 mL, 11.54 mmol of a 2.5 M solution in hexane) dropwise over a period of 10 min. This solution was stirred for 20 min before adding acetaldehyde (377 μL, 6.75 mmol). This mixture was allowed to warm slowly to ambient temperature over several hours. The reaction was then quenched by adding aqueous saturated sodium bicarbonate solution. The aqueous mixture was extracted with two portions of EtOAc and the organic phase was dried over anhydrous sodium sulfate and then concentrated *in vacuo* to an orange oil. The oil was purified by column chromatography (EtOAc/hexane 1:2) to give 1.27 g (91% yield) of the product as a colorless oil; MS (DCI/NH_3) *m/e* 240 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 6.6 Hz, 3 H), 1.48 (s, 9 H), 1.4–2.1 (m, 4 H), 3.2–3.5 (m, 3 H), 4.45 (br s, 1 H), 4.53 (q, J = 6.6 Hz, 1 H).

To a solution of oxalyl chloride (1.28 mL, 14.7 mmol) in CH_2Cl_2 (30 mL) at −60 °C was added DMSO (1.12 mL, 15.8 mmol). The reaction mixture was stirred for 10 min at −60 °C, and then a solution of the alcohol (1.26 g, 5.26 mmol) in CH_2Cl_2 (5 mL) was slowly added over a 2 min period. This mixture was stirred for 15 min at −60 °C before diisopropylethylamine (5.5 mL, 31.6 mmol) was added. After an additional 10 min of stirring at −60 °C, the reaction mixture was warmed to 0 °C and quenched with aqueous saturated ammonium chloride. The aqueous phase was extracted with CH_2Cl_2 and the organic extract was combined with organic phase from the original reaction mixture. The combined organic phases were then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/hexane 1:1) to give 824 mg (66% yield) of the product as a colorless oil: $[\alpha]^{22}_D = -142.3°$ (*c* 1.4, CH_2Cl_2); MS (DCI/NH_3) *m/e* 238 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 1.3–1.5 (m, 9 H), 1.80–2.29 (m, 3 H), 2.30 (s, 2 H), 3.20–3.40 (m, 4 H), 4.60 (br s, 1 H).

3-Keto-1-[*N*-(*tert*-butyloxycarbonyl)-2(R)-pyrrolidinyl]-1-butyne (37b) was prepared in a manner similar to that described for **37a**: $[\alpha]^{23}_D = +143.6°$ (*c* 1.6, CH_2Cl_2).

3-Methyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*S*)-pyrrolidinyl)isothiazole (38a) was prepared using a modification of the procedure described by Lucchesini *et al.*[21] A solution of **37a** in 50% aqueous methanol (8 mL) was cooled to 0 °C. (Hydroxylamino)sulfonic acid (338 mg, 3 mmol) was added to the solution and the reaction mixture was stirred for 45 min. After the 45 min of mixing, solid sodium bicarbonate (250 mg, 3 mmol) was added to the reaction mixture, followed by the addition of 2.3 mL of a 1.4 M aqueous solution of sodium hydrosulfide (3.3 mmol). The reaction mixture was then stirred at ambient temperature for 6.5 h. The reaction mixture was diluted with brine and extracted with two portions of EtOAc. The aqueous phase was made basic by the addition of excess sodium bicarbonate and additional sodium hydrosulfide (800 μL of 1.4 M solution) was added to the aqueous reaction mixture which was then stirred overnight. The aqueous phase was again extracted with EtOAc and the organic extract was combined with the organic extracts from the previous day. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/hexane 1:1) to yield 135 mg (17% yield) of the product as a yellow oil: $[\alpha]^{23}_D = -90.9°$ (*c* 1.28, CH_2Cl_2); MS (DCI/NH_3) *m/e* 269 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 1.36 (s, 9 H), 1.83–1.98 (m, 3 H), 2.31 (s, 1 H), 2.37 (s, 3 H), 3.40 (dd, J = 7.5, 6.1 Hz, 2 H), 5.14 (dd, J = 9.8, 2.4 Hz, 1 H), 6.96 (s, 1 H).

3-Methyl-5-(*N*-(*tert*-butyloxycarbonyl)-2(*R*)-pyrrolidinyl)isothiazole (38b) was prepared in a manner similar to that described for **38a**: $[\alpha]^{23}_D = +107.7°$.

3-Methyl-5-(2(*S*)-pyrrolidinyl)isothiazole Hydrochloride (21a·HCl). A saturated solution of hydrogen chloride in dioxane (2 mL) was added to **38a** (115 mg, 0.43 mmol). The reaction mixture was left at ambient temperature for 30 min before it was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 40 mg of a yellow oil. A sample of this oil (9.5 mg) was purified by column chromatography on silica gel (10% EtOH/EtOAc) to afford 9 mg of a colorless oil. This amine was dissolved in ethanol (1 drop) and diethyl ether (~1.5 mL). A saturated solution of hydrogen chloride in diethyl ether was then added to this solution. A precipitate formed and was collected by centrifugation. The collected precipitate was washed with diethyl ether and dried *in vacuo* to yield the product as a white powder: mp = 129–130 °C; $[\alpha]^{23}_D = +13.4°$ (*c* 0.8, MeOH); MS (DCI/NH_3) *m/e* 169 $(M + H)^+$; ^1H NMR (D_2O) δ 2.15–2.37

(m, 3 H), 2.49 (s, 3 H), 2.65 (m, 1 H), 3.47–3.56 (m, 2 H), 5.07 (dd, J = 8.5, 6.6 Hz, 1 H), 7.31 (s, 1 H). Anal. ($C_8H_{12}N_2S$·1.2HCl·0.1Et_2O) C, H, N.

3-Methyl-5-(2(*R*)-pyrrolidinyl)isothiazole hydrochloride (21b·HCl) was prepared from **38b** (957.2 mg, 4.03 mmol) in a similar fashion as that described for **21a·HCl** to give 514 mg (62% yield) of the product as a beige solid: mp = 132–133 °C; $[\alpha]^{23}_D$ = −14.8° (*c* 0.7, MeOH). Anal. ($C_8H_{11}N_2S$·HCl) C, H, N.

3-Methyl-5-(1-methyl-2(*S*)-pyrrolidinyl)isothiazole Hydrochloride (22a). Methylation of **21a** (30 mg, 0.15 mmol) according to method D and salt formation according to method E gave, after evaporation of the solvent and recrystallization from EtOH/Et_2O, the product as a white powder in 30% yield: mp = 153–154 °C; MS (DCI/NH_3) *m/e* 183 (M + H)$^+$, 270 (M + NH_4)$^+$; ^{1}H NMR (D_2O) δ 2.21–2.39 (m, 3 H), 2.51 (s, 3 H), 2.72 (m, 1 H), 2.84 (br s, 3 H), 3.35 (m, 1 H), 3.78 (m, 1 H), 4.79 (m, 1 H), 7.39 (s, 1 H). Anal. ($C_9H_{14}N_2S$·HCl·0.25 H_2O) C, H, N.

3-Methyl-5-(1-methyl-2(*R*)-pyrrolidinyl)isothiazole Hydrochloride (22b). Methylation of **21b** (150 mg, 0.89 mmol) according to method D and salt formation according to method E gave, after evaporation of the solvent and recrystallization from EtOH/Et_2O, the product as a white powder in 30% yield: mp = 147–149 °C. Anal. ($C_9H_{14}N_2S$·HCl·0.4H_2O) C, H, N.

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