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Tetrahedron
Tetrahedron 61 (2005) 3525–3531

Efficient approach to the unknown isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine system by regioselective intramolecular nitrone cycloadditions

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Received 5 November 2004; revised 14 January 2005; accepted 28 January 2005

Abstract—An effective approach to the new isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine system was provided by way of an intramolecular nitrone cycloaddition. The required nitrones were built in good yields starting from thiophene-2-carboxylic acids. The same skeleton was achieved in optically active form employing chiral nitrones derived from *N*-α-methylbenzyl- and the *N*-α-hydroxymethylbenzyl-hydroxylamines. The absolute configuration of the products was assigned by X-ray analysis.

1. Introduction

1,3-Dipolar cycloadditions furnish an extensively studied and widely used method for the synthesis of five-membered heterocycles.[1] Among them, those involving nitrones constitute an efficient and versatile entry to isoxazolidines, which in turn represent valuable intermediates in organic synthesis.[2] In particular, the intramolecular nitrone cycloaddition leads directly to isoxazolidines annulated with another ring in a fused or bridged mode. Furthermore, they often benefit from highly regio- and stereoselective outcomes.[3]

Dealing with our interest to the synthesis of nitrogenated heteropolycylic compounds in enantiopure form, we studied the intramolecular cycloadditions of nitrones already containing a heterocyclic unit, namely pyrrole,[4] indole[5] and imidazole,[6] bearing an allylic pendant at the nitrogen atom. At this point, we decided to extend such a synthetic approach by using nitrones having a non-nitrogenated heterocycle skeleton, but endowed with an allylic pendant linked to a ring carbon through a protected amine functionality.

In this paper, we report the results on the intramolecular 1,3-dipolar cycloadditions of thienyl-tethered nitrones derived from the aldehydes **5**, which seemed potentially able to furnish interesting thieno-piperidine derivatives. The latter may well be of interest in view of the pharmacological properties of some thieno-fused azaheterocycles.[7]

2. Results and discussion

Aldehydes **5** were synthesized starting from carboxylic acids of formula **1** by the synthetic sequence depicted in Scheme 1. The first step was the conversion to the acyl azides **2**[8] via the corresponding acyl chlorides. Azides **2** were submitted to Curtius degradation in EtOH, in the absence of water, with the aim to produce directly the carbamates **3**, which were then *N*-allylated by a standard procedure. Finally, a Vilsmeier formylation permitted an entry to the desired aldehydes **5**. It must be noted that this formylation took place exclusively at the C-3 ring carbon in both cases, reasonably because of the *o*,*p*-directing effect of the aminosubstituent which predominates over that of the methyl group of **4a**.

The generation of the suitable nitrones was performed employing the commercially available *N*-benzylhydroxylamine. However, addition of the aldehydes **5** to a suspension containing the *N*-benzylhydroxylamine hydrochloride, $NaHCO_3$ and $MgSO_4$ in diethyl ether at room temperature

Keywords: Nitrones; Intramolecular cycloadditions; Regioselectivity; Fused-ring thiophenes.
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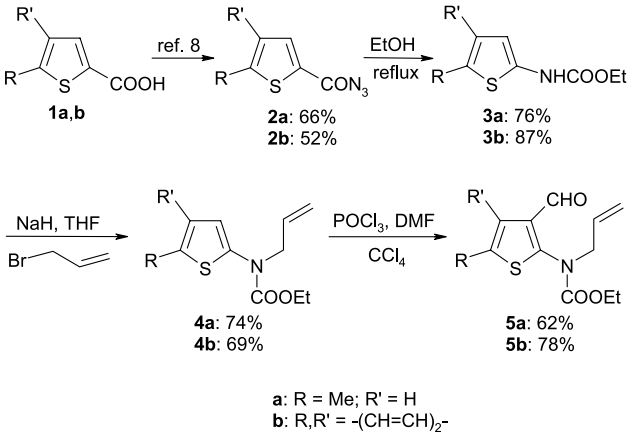
doi:10.1016/j.tet.2005.01.121

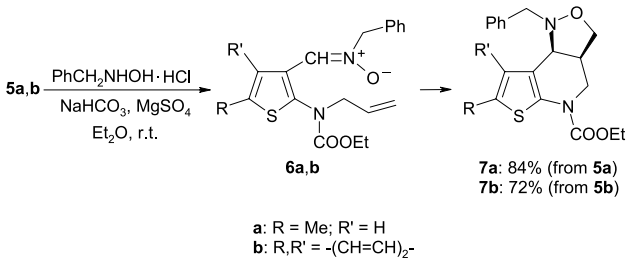


Scheme 1. Preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophene-3-carbaldehydes.

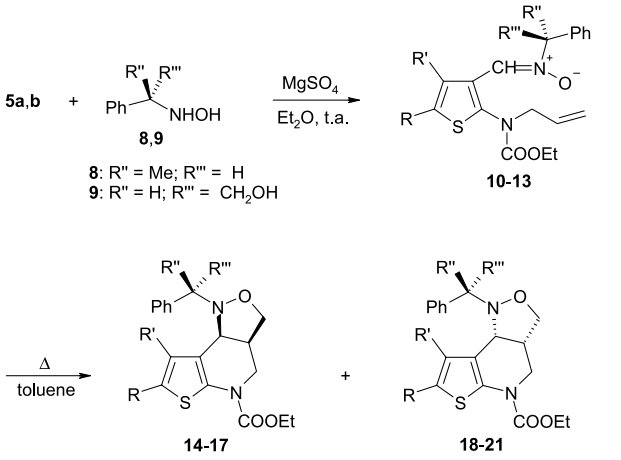
showed somehow different results (Scheme 2). The nitrone **6a** was isolated and characterized and successively cyclized on heating in refluxing toluene. Conversely, the nitrone **6b** directly underwent cyclization at room temperature. This fact does not find a clear explanation, but confirms the subtle interplay of steric and electronic factors in dictating intramolecular nitrone cycloadditions.[9] In every case, a single cycloadduct was obtained in excellent yield. Comprehensive 2D NMR studies have indicated a spatial relationship between the methynic hydrogens, thus establishing a fused-type tricyclic structure with a *cis* ring junction. This means that the cycloaddition proceeded with total regioselectivity and diastereoselectivity.

In the light of the satisfactory trend of the cycloaddition in terms of both selectivity and yields, we directed our attention to the preparation of the related structures in optically active form. The devised way to achieve this goal was to generate nitrones by enantiopure chiral benzyl-type hydroxylamines. In particular, we envisaged the (*R*)-α-methylbenzylhydroxylamine (**8**) and the (*R*)-α-(hydroxymethyl)benzylhydroxylamine (**9**), whose preparations have been described in the literature.[10,11]

The aldehydes **5** showed the same behaviour toward **8** and **9** already noticed with the benzylhydroxylamine, that is only the nitrones derived from **5a** were isolated and fully characterized. However, all the nitrones **10–13** underwent a totally regioselective cycloaddition in agreement to the behaviour of the achiral compounds **6**, but each giving two diastereoisomeric products. Analytical and spectral data of the cycloadduct pairs were in accordance for diastereoisomeric *cis* ring-fused structures (Scheme 3).



Scheme 2. Reaction of aldehydes **5a**,**b** with *N*-benzylhydroxylamine.



Reagents				Nitrones	Products (% yields)
	R	R'	R'' R'''		
5a	Me	H	**8** Me H	**10**	(α*R*,3a*S*,8b*S*)-**14** (42) (α*R*,3a*R*,8b*R*)-**18** (31)
5b	-(CH=CH)$_2$-		**8** Me H	**11**	(α*R*,3a*S*,10c*S*)-**15** (34) (α*R*,3a*R*,10c*R*)-**19** (14)
5a	Me	H	**9** H CH_2OH	**12**	(α*R*,3a*S*,8b*S*)-**16** (17) (α*R*,3a*R*,8b*R*)-**20** (51)
5b	-(CH=CH)$_2$-		**9** H CH_2OH	**13**	(α*R*,3a*S*,10c*S*)-**17** (25) (α*R*,3a*R*,10c*R*)-**21** (54)

Scheme 3. Reaction of aldehydes **5a**,**b** with enantiopure hydroxylamines **8** and **9**.

The absolute stereochemistry of the cycloadducts **14/18**, **16/20** and **17/21** was unequivocally inferred by X-ray diffractometric analysis carried out on the minor products of each pair (Figs. 1–3).[12] In all instances, the relative configuration of the new stereocentres was *cis*, in particular *R*,*R* in the case of the (*R*)-α-methylbenzyl pendant and *S*,*S* in the case of the (*R*)-α-(hydroxymethyl)benzyl one. Unfortunately, neither **15** nor **19** gave crystals suitable for the diffractometric analysis; hence, by analogy with the above evidence, we tentatively assigned the *R*,*R* absolute configuration to **19** as being the minor product with the (*R*)-α-methylbenzyl pendant.

From the point of view of the stereochemistry, it must be noted that a modest asymmetric induction was operative in the case of the *N*-α-methylbenzyl-substituted nitrones **10** and **11**, in line with previous results obtained in intramolecular reactions of nitrones bearing the same chiral

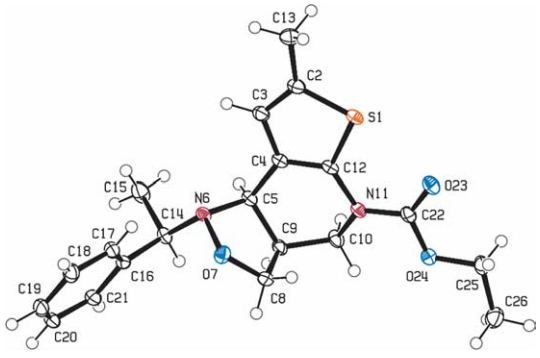


Figure 1. ORTEP plot of **18** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

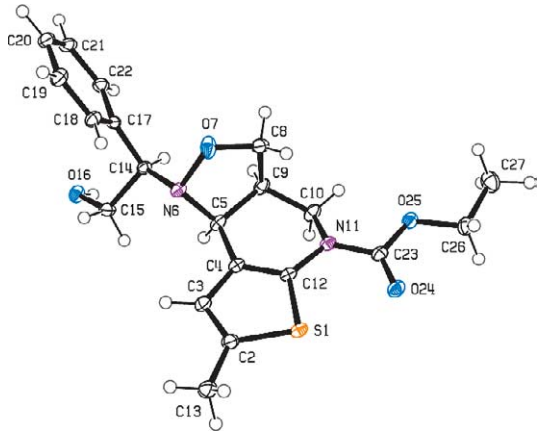


Figure 2. ORTEP plot of **16** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

auxiliary.[13] However, the diastereoselectivity increased when the nitrones having the α-(hydroxymethyl)benzyl-pendant were used; in the crude product mixture arising from **12** and **13** the diastereoisomeric ratio was determined to be 75:25 by ^{1}H NMR spectroscopy. The better effectiveness of hydroxylated chiral residue may be reasonably ascribed to the formation of a hydrogen bond with the nitrone oxygen, so making the substrate less flexible and consequently increasing the diastereofacial discrimination of the dipole. Therefore, the allylic moiety approaches the dipole from the face opposite to the phenyl group and the latter is forced to move outside during the rehybridization of the reaction centers, as depicted in Figure 4 representing the suggested transition state for the formation of the major diastereoisomer **20** from **12**.

With the aim to improve the degree of diastereoselectivity and taking into account the known chelating ability[14] of the (*R*)-α-(hydroxymethylbenzyl)hydroxylamine, we carried out the cycloaddition of the nitrone **12** in the presence of metal cations. The reaction was tested with a wide range of Lewis acid [$Zn(OTf)_2$, $Sc(OTf)_2$, $MgBr_2$, $TiCl_4$, $Co(OAc)_2$, AgOAc] and TEA, in different solvents (i.e. CH_2Cl_2 and toluene) and temperatures. Unfortunately, all the experiments gave no improvement of diastereoselectivity or even no reaction, probably because of an excessively strong nitrone oxygen chelation.

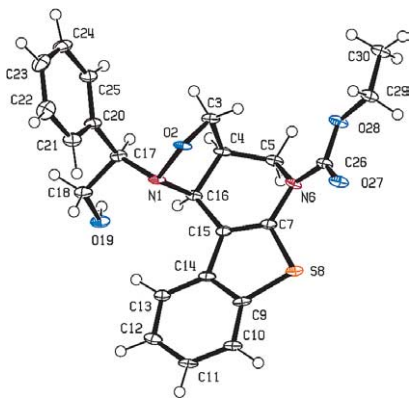


Figure 3. ORTEP plot of **17** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

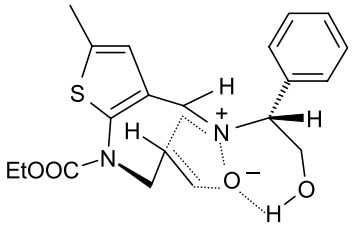


Figure 4. Proposed transition state for the compound **20**.

In conclusion, we have developed a strategy for the synthesis of the new isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine skeleton starting from thiophene-2-carboxylic acids. The three fused-ring system was assembled directly from a nitrone intramolecular cycloaddition.

3. Experimental

3.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on an AVANCE Bruker 400. Chemical shifts are given in ppm downfield from $SiMe_4$. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer. Mass spectra were determined on a WG-70EQ instrument.

3.2. Preparation of acyl azides 2a and 2b

The compounds were prepared as described in the literature.[8a,b]

3.3. General procedure for the preparation of 2-(*N*-carbethoxy-amino)-thiophenes (3a,b)

A solution of **2** (11.7 mmol) in EtOH (20 ml) and toluene (30 ml) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure to give directly **3a**,**b**.

3.3.1. 2-(*N*-Carbethoxy-amino)-5-methyl-thiophene (3a). Yield: 76%. Mp 72–73 °C (cream crystals from diisopropyl ether). IR (nujol): 3246, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz), 2.40 (3H, s), 4.24 (2H, q, J=7.1 Hz), 6.41 (1H, d, J=3.6 Hz), 6.46 (1H, d, J=3.6 Hz), 7.03 (1H, br s, missing after deuteriation). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 15.3 (q), 62.0 (t), 113.3 (d), 122.7 (d), 131.9 (s), 137.9 (s), 154.7 (s). Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56. Found C, 52.01; H, 5.78; N, 7.62.

3.3.2. 2-(*N*-Carbethoxy-amino)-benzothiophene (3b). Yield: 87%. Mp 154–155 °C (white crystals from diisopropyl ether). IR (nujol): 3300, 1691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.83 (1H, s), 7.24 (1H, dd, J=7.3, 7.8 Hz), 7.32 (1H, dd, J=7.3, 7.9 Hz), 7.55 (1H, s), 7.60 (1H, d, J=7.9 Hz), 7.73 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9

(q), 62.7 (t), 107.0 (d), 122.2 (d), 122.4 (d), 123.4 (d), 125.0 (d), 135.3 (s), 138.3 (s), 140.4 (s), 153.6 (s). Anal. calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found C, 59.79; H, 4.88; N, 6.12.

3.4. General procedure for the preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophenes (4a,b)

A solution of **3** (2.4 mmol) in THF (5 ml) was added dropwise to a suspension of 60% NaH (150 mg, 3.6 mmol) in dry THF (33 ml), under nitrogen atmosphere. Allyl bromide (0.42 ml, 4.8 mmol) was added at −5 °C, then the mixture was heated to reflux for 24 h. After cooling to room temperature, H_2O (30 ml) was added. The mixture was extracted with CH_2Cl_2 (2×60 ml) and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **4**.

3.4.1. 2-(*N*-Allyl-*N*-carbethoxy-amino)-5-methyl-thiophene (4a). Yield: 74%. Colourless oil. IR (nujol): 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=6.9 Hz), 2.41 (3H, s), 4.20–4.28 (4H, overlapping), 5.18 (1H, dd, J=1.5, 17.0 Hz), 5.21 (1H, dd, J=1.5, 10.3 Hz), 5.90 (1H, tdd, J=5.6, 10.3, 17.0 Hz), 6.49 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 15.6 (q), 54.7 (t), 62.3 (t), 117.5 (t), 122.8 (d), 126.7 (d), 133.9 (d), 142.0 (s), 146.3 (s), 154.0 (s). Anal. calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found C, 58.61; H, 6.87; N, 6.09.

3.4.2. 2-(*N*-Allyl-*N*-carbethoxy-amino)-benzothiophene (4b). Yield: 69%. Colourless oil. IR (nujol): 1696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 4.33 (2H, q, J=7.1 Hz), 4.48 (2H, d, J=4.8 Hz), 5.26 (1H, d, J=10.2 Hz), 5.29 (1H, d, J=16.4 Hz), 5.97 (1H, tdd, J=4.8, 10.2, 16.4 Hz), 6.85 (1H, s), 7.26 (1H, dd, J=7.3, 7.9 Hz), 7.33 (1H, dd, J=7.3, 7.8 Hz), 7.65 (1H, d, J=7.8 Hz), 7.74 (1H, d, J=7.9 Hz). ^1H NMR (400 MHz, CD_3OD) δ: 1.32 (3H, t, J=7.1 Hz), 4.27 (2H, q, J=7.1 Hz), 4.49 (2H, br s), 5.22 (1H, dd, J=1.1, 10.3 Hz), 5.25 (1H, dd, J=1.1, 17.1 Hz), 5.96 (1H, tdd, J=5.3, 10.3, 17.1 Hz), 6.94 (1H, s), 7.24 (1H, dd, J=7.1, 7.6 Hz), 7.30 (1H, dd, J=7.1, 7.8 Hz), 7.64 (1H, d, J=7.6 Hz), 7.71 (1H, d, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 60.8 (t), 63.3 (t), 117.8 (t), 122.1 (d), 122.9 (d), 123.8 (d), 124.5 (d), 124.8 (d), 132.8 (d), 137.2 (s), 138.1 (s), 144.8 (s), 154.6 (s). Anal. calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found C, 64.18; H, 5.75; N, 5.22.

3.5. General procedure for the preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophene-3-carbaldehydes (5a,b)

To a solution of $POCl_3$ (0.82 ml, 8.8 mmol) and DMF (0.90 ml, 12.0 mmol) in CCl_4 (40 ml), cooled at 0 °C, **4** (5.8 mmol) was added. The mixture was heated at reflux for 24 h, then the solvent was removed under reduced pressure. The residue was treated with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (50 ml×3). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified through a silica gel column with light petroleum/AcOEt (10:1) as eluent to afford **5**.

3.5.1. 2-(*N*-Allyl-*N*-carbethoxy-amino)-5-methyl-thiophene-3-carbaldehyde (5a). Yield: 62%. Pale yellow oil. IR (nujol): 1714, 1682 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (3H, t, J=6.9 Hz), 2.44 (3H, s), 4.20 (2H, q, J=6.9 Hz), 4.28 (2H, d, J=6.4 Hz), 5.20 (1H, dd, J=17.0 Hz), 5.23 (1H, dd, J=10.3 Hz), 5.91 (1H, tdd, J=6.4, 10.3, 17.0 Hz), 6.96 (1H, s), 9.71 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (q), 15.7 (q), 55.1 (t), 62.9 (t), 119.6 (t), 121.8 (d), 132.5 (d), 136.3 (s), 137.7 (s), 151.8 (s), 155.0 (s), 183.8 (d). Anal. calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found C, 56.98; H, 6.11; N, 5.42.

3.5.2. 2-(*N*-Allyl-*N*-carbethoxy-amino)-benzothiophene-3-carbaldehyde (5b). Yield: 78%. Pale yellow oil. IR (nujol): 1719, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 4.21 (2H, q, J=7.0 Hz), 4.38 (2H, d, J=6.4 Hz), 5.10–5.28 (2H, overlapping), 5.94 (1H, tdd, J=6.4, 10.5, 17.1 Hz), 7.38 (1H, dd, J=7.3, 8.1 Hz), 7.46 (1H, dd, J=7.3, 7.8 Hz), 7.74 (1H, d, J=7.8 Hz), 8.61 (1H, d, J=8.1 Hz), 10.05 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 55.4 (t), 63.6 (t), 120.6 (t), 122.4 (d), 125.3 (d), 126.5 (d), 126.6 (d), 129.4 (s), 132.1 (d), 134.8 (s), 136.3 (s), 155.0 (s), 158.5 (s), 184.9 (d). Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found C, 62.45; H, 5.07; N, 5.02.

3.6. General procedure for the reactions between 5a,b and benzylhydroxylamine

A suspension of benzylhydroxylamine hydrochloride (90 mg, 0.56 mmol), $NaHCO_3$ (138 mg, 1.65 mmol) and $MgSO_4$ (1.13 g, 4.46 mmol) in Et_2O (30 ml) was stirred for 15 min. A solution of **5** (0.44 mmol) in Et_2O (2 ml) was added and the mixture was stirred at r.t. for 24 h. After filtration, the evaporation of the solvent under reduced pressure followed by recrystallization gave **6a** or **7b**.

3.6.1. *N*-Benzyl-*C*-[2-(*N*-carbethoxy-allylamino)-5-methyl-thien-3-yl]nitrone (6a). Yield: 89%. Mp 116–117 °C (cream crystals from diisopropyl ether). IR (nujol): 1711, cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, t, J=6.7 Hz), 2.43 (3H, s), 4.09–4.14 (4H, overlapping), 4.98 (2H, s), 5.10 (1H, d, J=16.5 Hz), 5.14 (1H, d, J=10.3 Hz), 5.72 (1H, tdd, J=6.3, 10.3, 16.5 Hz), 7.13 (1H, s), 7.37–7.45 (5H, overlapping), 8.00 (1H, s), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (q), 16.1 (q), 55.1 (t), 62.9 (t), 70.7 (t), 119.6 (t), 124.2 (d), 127.8 (d), 128.3 (d), 128.7 (d), 129.2 (d), 129.5 (d), 129.6 (d), 132.5 (d), 133.7 (s), 137.1 (s), 137.7 (s), 142.9 (s), 155.5 (s). Anal. calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.81. Found C, 63.57; H, 6.04; N, 7.62.

3.6.2. (3a*R,10c*R**)-1-Benzyl-5-carbethoxy-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (7b).** Yield: 72%. Mp 139–140 °C (white crystals from diisopropyl ether). IR (nujol): 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.42 (3H, br s), 3.25 (1H, br s), 3.88 (1H, br s), 4.12 (4H, br s), 4.32–4.70 (4H, overlapping), 7.19–7.55 (8H, overlapping), 7.73 (1H, br s). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.43 (3H, t, J=7.1 Hz), 3.25 (1H, br s), 3.87 (1H, dd, J=4.9, 8.2 Hz), 3.98–4.25 (4H, overlapping), 4.33–4.52 (4H, overlapping), 7.23 (1H, ddd, J=1.3, 7.2, 7.2 Hz), 7.27–7.32 (2H, overlapping), 7.35 (2H, dd, J=7.2, 7.5 Hz), 7.42 (2H, d, J=7.0 Hz), 7.46 (1H, d, J=7.2 Hz), 7.71 (1H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 40.6 (d), 46.2 (t), 60.1 (d), 60.2 (t), 63.5 (t), 68.6 (t), 121.2 (d), 122.0 (d), 123.6 (d), 124.6 (d), 127.8

(d), 128.7 (d), 129.5 (d), 135.9 (s), 137.4 (s), 138.0 (s), 140.9 (s), 153.8 (s), 155.4 (s). Anal. calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found C, 67.01; H, 5.47; N, 7.22.

3.6.3. Cycloaddition reaction of nitrone 6a. A solution of **6a** (568 mg, 1.6 mmol) in toluene (8 ml) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure to give (3a*R**,8b*R**)-1-benzyl-5-carbethoxy-1,3,3a,4,5,10c-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (**7a**) as a pure colourless oil. Yield: 94%. Oil. IR (nujol): 1697, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.38 (3H, t, $J=7.1$ Hz), 2.38 (3H, s), 3.00 (1H, br s), 3.70 (1H, dd, $J=4.4$, 8.2 Hz), 3.73–3.82 (2H, overlapping), 4.00 (1H, d, $J=13.4$ Hz), 4.11 (1H, dd, $J=4.6$, 12.8 Hz), 4.24–4.31 (2H, overlapping), 4.33 (2H, q, $J=7.1$ Hz), 6.40 (1H, s), 7.30–7.38 (3H, overlapping), 7.42 (2H, d, $J=7.3$ Hz).^1H NMR (400 MHz, DMSO, 100 °C) δ: 1.31 (3H, t, $J=7.1$ Hz), 2.32 (3H, s), 3.11–3.16 (1H, m), 3.57 (1H, dd, $J=4.5$, 8.1 Hz), 3.69 (1H, dd, $J=8.1$, 12.9 Hz), 3.90–4.02 (2H, overlapping), 3.97, 4.14 (2H, sistema AB, $J=13.8$ Hz), 4.21 (1H, dd, $J=8.0$, 8.1 Hz), 4.25 (2H, q, $J=7.1$ Hz), 6.46 (1H, s), 7.30–7.43 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.3 (d), 45.2 (t), 61.0 (t), 62.2 (d), 63.0 (t), 68.8 (t), 118.1 (s), 123.2 (d), 127.8 (d), 128.8 (d), 129.3 (d), 131.7 (s), 136.4 (s), 137.9 (s), 153.4 (s). Anal. calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.81. Found C, 63.82; H, 6.01; N, 7.98.

3.7. General procedure for the reactions between 5a,b and 8

A solution of **5** (1.58 mmol), **8** (195 mg, 1.42 mmol), and $MgSO_4$ (1.90 g, 15.8 mmol) in Et_2O (15 ml) was stirred at rt for 72 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to afford **10** or **15** and **19**.

3.7.1. (*R*)-*N*-(α-Methylbenzyl)-*C*-[5-methyl-2-(*N*-carbethoxy-allylamino)-thien-3-yl] nitrone (10). Yield: 81%. Pale yellow oil. $[\alpha]_D^{23}=+39.2$ ($c=1.00$, EtOH). IR (nujol): 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, br s), 1.84 (3H, d, $J=6.9$ Hz), 2.41 (3H, s), 4.05–4.12 (4H, overlapping), 5.04–5.14 (3H, overlapping), 5.75 (1H, tdd, $J=6.6$, 11.2, 17.2 Hz), 7.20 (1H, s), 7.33–7.40 (3H, overlapping), 7.47 (2H, d, $J=7.6$ Hz), 8.00 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 16.1 (q), 19.2 (q), 55.1 (t), 62.8 (t), 74.9 (d), 119.7 (t), 124.4 (d), 126.8 (d), 127.6 (d), 128.8 (s), 129.1 (d), 129.2 (d), 132.6 (d), 137.1 (s), 138.9 (s), 142.5 (s), 155.7 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.65; H, 6.36; N, 7.34.

3.7.2. (α*R*,3a*S*,10c*S*)-5-Carbethoxy-1-(α-methylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (15). Yield: 34%. Mp 194–195 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+148.5$ ($c=0.13$, $CHCl_3$). IR (nujol): 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.42 (3H, t, $J=7.1$ Hz), 1.56 (3H, d, $J=6.4$ Hz), 3.25–3.61 (2H, overlapping), 3.93 (1H, dd, $J=5.7$, 5.8 Hz), 3.99 (1H, q, $J=6.4$ Hz), 4.29–4.47 (3H, overlapping), 4.49–4.67 (2H, overlapping), 6.89 (1H, br s), 7.09 (1H, dd, $J=7.3$, 7.7 Hz), 7.16 (1H, dd, $J=7.2$, 7.8 Hz), 7.42 (1H, dd, $J=7.2$, 7.3 Hz), 7.47 (2H, dd, $J=7.1$, 7.5 Hz), 7.53 (2H, d, $J=7.4$ Hz), 7.61 (1H, d, $J=7.9$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 20.5 (q), 41.2 (d), 46.2 (t), 59.3 (d), 63.4 (t), 63.6 (d), 68.0 (t), 121.6 (d), 122.0 (d), 123.5 (d), 124.0 (d), 128.6 (d), 129.0 (d), 129.2 (d), 135.9 (s), 137.1 (s), 140.8 (s), 142.8 (s), 143.3 (s), 154.1 (s). Anal. calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found C, 67.49; H, 5.88; N, 6.98.

3.7.3. (α*R*,3a*R*,10c*R*)-5-Carbethoxy-1-(α-methylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (19). Yield: 14%. Mp 151–152 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-65.5$ ($c=0.09$, $CHCl_3$). IR (nujol): 1721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.39 (3H, t, $J=7.2$ Hz), 1.68 (3H, d, $J=6.6$ Hz), 3.15–3.24 (1H, m), 3.55–3.62 (1H, m), 3.68 (1H, dd, $J=7.3$, 7.5 Hz), 4.05–4.15 (2H, overlapping), 4.27–4.42 (2H, overlapping), 4.43–4.50 (1H, m), 4.88 (1H, d, $J=7.5$ Hz), 7.22–7.31 (2H, overlapping), 7.32 (2H, dd, $J=6.9$, 7.6 Hz), 7.37 (1H, dd, $J=7.1$, 8.1 Hz), 7.43–7.52 (2H, overlapping), 7.71 (1H, d, $J=7.9$ Hz), 7.84 (1H, d, $J=8.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 22.9 (q), 40.9 (d), 44.8 (t), 58.8 (d), 63.4 (t), 63.6 (d), 67.9 (t), 121.8 (d), 122.0 (d), 123.6 (d), 124.5 (d), 127.8 (d), 128.7 (d), 129.2 (d), 137.1 (s), 140.8 (s), 142.6 (s), 143.3 (s), 143.5 (s), 154.0 (s). Anal. calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found C, 67.55; H, 6.05; N, 6.93.

3.8. Cycloaddition reaction of nitrone 10

A solution of **10** (350 mg, 0.9 mmol) in toluene (8 ml) was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to give **18** and **14**.

3.8.1. (α*R*,3a*R*,8b*R*)-5-Carbethoxy-7-methyl-1-(α-methylbenzyl)-1,3,3a,4,5,8b-hexahydro-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (18). Yield: 38%. Mp 132–133 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+52.2$ ($c=0.23$, $CHCl_3$). IR (nujol): 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.36 (3H, t, $J=7.1$ Hz), 1.57 (3H, d, $J=6.7$ Hz), 2.41 (3H, s), 2.86 (1H, br s), 3.63 (1H, dd, $J=4.7$, 8.1 Hz), 3.80–3.86 (1H, m), 3.93 (1H, dd, $J=4.7$, 12.9 Hz), 4.03 (1H, dd, $J=7.7$, 7.8 Hz), 4.05–4.12 (2H, overlapping), 4.30 (2H, q, $J=7.1$ Hz), 6.55 (1H, s), 7.29 (1H, d, $J=8.2$ Hz), 7.37 (2H, dd, $J=8.2$, 8.2 Hz), 7.48 (2H, d, $J=8.2$ Hz). ^1H NMR (400 MHz, DMSO, 80 °C) δ: 1.28 (3H, t, $J=7.1$ Hz), 1.41 (3H, d, $J=6.6$ Hz), 2.35 (3H, s), 3.08–3.18 (1H, m), 3.42 (1H, dd, $J=5.2$, 8.0 Hz), 3.76–3.84 (2H, overlapping), 3.97 (1H, dd, $J=8.0$, 8.1 Hz), 4.05 (1H, q, $J=6.6$ Hz), 4.17–4.28 (3H, overlapping), 6.56 (1H, s), 7.24 (1H, d, $J=8.2$ Hz), 7.32 (2H, dd, $J=8.2$, 8.2 Hz), 7.39 (2H, d, $J=8.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 22.3 (q), 41.3 (d), 44.9 (t), 58.7 (d), 62.9 (t), 63.8 (d), 68.2 (t), 120.7 (s), 123.4 (d), 127.7 (d), 128.7 (d), 131.9 (s), 136.2 (s), 142.3 (s), 153.6 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.54; H, 6.40; N, 7.63.

3.8.2. (α*R*,3a*S*,8b*S*)-5-Carbethoxy-7-methyl-1-(α-methylbenzyl)-1,3,3a,4,5,8b-hexahydro-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (14). Yield: 51%. Mp 164–165 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+27.7$ ($c=$

1.00, $CHCl_3$).IR (nujol): 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.36 (3H, t, J=7.1 Hz), 1.52 (3H, d, J=6.4 Hz), 2.31 (3H, s), 3.18–3.24 (1H, m), 3.59 (1H, br d, J=14.6 Hz), 3.80 (1H, dd, J=5.9, 8.1 Hz), 3.92 (1H, q, J=6.4 Hz), 4.09 (1H, d, J=7.4 Hz), 4.20 (1H, br s), 4.26–4.34 (3H, overlapping), 6.13 (1H, s), 7.32 (1H, d, J=8.2 Hz), 7.38 (2H, dd, J=8.2, 8.2 Hz), 7.45 (2H, d, J=8.2 Hz). ^1H NMR (400 MHz, DMSO, 80 °C) δ: 1.28 (3H, t, J=7.1 Hz), 1.37 (3H, d, J=6.4 Hz), 2.26 (3H, s), 3.22–3.36 (1H, m), 3.57 (1H, dd, J=5.9, 8.1 Hz), 3.61 (1H, dd, J=3.5, 13.2 Hz), 3.94–4.08 (3H, overlapping), 4.18–4.28 (3H, overlapping), 6.08 (1H, s), 7.36 (1H, d, J=8.2 Hz), 7.39 (2H, dd, J=8.2, 8.2 Hz), 7.43 (2H, d, J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 21.9 (q), 40.3 (d), 45.0 (t), 60.1 (d), 63.0 (t), 64.1 (d), 68.1 (t), 122.2 (s), 123.1 (d), 128.2 (d), 129.2 (d), 131.7 (s), 136.1 (s), 143.6 (s), 153.8 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.41; H, 6.68; N, 7.34.

3.9. General procedure for the reactions between 5a,b and 9

A solution of **5** (1.65 mmol), **9** (315 mg, 2.06 mmol) and $MgSO_4$ (2.00 g, 16.5 mmol) in Et_2O (20 ml) was stirred at r.t. for 72 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to afford **12** or **17** and **21**.

3.9.1. (*R*)-*N*-(α-Hydroxymethylbenzyl)-*C*-[5-methyl-2-(*N*-carbethoxy-allylamino)-thien-3-yl] nitrone (12). Yield: 74%. Pale yellow oil. $[\alpha]_D^{23}=-64.3$ (c=1.00, $CHCl_3$). IR (nujol): 3414, 1726 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, br s), 2.46 (3H, s), 3.80 (1H, br s, missing after deuteriation), 3.92 (1H, dd, J=3.4, 12.2 Hz), 4.01–4.15 (4H, overlapping), 4.53 (1H, dd, J=8.9, 12.2 Hz), 5.01–5.08 (2H, overlapping), 5.10 (1H, d, J=10.2 Hz), 5.73 (1H, tdd, J=6.5, 10.2, 16.8 Hz), 7.18 (1H, s), 7.37–7.42 (3H, overlapping), 7.44–7.48 (2H, overlapping), 7.99 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (q), 16.1 (q), 55.1 (t), 62.9 (t), 63.9 (t), 79.9 (d), 119.8 (t), 124.2 (d), 127.9 (d), 128.2 (s), 129.2 (d), 129.3 (d), 129.4 (d), 130.0 (d), 132.4 (d), 135.5 (s), 137.3 (s), 143.7 (s), 155.6 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.91; H, 6.39; N, 7.11.

3.9.2. (α*R*,3a*S*,10c*S*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (17). Yield: 25%. Mp 197–198 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+76.8$ (c=0.04, $CHCl_3$). IR (nujol): 3432, 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, br s), 2.47 (1H, br s), 2.83 (1H, br s, missing after deuteriation), 3.45 (1H, br s), 3.65 (1H, dd, J=7.6, 7.6 Hz), 3.77 (1H, dd, J=3.6, 10.2 Hz), 3.94 (1H, dd, J=8.0, 8.2 Hz), 4.12–4.44 (5H, overlapping), 4.83 (1H, br s), 7.29 (1H, dd, J=7.6, 7.7 Hz), 7.38–7.44 (4H, overlapping), 7.48–7.54 (2H, overlapping), 7.74 (2H, d, J=7.4 Hz). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.38 (3H, t, J=7.1 Hz), 2.58 (2H, br s, missing after deuteriation), 3.53 (1H, dd, J=3.5, 9.2 Hz), 3.66 (1H, dd, J=7.6, 7.6 Hz), 3.78 (1H, dd, J=3.6, 10.2 Hz), 3.94 (1H, dd, J=8.0, 8.2 Hz), 4.12–4.44 (5H, overlapping), 4.83 (1H, d, J=7.6 Hz), 7.27 (1H, dd, J=7.6, 7.7 Hz), 7.38–7.44 (4H, overlapping), 7.48–7.54 (2H, overlapping), 7.73 (1H, d, J=7.4 Hz), 7.75 (1H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 40.8 (d), 44.1 (t), 60.1 (d), 63.5 (t), 64.3 (t), 72.5 (d), 68.0 (t), 121.4 (d), 122.2 (d), 123.7 (d), 124.8 (d), 129.0 (d), 129.2 (d), 129.7 (d), 135.9 (s), 137.4 (s), 137.6 (s), 137.7 (s), 139.6 (s), 153.9 (s). Anal. calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60. Found C, 64.90; H, 5.58; N, 6.78.

3.9.3. (α*R*,3a*R*,10c*R*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (21). Yield: 54%. Mp 170–171 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-392.0$ (c=0.05, $CHCl_3$). IR (nujol): 3429, 1742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.49 (3H, br s), 2.91 (1H, br s, missing after deuteriation), 3.51 (1H, br s), 3.61 (1H, br s), 3.84–3.90 (1H, m), 3.97 (1H, dd, J=6.9, 7.4 Hz), 4.07 (1H, dd, J=3.6, 6.8 Hz), 4.27–4.40 (3H, overlapping), 4.51–4.62 (3H, overlapping), 6.99–7.22 (3H, overlapping), 7.42–7.58 (5H, overlapping), 7.65 (1H, br s). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.42 (3H, t, J=7.1 Hz), 2.72 (1H, br s, missing after deuteriation), 3.51 (1H, br d, J=13.0 Hz), 3.53–3.59 (1H, m), 3.89 (1H, br d, J=10.2 Hz), 3.96 (1H, dd, J=6.4, 7.8 Hz), 4.06 (1H, dd, J=4.0, 6.4 Hz), 4.26 (1H, dd, J=6.5, 11.7 Hz), 4.32–4.45 (2H, overlapping), 4.48–4.67 (3H, overlapping), 7.10 (1H, br s), 7.16 (1H, ddd, J=1.1, 7.1, 7.1 Hz), 7.20 (1H, ddd, J=1.6, 7.1, 7.1 Hz), 7.41–7.59 (5H, overlapping), 7.64 (1H, dd, J=1.6, 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 40.6 (d), 45.2 (t), 60.1 (d), 63.6 (t), 67.7 (t), 68.2 (t), 69.5 (d), 121.9 (d), 122.4 (d), 123.7 (d), 124.2 (d), 129.1 (d), 129.5 (d), 129.6 (d), 135.5 (s), 136.7 (s), 138.0 (s), 138.1 (s), 141.0 (s), 154.0 (s). Anal. calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60. Found C, 65.06; H, 5.81; N, 6.38.

3.10. Cycloaddition reaction of nitrone 12

A solution of **12** (250 mg, 0.6 mmol) in toluene (8 ml) was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane/AcOEt (5:1) as eluent to give **16** and **20**.

3.10.1. (α*R*,3a*S*,8b*S*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,8b-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (16). Yield: 22%. Mp 131–132 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-72.4$ (c=0.25, $CHCl_3$). IR (nujol): 3447, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.37 (3H, t, J=7.1 Hz), 1.56 (1H, br s, missing after deuteriation), 2.43 (3H, s), 2.61 (1H, br s), 3.64 (1H, dd, J=4.3, 7.8 Hz), 3.67 (1H, dd, J=9.5, 12.7 Hz), 3.70–3.79 (1H, m), 3.90–3.98 (2H, overlapping), 4.04 (1H, br dd, J=4.3, 12.9 Hz), 4.09–4.18 (2H, overlapping), 4.31 (2H, q, J=7.1 Hz), 6.57 (1H, s), 7.36–7.43 (3H, overlapping), 7.49–7.54 (2H, overlapping). ^1H NMR (400 MHz, DMSO, 100 °C) δ: 1.29 (3H, t, J=7.1 Hz), 2.37 (3H, s), 2.97–3.09 (1H, m), 3.44 (1H, dd, J=3.6, 7.3 Hz), 3.63–3.73 (1H, m), 3.78–3.88 (3H, overlapping), 3.91 (1H, dd, J=8.0, 8.0 Hz), 4.00 (1H, dd, J=5.1, 7.3 Hz), 4.23 (2H, q, J=7.1 Hz), 4.46 (1H, d, J=7.2 Hz), 6.63 (1H, s), 7.28–7.34 (3H, overlapping), 7.39–7.44 (2H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.4 (d), 44.7 (t), 57.7 (d), 63.0

(t), 64.4 (t), 69.0 (t), 69.4 (d), 122.9 (d), 128.7 (d), 128.8 (d), 129.2 (s), 130.6 (d), 131.8 (s), 136.3 (s), 136.9 (s), 153.3 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.84; H, 6.08; N, 7.37.

3.10.2. (α*R*,3a*R*,8b*R*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,8b-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (20). Yield: 68%. Mp 117–118 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23} = -31.1$ ($c=0.24$, $CHCl_3$). IR (nujol): 3455, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.37 (3H, t, $J=7.1$ Hz), 2.33 (3H, s), 2.91–2.96 (1H, m), 3.24–3.32 (1H, m), 3.51–3.57 (1H, m), 3.77 (1H, ddd, $J=3.3$, 8.6, 11.9 Hz), 3.87 (1H, dd, $J=6.8$, 7.7 Hz), 3.99 (1H, dd, $J=3.4$, 6.8 Hz), 4.12–4.20 (2H, overlapping), 4.25–4.37 (3H, overlapping), 4.44 (1H, dd, $J=7.9$, 9.3 Hz), 6.20 (1H, s), 7.35–7.47 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.1 (d), 44.5 (t), 61.0 (d), 63.2 (t), 68.4 (t), 68.9 (t), 69.9 (d), 121.3 (s), 122.7 (d), 128.6 (d), 128.9 (d), 129.5 (d), 132.2 (s), 135.3 (s), 138.6 (s), 153.8 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.69; H, 6.32; N, 7.07.

Acknowledgements

We are grateful to MURST and CNR for financial support.

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