Synthesis L. Tenora et al. Paper

The Synthesis of Two Regioisomeric Aldehydes with a Tetrahydrobenzo[*b*]thiophene Scaffold and Their Application in Solvent-Free Intramolecular 1,3-Dipolar Cycloaddition Reactions

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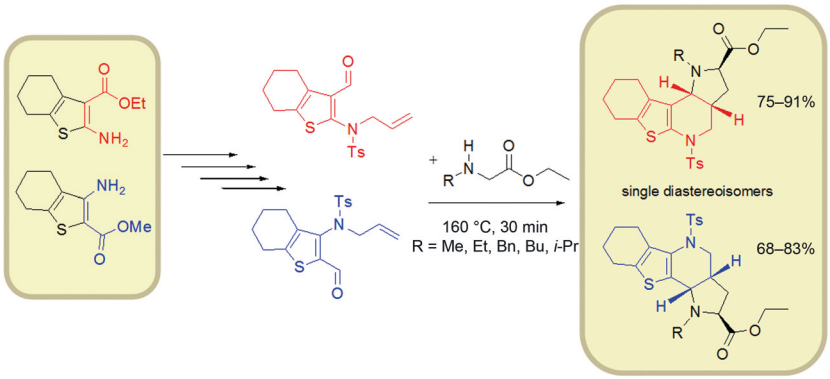


Received: 12.02.2016
Accepted after revision: 07.03.2016
Published online: 26.04.2016
DOI: 10.1055/s-0035-1561428; Art ID: ss-2016-t0108-op

Abstract The paper describes the synthesis of two regioisomeric 2-amino-3-formyl- and 3-amino-2-formyl-substituted derivatives of tetrahydrobenzo[*b*]thiophene and their subsequent thermally initiated reactions with secondary amines to give azomethine ylides that undergo intramolecular 1,3-dipolar cycloadditions. In this way, two series of new fused heterocyclic compounds with three stereogenic centers were prepared. The compounds were identified and their structures were determined.

Key words dipolar cycloadditions, benzothiophenes, polycycles, heterocycles, azomethine ylides

Fused heterocyclic compounds are known for their important biological properties and they are often used in medicine as effective drugs. Studies have shown that the substituted 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene skeleton exhibits activity against cancer cells,[1,2] as well as antimicrobial activity.[3] Derivatives of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene have recently been applied in medicine as antidepressants[4] and as useful agents for the treatment of metabolic disorders (diabetes type II and obesity).[5] These activities are retained and even enhanced when the skeleton is fused to other heterocyclic systems.[6–9] Furthermore, it is interesting to note that the use of such compounds in electroluminescent devices has also been patented.[10]

In this study, we decided to extend our synthesis of benzothiophenes to more-complex structures for which the starting molecules were regioisomeric substituted tetrahydrobenzo[*b*]thiophenes (Figure 1) and to apply 1,3-dipolar cycloaddition.

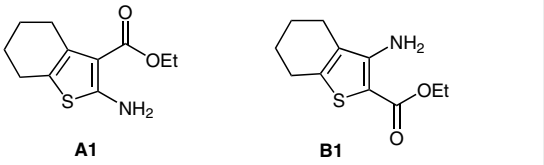
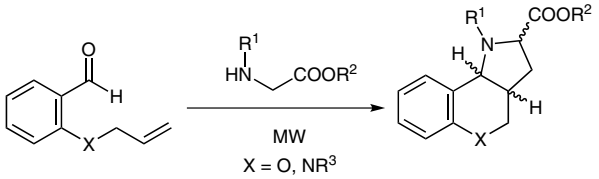


Figure 1 Starting regioisomeric molecules **A1** and **B1**

1,3-Dipolar cycloaddition is a powerful tool for the synthesis of five-membered heterocyclic compounds. For the reaction, a dipole and a dipolarophile are required. Several types of dipoles can enter into these cyclization reactions.[11] In the case of a molecule that contains two assemblies of atoms, one acting as a dipole and the other as a dipolarophile, it is possible to achieve intramolecular 1,3-dipolar cycloaddition and, in this way, to form new fused rings. Such reactions are characterized by high regio- and stereoselectivities. A frequently used method for preparing azomethine ylide involves an aldehyde and an amino ester.

In our laboratory, we have experience in the application of thermally initiated intramolecular 1,3-dipolar cycloaddition reactions and have published results concerning the synthesis and stereoselectivity of fused heterocyclic compounds, generally through the application of microwaves. For example, we used this method to synthesize hexahydrochromeno[4,3-*b*]pyrroles (X = O) and hexahydropyrrolo[3,2-*c*]quinolines (X = NR[2]) (Scheme 1).[12–15]

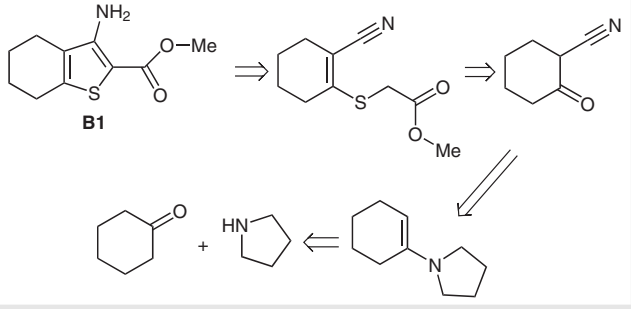
Whereas amino ester **A1** is readily available by means of the Gewald procedure,[16] in which cyclohexanone reacts with ethyl cyanoacetate and sulfur in the presence of a base (usually pyridine), its regioisomer **B1**, with an amino group in the 3-position, is not as easily prepared. There is little information available about its synthesis or the synthesis of



Scheme 1 Microwave-initiated 1,3-dipolar cycloaddition to give hexahydrochromeno[4,3-*b*]pyrroles or hexahydropyrrolo[3,2-*c*]quinolines

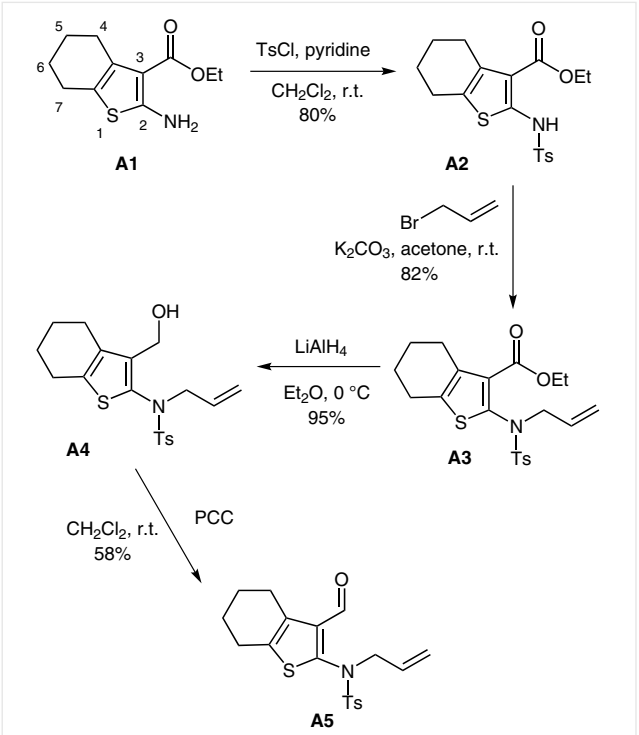
its derivatives. In the patent literature, Edwards et al. describe a method for the preparation of amino ester **B1**, but they focus mainly on its properties and applications.[8] Derivatives of **B1** are potential nucleic acid antimetabolites, and they have been used as modulators of histamine H4 receptors and for the treatment of disease states, disorders, and conditions mediated by the receptors connected with allergy-related diseases.[8,9]

However, when we used Edwards's procedure, the yield did not exceed 40%. We therefore developed a new improved method for the synthesis of this scaffold, which we recently published.[17] This new procedure also starts from cyclohexanone, but proceeds according to Kuehne's protocol.[18] Details of this procedure are described in our published paper[17] and our retrosynthetic approach is shown in Scheme 2.



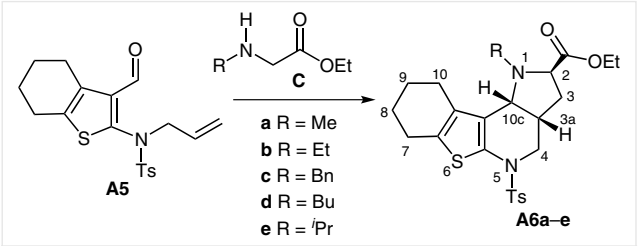
Scheme 2 Retrosynthetic approach to ester **B1**

To achieve intramolecular 1,3-dipolar cycloaddition, we needed an appropriate amino aldehyde with an allyl substituent in the β-position. Consequently, our previously prepared β-amino esters **A1** and **B1** required further modification. First, the amino group was protected from further reactions by the introduction of a tosyl group. Tosylation with tosyl chloride in dichloromethane in the presence of pyridine at room temperature for 24 hours gave, after crystallization, a white product in 80% yield. The next step was to introduce an allyl group onto the partially protected amino group. Allylation with allyl bromide was conducted in acetone in the presence of potassium carbonate. An excess of allyl bromide (the total molar amount was three times that of the starting molecule) was slowly added in several portions over 24 hours to give the allyl derivative **A3** as white crystals in 82% yield (Scheme 3). Subsequently, the ester group was reduced to an alcohol by treatment with $LiAlH_4$ (95%) in diethyl ether at ~0 °C. The final preliminary step, before attempting the intramolecular dipolar cycloaddition, was to oxidize the alcohol to an aldehyde. For this oxidation, we tested Swern oxidation and oxidation with PCC; the latter gave alcohol **A4** in 58% yield. Both the temperature of the reaction mixture and the method of reagent addition were crucial in this reaction (see the experimental section). The second regioisomer **B1** was similarly converted into the corresponding aldehyde, except that the methyl ester derivative was used instead of the ethyl ester. In the final oxidizing step, PCC was the preferred oxidant (68%).

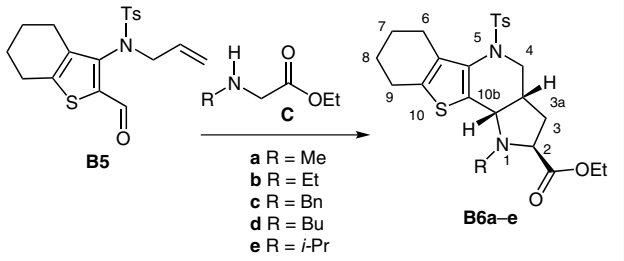


Scheme 3 Overview of synthetic pathway to product **A5**

Azomethine ylides were formed in situ from aldehydes **A5** (Scheme 4) and **B5** (Scheme 5) with various *N*-substituted ethyl 2-aminoacetates **C**.



Scheme 4 Summary of intramolecular 1,3-dipolar cycloaddition of aldehyde **A5** with amino esters **C** and the formation of products **A6a–e** as the only diastereoisomers (one enantiomer is depicted)



Scheme 5 Summary of intramolecular 1,3-dipolar cycloaddition of aldehyde **B5** with amino esters **C** and the formation of products **B6a–e** as the only diastereoisomers (one enantiomer is depicted)

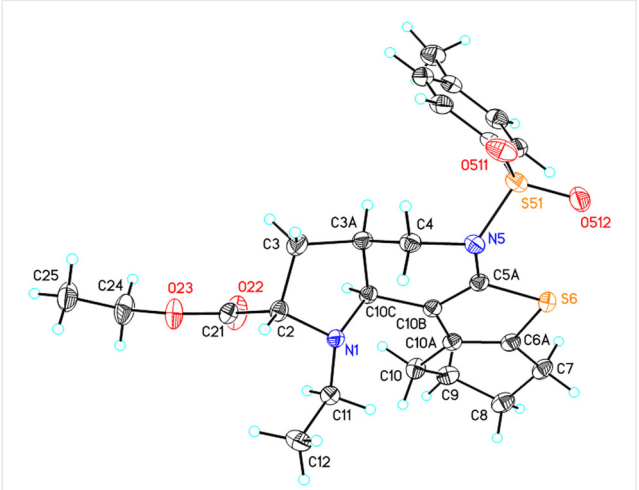


Figure 2 ORTEP diagram of the racemic compound **A6b**

First, we attempted to establish optimal conditions for the reaction by varying the reaction temperature, the reaction time, and the molar ratio of the two components. For this optimization, ethyl (ethylamino)acetate (ethyl *N*-ethylglycinate) was chosen as the reference amine. Reactions were carried out in a preheated oil bath, and the temperature (140–200 °C), reaction time (5–90 min), and excess of the secondary amine (1–2.5 mol) were varied. The progress of the reaction was monitored by both TLC and ^{1}H NMR. The following conditions were found to be optimal: temperature, 160 °C; time, 30 min; and aldehyde/secondary amine molar ratio, 1:2. Under these conditions, we observed full conversion. Only with **Ce** (R = *i*-Pr) did a prolonged reaction time (60 min) and molar ratio of 1:2.5 have to be used. The yields of products **A6a–e** and **B6a–e** are summarized in Table 1. The multiplet of the allyl group (δ = 3.7 to 3.9 ppm) and the signal of the aldehyde group (δ = 9.90 ppm) in the ^{1}H NMR spectrum were used as indicators of the progress of the reaction. For structural assignments, ^{1}H and ^{13}C NMR spectra were used, with confirmation by 2D HSQC NMR. The structures of the tetracyclic products were finally confirmed by an X-ray structure analysis of **A6b** (Figure 2 and Supporting Information).

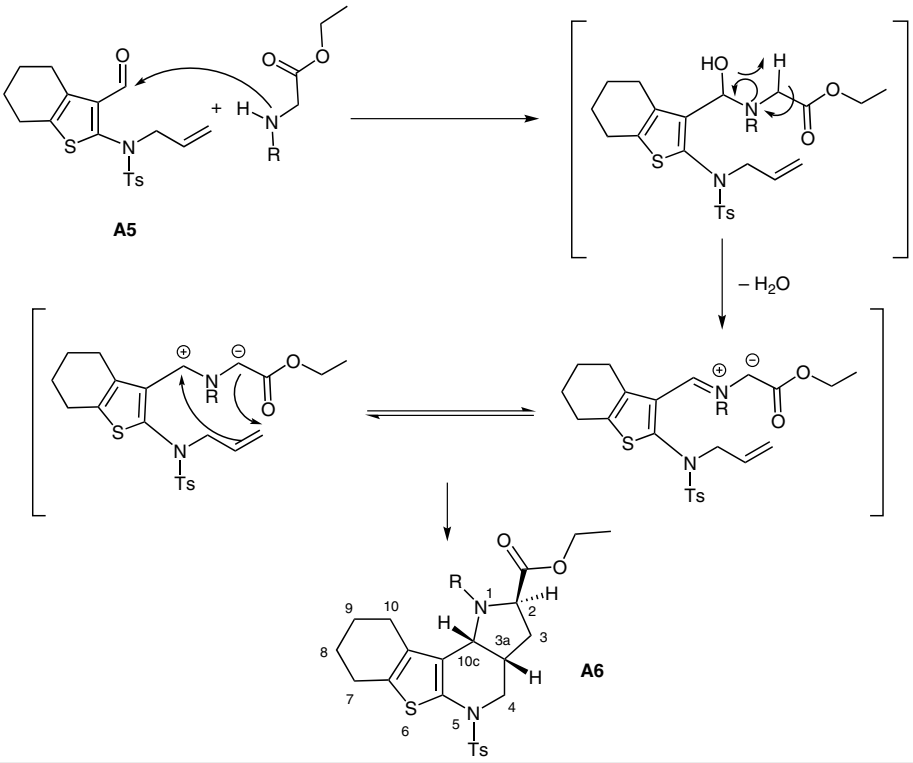
Table 1 1,3-Dipolar Cycloaddition Reaction with *N*-Substituted Ethyl Aminoacetates **C**

	R	Yield (%) of isomer **A6**	Yield (%) of isomer **B6**
a	Me	79	68
b	Et	91	77
c	Bn	88	70
d	Bu	86	83
e	*i*-Pr	75	74

The proposed mechanism for the formation of product **A6** is presented in Scheme 6. Cyclization to product **B6** proceeds analogously. The nucleophilic secondary amine attacks the electrophilic carbon atom of the aldehyde and, after water splits off, a 1,3-dipole azomethine ylide is formed in situ. This enters into intramolecular 1,3-dipolar cycloaddition to form two new heterocyclic systems.

During the intramolecular 1,3-dipolar cycloaddition, three stereogenic centers are created in positions 2, 3a, and 10c (Scheme 6). We might therefore expect the formation of four racemic diastereoisomers. However, even when the temperature of the reaction was varied, only one racemic diastereomer was obtained. The NOESY spectrum suggested that the hydrogen atoms at the 10c- and 3a-positions are oriented toward one side, and to the side opposite to the hydrogen atom in the 2-position. This idea was supported by the observation of the hydrogen atoms in the 3′ and 3″ positions. NOESY interactions were observed only between the hydrogen atoms in the 2 and 3′ positions and between those in the 3″ and 3a positions, which indicated opposite orientations for the hydrogen atoms in the 2 and 3a positions. These conclusions were confirmed by X-ray crystal structure analysis.[20]

In summary, two regioisomeric derivatives of aminotetrahydrobenzothiophenecarbaldehyde were prepared and derivatized to permit subsequent formation of the corresponding azomethine ylides. Under thermal initiation, the aldehydes reacted with alkyl (alkylamino)acetates to give azomethine ylides in situ; these azomethine ylides reacted further to form new heterocyclic systems. Thus, by this reaction, we prepared two new series of polycyclic systems containing three stereogenic centers. Their structures, including the stereochemical arrangement at the stereogenic centers, were determined. We found that one racemic diastereoisomer was obtained in each case. The configurations of all three stereogenic centers in the molecule were the same in both regioisomers.



Scheme 6 Plausible mechanism for the 1,3-dipolar cycloaddition of compound **A5** and N-R substituted 2-amino ethyl acetate **C** (one enantiomer of compound **A6** is depicted).

All chemicals were used as purchased. If necessary, solvents were dried according to procedures reported in the literature.[19] CH_2Cl_2 was distilled sequentially from anhyd $CaCl_2$ and P_2O_5 then stored over MS (3 Å). Et_2O was dried over Na anhydrous freshly distilled before use. Pyridine was distilled from KOH and stored over MS (3 Å). PE for chromatography was fractionally distilled before use. The series of secondary amines[13] and both starting esters **A1** and **B1** were prepared according to the reported methods.[16,17]

Most of the reactions were carried out under a dry argon, and all reactions were monitored by TLC (Merck F254 silica gel). Column chromatography was performed on a Horizon HPFC system (Biotage, Uppsala) with a FLASH Si 25+M cartridge. Melting points were measured on an MPM HV2 instrument. FT-IR spectra were recorded on a Genesis ATI (Mattson/Unicam) spectrometer. ^1H and ^{13}C NMR spectra were recorded by using a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^1H) or 75.47 MHz (^{13}C), with $CDCl_3$ as the solvent. TMS (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.27 ppm) served as internal standards for ^1H NMR spectroscopy, and $CDCl_3$ (δ = 77.23 ppm) for ^{13}C NMR spectroscopy. GC/MS data were obtained on a ThermoQuest Trace MS apparatus with EI ionization at 70 eV or on a Shimadzu GCMS-QP2010 operated in EI mode at 70 eV. MS data were obtained on a Fisons Instruments TRIO 1000 spectrometer at 70 eV in EI mode and by thermal desorption. High-resolution mass spectra were recorded on a Q-Tof Micromass instrument operated in the positive ESI (CV = 30 V) mode. X-ray diffraction data were collected on a Kuma KM-4 four-circle CCD diffractometer, and were corrected for Lorentz and polarization effects. The structures were resolved by direct methods and refined by full-matrix least-squares methods using the SHELXTL program package.[21] The hydrogen atoms were placed in calculated idealized positions and refined as riding.

Ethyl 2-(Tosylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (A2)

Compound **A1** (10.0 g, 44.4 mmol, 1 equiv) was dissolved in distilled CH_2Cl_2 (105 mL), and TsCl (13.1 g, 68.9 mmol, 1.6 equiv) and pyridine (5.89 g, 74.8 mmol, 1.7 equiv) were added. The mixture was stirred for 24 h at r.t. under argon. H_2O (70 mL) was added, and the mixture was stirred for a further 2 h. The organic phase was separated and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude red-brown solid was recrystallized from EtOH to give colorless crystals; yield: 13.1 g (80%); mp 132–133 °C.

IR (KBr): 1028, 1090, 1165, 1223, 1381, 1502, 1660, 2943, 3122, 3413, 3475, 3548 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.69–1.78 (m, 4 H, H5 + H6), 2.41 (s, 3 H, $C_6H_4CH_3$), 2.55–2.71 (m, 4 H, H4 + H7), 4.26 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 7.27 (d, *J* = 8.6 Hz, 2 H, $C_6H_4CH_3$), 7.81 (d, *J* = 8.6 Hz, 2 H, $C_6H_4CH_3$), 10.44 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 21.7 ($C_6H_4CH_3$), 21.7 and 23.0 (CH_2-C5 + C6), 24.6 (CH_2-C4), 26.6 (CH_2-C7), 60.8 (CH_2CH_3), 113.6 (C), 126.8 (C), 127.5 and 129.9 (2 × 2 CH-$C_6H_4CH_3$), 132.2 (C), 136.2 (C), 144.4 (C), 148.1 (C), 166.0 (*C*OOEt).

MS (EI, 70 eV): *m/z* (%) = 379 [M^+] (90), 333 (15), 269 (20), 224 (100), 178 (80), 91 (60).

Methyl 3-(Tosylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (B2)

Compound **B1** (5.00 g, 23.7 mmol, 1 equiv) was dissolved in distilled CH_2Cl_2 (50 mL) and then TsCl (6.77 g, 35.5 mmol, 1.5 equiv) and pyridine (2.81 g, 35.5 mmol, 1.5 equiv) were added. The mixture was stirred for 22 h at r.t. under argon. The starting ester was still detected by TLC (CH_2Cl_2) and therefore extra TsCl (4.51 g, 23.7 mmol, 1 equiv) and pyridine (1.87 g, 23.7 mmol, 1 equiv) were added and the mixture was stirred for a further 21 h. H_2O (35 mL) was then added and the mixture was stirred for 2 h. The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude brown solid was recrystallized (EtOH) to give a colorless solid; yield: 5.80 g (67%); mp 114–116 °C.

IR (KBr): 1057, 1095, 1163, 1186, 1198, 1284, 1323, 1396, 1446, 1475, 1560, 1595, 1680, 2931, 2953, 3153, 3190, 3207 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.74–1.77 and 1.86–1.90 (m, 4 H, H5 + H6), 2.39 (s, 3 H, $C_6H_4CH_3$), 2.74–2.83 (m, 4 H, H4 + H7), 3.54 (s, 3 H, $COOCH_3$), 7.19 (d, *J* = 7.5 Hz, 2 H, $C_6H_4CH_3$), 7.53 (d, *J* = 7.5 Hz, 2 H, $C_6H_4CH_3$), 8.17 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 ($C_6H_4CH_3$), 22.3 and 22.9 (CH_2-C5 + C6), 24.9 (CH_2-C4), 26.0 (CH_2-C7), 51.7 ($COOCH_3$), 116.8 (C), 127.6 and 129.1 (2 × 2CH-$C_6H_4CH_3$), 135.1 (C), 135.4 (C), 140.6 (C), 143.5 (C), 143.9 (C), 163.1 ($COOCH_3$).

MS (EI, 70 eV): *m/z* (%) = 365 [M^+] (10), 210 (100), 196 (10), 178 (20), 154 (10), 91 (15), 65 (10).

Ethyl 2-[Allyl(tosyl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (A3)

Ester **A2** (10.0 g, 26.4 mmol, 1 equiv) was dissolved in acetone (120 mL). K_2CO_3 (5.64 g, 40.8 mmol, 1.5 equiv) was added in a single portion, and then allyl bromide (4.62 g, 38.2 mmol, 1.4 equiv) was added dropwise. The suspension was stirred for 24 h at r.t. while the reaction was monitored by TLC (CH_2Cl_2). After this time, the conversion to product was incomplete, so a second portion of allyl bromide (4.62 g, 38.2 mmol, 1.4 equiv) was added and the mixture was stirred for a further 16 h, after which the starting compound was completely consumed. The mixture was filtered and the solid residue was washed with acetone (20 mL). The solvent was removed under reduced pressure and the crude orange solid was recrystallized from EtOH to give colorless crystals; yield: 9.1 g (82%); mp 122–123 °C.

IR (KBr): 1061, 1088, 1165, 1242, 1267, 1352, 1417, 1707, 2845, 2931, 3089 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.70–1.79 (m, 4 H, H5 + H6), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.60–2.85 (m, 4 H, H4 + H7), 4.11 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.22 (d, *J* = 8.3 Hz, 2 H, CH_2CH), 5.10–5.18 (m, 2 H, $=CH_2$), 5.80–5.95 (m, 1 H, CH_2CH), 7.27 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$), 7.65 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 21.7 ($C_6H_4CH_3$), 22.6 and 22.9 (CH_2-C5 + C6), 25.3 (CH_2-C4), 25.9 (CH_2-C7), 55.9 (CH_2CH), 60.7 (CH_2CH_3), 119.3 ($=CH_2$), 128.0 and 129.6 (2 × 2CH-$C_6H_4CH_3$), 130.7 (C), 133.0 (CH_2CH), 134.5 (C), 135.6 (C), 136.5 (C), 141.4 (C), 143.7 (C), 163.0 (COOEt).

MS (EI, 70 eV): *m/z* (%) = 419 [M^+] (10), 264 (95), 218 (100), 91 (50).

Methyl 3-[Allyl(tosyl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (B3)

Compound **B2** (5.00 g, 13.7 mmol, 1 equiv) was dissolved in acetone (60 mL). K_2CO_3 (3.78 g, 27.4 mmol, 2 equiv) was added in a single portion, and then allyl bromide (3.31 g, 27.4 mmol, 2 equiv) was added dropwise. The suspension was stirred for 4 h at r.t. until no compound **B2** was detected by TLC (EtOAc–PE, 1:5). The mixture was filtered and the solid residue was washed with acetone (20 mL). The solvent was removed under reduced pressure and the crude yellow solid was recrystallized (EtOH) to give colorless crystals; yield 4.44 g (80%); mp 117–118 °C.

IR (KBr): 1074, 1115, 1161, 1259, 1342, 1446, 1464, 1552, 1597, 1718, 2854, 2943 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.90 (m, 4 H, H5 + H6), 2.41 (s, 3 H, $C_6H_4CH_3$), 2.45–2.83 (m, 4 H, H4 + H7), 3.39 (s, 3 H, $COOCH_3$), 4.01 (dd, *J* = 14.6, 8.3 Hz, 1 H, $=CH_2$), 4.45 (dd, *J* = 14.6, 5.6 Hz, 1 H, $=CH_2$), 5.03 (d, *J* = 7.3 Hz, 2 H, CH_2CH), 5.88 (m, 1 H, CH_2CH), 7.25 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.60 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 ($C_6H_4CH_3$), 22.3 and 23.2 (CH_2-C5 + C6), 24.7 (CH_2-C4), 26.0 (CH_2-C7), 51.6 ($COOCH_3$), 54.5 (CH_2CH), 118.9 ($=CH_2$), 125.1 (C), 127.9 and 129.5 (2 × 2CH-$C_6H_4CH_3$), 134.1 (CH_2CH), 137.6 (C), 139.2 (C), 139.8 (C), 142.0 (C), 143.2 (C), 161.0 (COOMe).

MS (EI, 70 eV): *m/z* (%) = 405 [M^+] (<5), 250 (55), 218 (100), 210 (15), 190 (10), 162 (10), 91 (15), 65 (10).

***N*-Allyl-*N*-[3-(hydroxymethyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl]-4-toluenesulfonamide (A4)**

$LiAlH_4$ (0.95 g, 25.0 mmol, 1.05 equiv) was suspended in freshly distilled Et_2O (100 mL), and the mixture was cooled in an ice–salt bath to 0 °C. Compound **A3** (10.0 g, 23.8 mmol, 1 equiv) was added gradually in several portions, and the suspension was stirred at 0 °C under an inert atmosphere for 60 min, then warmed to r.t. Distilled H_2O (20 mL) was added dropwise to decompose excess reducing agent. The organic phase was decanted, and the pasty residue was washed with Et_2O (3 × 15 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo to give a white crystalline compound; yield: 8.57 g (95%); mp 107–108 °C. This was used in the subsequent step without purification.

IR (KBr): 1026, 1072, 1165, 1288, 1342, 1394, 1495, 1597, 2845, 2926, 2951, 3086, 3415, 3537 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 2 H, CH_2OH), 1.73–1.83 (m, 4 H, H5 + H6), 2.45 (s, 3 H, $C_6H_4CH_3$), 2.56–2.80 (m, 4 H, H4 + H7), 4.05 (br s, 1 H, CH_2OH), 4.43 (d, *J* = 5.9 Hz, 2 H, CH_2CH), 5.03–5.20 (m, 2 H, $=CH_2$), 5.65–5.83 (m, 1 H, CH_2CH), 7.29 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$), 7.65 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 ($C_6H_4CH_3$), 22.5 and 23.3 (CH_2-C5 + C6), 24.2 (CH_2-C4), 25.4 (CH_2-C7), 56.0 and 56.1 (CH_2OH, CH_2CH), 120.1 ($=CH_2$), 128.6 and 129.8 (2 × 2CH-$C_6H_4CH_3$), 132.3 (CH_2CH), 133.7 (C), 134.0 (C), 134.3 (C), 135.6 (C), 140.7 (C), 144.4 (C).

MS (EI, 70 eV): *m/z* (%) = 377 [M^+] (20), 222 (75), 194 (100), 91 (45), 41 (50).

***N*-Allyl-*N*-[2-(hydroxymethyl)-4,5,6,7-tetrahydro-1-benzothien-3-yl]-4-toluenesulfonamide (B4)**

$LiAlH_4$ (0.52 g, 13.6 mmol, 1.1 equiv) was suspended in freshly distilled Et_2O (50 mL), and the mixture was cooled in an ice–salt bath to 0 °C. A suspension of compound **B3** (5.00 g, 12.3 mmol, 1 equiv) in Et_2O (25 mL) was added by syringe, and the mixture was stirred at 0 °C under an inert atmosphere for 60 min, then warmed to r.t. (1.5 h). Distilled H_2O (10 mL) was added dropwise to decompose excess reducing agent. The organic phase was decanted and the pasty residue was washed with Et_2O (3 × 10 mL). The organic fractions were

combined, dried ($MgSO_4$), and concentrated in vacuo to give a colorless oily compound; yield: 3.91 g (84%). The crude product was used in the subsequent step without purification.

IR (neat): 1028, 1095, 1159, 1336, 1408, 1444, 1489, 1595, 2856, 2929, 3438, 3523 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.98 (m, 6 H, H4 + H5 + H6), 2.43 (s, 3 H, $C_6H_4CH_3$), 2.63–2.67 (m, 2 H, H7), 3.06 (br s, 1 H, CH_2OH), 3.71 (dd, *J* = 14.5, 7.8 Hz, 1 H, =CH_2), 4.35 (d, *J* = 10.7 Hz, 1 H, CH_2OH), 4.43 (dd, *J* = 14.5, 5.0 Hz, 1 H, =CH_2), 4.71 (d, *J* = 13.0 Hz, 1 H, CH_2OH), 5.07 (d, *J* = 8.0 Hz, 2 H, CH_2CH), 5.80 (m, 1 H, CH_2CH), 7.28 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.58 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 ($C_6H_4CH_3$), 22.4 and 23.3 (CH_2-C5 + C6), 24.0 (CH_2-C4), 25.5 (CH_2-C7), 53.3 (CH_2CH), 56.8 (CH_2OH), 119.2 (=CH_2), 127.4 and 129.8 (2 × 2CH–$C_6H_4CH_3$), 131.3 (C), 132.6 (C), 133.2 (CH_2CH), 135.3 (C), 137.1 (C), 139.9 (C), 144.0 (C).

MS (EI, 70 eV): *m/z* (%) = 377 [M^+] (5), 221 (45), 204 (100), 194 (65), 178 (10), 166 (50), 153 (45), 125 (20), 91 (35), 79 (10), 65 (15).

N-Allyl-*N*-(3-formyl-4,5,6,7-tetrahydro-1-benzothien-2-yl)-4-toluenesulfonamide (A5)

PCC (8.56 g, 39.7 mmol, 1.5 equiv) was dissolved in CH_2Cl_2 (70 mL), and the orange mixture was stirred under argon while a solution of compound **A4** (10.0 g, 26.5 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added by syringe over a few seconds. The solution, which became black within a few minutes, was stirred for 2 h while the reaction was monitored by TLC (CH_2Cl_2). When the starting material was no longer detected, the mixture was diluted with Et_2O (200 mL). The black solid residue was washed with additional Et_2O (2 × 15 mL). The organic phases were combined, filtered through a layer of Florisil (10 cm), and concentrated under reduced pressure. The crude product was recrystallized (EtOH) to give a white solid; yield: 5.79 g (58%); mp 102–103 °C.

IR (KBr): 1088, 1165, 1228, 1309, 1352, 1414, 1485, 1597, 1680, 2754, 2837, 2941, 3089 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.70–2.00 (m, 4 H, H5 + H6), 2.46 (s, 3 H, $C_6H_4CH_3$), 2.64–2.85 (m, 4 H, H4 + H7), 4.14 (d, *J* = 5.8 Hz, 2 H, CH_2CH), 5.05–5.30 (m, 2 H, =CH_2), 5.70–5.90 (m, 1 H, CH_2CH), 7.33 (d, *J* = 8.1 Hz, 2 H, $C_6H_4CH_3$), 7.64 (d, *J* = 8.1 Hz, 2 H, $C_6H_4CH_3$), 9.90 (s, 1 H, HC=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 ($C_6H_4CH_3$), 22.3 and 22.8 (CH_2-C5 + C6), 25.3 (CH_2-C4), 25.6 (CH_2-C7), 56.6 (CH_2CH), 121.0 (=CH_2), 128.5 and 129.9 (2 × 2CH-$C_6H_4CH_3$), 131.6 (CH_2CH) 133.9 (C), 134.0 (C), 135.8 (C), 137.7 (C), 144.8 (C), 149.3 (C), 186.1 (HC=O).

MS (EI, 70 eV): *m/z* (%) = 375 [M^+] (<5), 220 (100), 192 (65), 178 (55), 91 (70), 41 (70).

N-Allyl-*N*-(2-formyl-4,5,6,7-tetrahydro-1-benzothien-3-yl)-4-toluenesulfonamide (B5)

Compound **B4** (5.00 g, 13.2 mmol, 1 equiv) was dissolved in distilled CH_2Cl_2 (35 mL), and PCC (4.28 g, 19.9 mmol, 1.5 equiv) was added in several portions. The dark-red mixture was stirred under argon for 2 h while the reaction was monitored by TLC (CH_2Cl_2). When conversion was complete, Et_2O (100 mL) was added. The black solid residue in the flask was washed with Et_2O (2 × 10 mL), and the organic phases were combined, filtered through Florisil (10 cm), and concentrated under reduced pressure. The crude product was recrystallized (EtOH) to give a colorless solid; yield: 3.38 g (68%); mp 109–110 °C.

IR (KBr): 1045, 1090, 1109, 1165, 1240, 1350, 1410, 1464, 1543, 1595, 1660, 2858, 2937 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.91 (m, 4 H, H5 + H6), 2.14–2.37 (m, 2 H, H4), 2.44 (s, 3 H, $C_6H_4CH_3$), 2.76–2.80 (m, 2 H, H7), 4.08 (dd, *J* = 14.4, 7.0 Hz, 1 H, =CH_2), 4.25 (dd, *J* = 14.4, 6.7 Hz, 1 H, =CH_2), 5.04–5.12 (m, 2 H, CH_2CH), 5.72–5.86 (m, 1 H, CH_2CH), 7.30 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.60 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 9.18 (s, 1 H, HC=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 ($C_6H_4CH_3$), 22.1 and 22.9 (CH_2-C5 + C6), 24.1 (CH_2-C4), 26.5 (CH_2-C7), 54.7 (CH_2CH), 120.3 (=CH_2), 127.5 and 130.1 (2 × 2CH-$C_6H_4CH_3$), 132.5 (CH_2CH), 136.3 (C), 137.2 (C), 137.4 (C), 141.7 (C), 144.5 (C), 146.9 (C), 182.1 (HC=O).

MS (EI, 70 eV): *m/z* (%) = 375 (M^+,<5), 220 (100), 192 (40), 178 (25), 159 (15), 91 (15).

Ethyl (2*R**,3a*R**,10c*R**)-5-Tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylates A6a–e and Ethyl (2*R**,3a*R**,10b*R**)-5-Tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylates B6a–e; General Procedure

Aldehyde **A5** or **B5** (200 mg, 0.53 mmol, 1 equiv) and the appropriate secondary amine **C** (**Ca**–**d**; 1.07 mmol, 2 equiv; **Ce**; 1.32 mmol, 2.5 equiv) were mixed in a test tube and stirred in a preheated oil bath (160 °C) under argon while the reaction was monitored by TLC (CH_2Cl_2). Heating was stopped when the aldehyde was consumed. The products were purified by column chromatography.

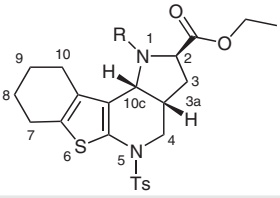


Figure 3 A6a–e

Ethyl (2*R**,3a*R**,10c*R**)-1-Methyl-5-tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (A6a)

Prepared by the general method using ethyl (methylamino)acetate (**Ca**; 125 mg), and purified by column chromatography(PE–EtOAc, 4:1) to give a colorless crystalline solid; yield: 200 mg (79%); mp 140–141 °C.

IR (KBr): 1030, 1090, 1161, 1184, 1294, 1352, 1446, 1591, 1729, 2852, 2940, 2976 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.52–1.97 (m, 6 H, H8 + H9 + H3a + 1H in H3), 2.02–2.14 (m, 1 H, H3), 2.29 (s, 3 H, NCH_3), 2.38 (s, 3 H, $C_6H_4CH_3$) 2.41–2.49 (m, 2 H, H10), 2.63–2.74 (m, 2 H, H7), 3.30 (dd, *J* = 12.8, 11.1 Hz, 1 H, H4), 3.56 (dd, *J* = 8.7, 4.4 Hz, 1 H, H2), 3.79 (d, *J* = 5.0 Hz, 1 H, H10c), 3.89 (dd, *J* = 12.8, 4.6 Hz, 1 H, H4), 4.14 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.23 (d, *J* = 8.1 Hz, 2 H, $C_6H_4CH_3$), 7.68 (d, *J* = 8.1 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 21.5 ($C_6H_4CH_3$), 22.8 and 23.4 (C8 + C9), 24.4 and 24.9 (C7 + C10), 31.2 (C3), 34.6 (C3a), 35.8 (NCH_3), 49.4 (C4), 55.6 (C10c), 60.2 (CH_2CH_3), 63.5 (C2), 122.4 (C_{Ar}), 127.2 (2 × CH-$C_6H_4CH_3$), 127.8 (C), 129.6 (2 × CH-$C_6H_4CH_3$), 132.5 (C), 134.9 (C), 135.2 (C), 143.9 (C), 174.0 (COOEt).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{31}N_2O_4S_2^+$: 475.1725; found: 475.1712.

Ethyl (2*R,3a*R**,10c*R**)-1-Ethyl-5-tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (A6b)**

Prepared by the general method using ethyl (ethylamino)acetate (**Cb**; 140 mg), and purified by column chromatography (PE–EtOAc, 4:1) to give a colorless crystalline solid; yield: 234 mg (91%); mp 111–113 °C.

IR (KBr): 1026, 1092, 1167, 1354, 1448, 1495, 1726, 2848, 2933 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.54–1.96 (m, 6 H, H8 + H9 + H3a + 1H in H3), 2.00–2.11 (m, 1 H, H3), 2.38 (s, 3 H, $C_6H_4CH_3$), 2.40–2.46 (m, 2 H, H10), 2.47–2.61 (m, 2 H, NCH_2CH_3), 2.68 (td, *J* = 5.4, 2.9 Hz, 2 H, H7), 3.27 (dd, *J* = 12.6, 11.3 Hz, 1 H, H4), 3.71 (dd, *J* = 9.1, 3.9 Hz, 1 H, H2), 3.86 (d, *J* = 4.7 Hz, 1 H, H10c), 3.88 (dd, *J* = 12.6, 4.6 Hz, 1 H, H4), 4.13 (dq, *J* = 7.1, 2.1 Hz, 2 H, CH_2CH_3), 7.23 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.69 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (NCH_2CH_3), 14.3 (CH_2CH_3), 21.5($C_6H_4CH_3$), 22.7 and 23.5 (C8 + C9), 24.4 and 24.8 (C7 + C10), 31.0 (C3), 34.3 (C3a), 42.2 (NCH_2CH_3), 49.3 (C4), 55.6 (C10c), 59.3 (C2), 60.1 (CH_2CH_3), 122.5 (C), 127.3 (2 × CH–$C_6H_4CH_3$), 127.7 (C), 129.6 (2 × CH–$C_6H_4CH_3$), 132.7 (C), 134.9 (C), 135.0 (C), 143.9 (C), 174.3 (COOEt).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{33}N_2O_4S_2^+$: 489.1882; found: 489.1873.

Ethyl (2*R,3a*R**,10c*R**)-1-Benzyl-5-tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (A6c)**

Prepared by the general method using ethyl (benzylamino)acetate (**Cc**; 206 mg), and purified by column chromatography (PE–EtOAc, 4:1) to give a colorless crystalline solid; yield: 258 mg (88%); mp 128–129 °C.

IR (KBr): 1005, 1025, 1088, 1124, 1167, 1294, 1354, 1450, 1498, 1595, 1724, 2845, 2933 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.64–2.09 (m, 7 H, H8 + H9 + H3a + H3), 2.44 (s, 3 H, $C_6H_4CH_3$) 2.45–2.55 (m, 2 H, H10), 2.62–2.73 (m, 2 H, H7), 3.28 (dd, *J* = 12.3, 10.0 Hz, 1 H, 1H in H4), 3.35 (dd, *J* = 9.3, 3.9 Hz, 1 H, H2), 3.73 (d, *J* = 2.7 Hz, 2 H, $NCH_2C_6H_5$), 3.97 (dd, *J* = 12.1, 4.4 Hz, 1 H, 1H in H4), 4.04–4.11 (m, 3 H, H10c, CH_2CH_3), 6.84–6.93 (m, 2 H, $NCH_2C_6H_5$), 7.10–7.18 (m, 3 H, $NCH_2C_6H_5$) 7.29 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.77 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 21.8 ($C_6H_4CH_3$), 22.9 and 23.6 (C8 + C9), 24.5 and 24.9 (C7 + C10), 31.4 (C3), 34.5 (C3a), 49.1 (C4), 51.8 ($NCH_2C_6H_5$), 55.4 (C10c), 58.7 (C2), 60.3 (CH_2CH_3), 121.7 (C), 127.0 (CH-$NCH_2C_6H_5$), 127.7 (2 × CH–$C_6H_4CH_3$), 128.0 (C), 128.2 and 128.4 (2 × 2 CH–$NCH_2C_6H_5$), 129.9 (2 × CH–$C_6H_4CH_3$), 132.8 (C), 134.6 (C), 135.4 (C), 139.4 (C), 144.2 (C), 174.3 (COOEt).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{35}N_2O_4S_2^+$: 551.2038; found: 551.2055.

Ethyl (2*R,3a*R**,10c*R**)-1-Butyl-5-tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (A6d)**

Prepared by the general method using ethyl (butylamino)acetate (**Cd**; 170 mg), and purified by column chromatography (PE–EtOAc, 4:1) to give a colorless crystalline solid; yield: 237 mg (86%); mp 71–73 °C.

IR (KBr): 1011, 1028, 1090, 1165, 1292, 1356, 1450, 1498, 1726, 2860, 2929 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.2 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 0.88–1.10 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.10–1.21 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.56–1.94 (m, 6 H, H8 + H9 + H3a + 1H in H3), 2.00–2.11 (m, 1 H, H3), 2.38 (s, 3 H, $C_6H_4CH_3$) 2.38–2.58 (m, 4 H, H10 + $NCH_2CH_2CH_2CH_3$), 2.68 (t, *J* = 5.9 Hz, 2 H, H7), 3.20 (dd, *J* = 12.3, 10.0 Hz, 1 H, 1H in H4), 3.67 (dd, *J* = 9.0, 4.2 Hz, 1 H, H2), 3.86 (d, *J* = 4.3 Hz, 1 H, H10c), 3.88 (dd, *J* = 11.0, 4.7 Hz, 1 H, 1H in H4), 4.13 (dq, *J* = 7.1, 1.6 Hz, 2 H, CH_2CH_3), 7.24 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$), 7.70 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 ($NCH_2CH_2CH_2CH_3$), 14.3 (CH_2CH_3), 20.1 ($NCH_2CH_2CH_2CH_3$), 21.5 ($C_6H_4CH_3$), 22.7 and 23.5 (C8 + C9), 24.3 and 24.8 (C7 + C10), 30.6 ($NCH_2CH_2CH_2CH_3$), 31.0 (C3), 34.3 (C3a), 47.3 ($NCH_2CH_2CH_2CH_3$), 49.0 (C4), 55.4 (C10c), 59.3 (C2), 60.1 (CH_2CH_3), 122.1 (C), 127.3 (2 × CH–$C_6H_4CH_3$), 127.5 (C), 129.6 (2 × CH–$C_6H_4CH_3$), 132.7 (C), 134.6 (C), 134.8 (C), 143.9 (C), 174.4 (COOEt).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{27}H_{37}N_2O_4S_2^+$: 517.2195; found: 517.2192.

Ethyl (2*R,3a*R**,10c*R**)-1-Isopropyl-5-tosyl-2,3,3a,4,5,7,8,9,10,10c-decahydro-1*H*-[1]benzothieno[2,3-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (A6e)**

Prepared by the general method using ethyl (isopropylamino)acetate (**Ce**; 194 mg), and purified by column chromatography (PE–EtOAc, 4:1) to give a yellowish crystalline solid; yield: 201 mg (75%); mp 102–104 °C.

IR (KBr): 1005, 1030, 1088, 1167, 1282, 1354, 1448, 1500, 1597, 1732, 2866, 2933 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.60 (d, *J* = 6.6 Hz, 3 H, $NCH(CH_3)_2$), 0.93 (d, *J* = 6.6 Hz, 3 H, $NCH(CH_3)_2$), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.60–2.09 (m, 7 H, H8 + H9 + H3a + H3), 2.38 (s, 3 H, $C_6H_4CH_3$) 2.40–2.55 (m, 2 H, H10), 2.65–2.73 (m, 2 H, H7), 2.99 [sept, *J* = 6.6 Hz, 1 H, $NCH(CH_3)_2$], 3.16 (dd, *J* = 12.3, 10.0 Hz, 1 H, 1H in H4), 3.75 (dd, *J* = 22.6, 3.9 Hz, 1 H, 1H in H4), 3.75 (dd, *J* = 4.4, 1.8 Hz, 1 H, H2), 4.11 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.21 (d, *J* = 4.5 Hz, 1 H, H10c), 7.24 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.73 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 21.1 [$NCH(CH_3)_2$], 21.8 ($C_6H_4CH_3$), 22.9 and 23.7 (C8 + C9), 24.6 and 24.8 (C7 + C10), 32.4 (C3), 35.5 (C3a), 46.1 [$NCH(CH_3)_2$], 49.1 (C4), 54.6 (C10c), 56.1 (C2), 60.5 (CH_2CH_3), 123.3 (C), 127.5 (2 × CH–$C_6H_4CH_3$), 128.0 (C), 129.8 (2 × CH–$C_6H_4CH_3$), 133.1 (C), 134.8 (C), 135.1 (C), 144.1 (C), 177.8 (COOEt).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{26}H_{35}N_2O_4S_2^+$: 503.2038; found: 503.2039.

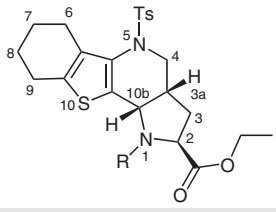


Figure 4 B6a–e

Ethyl (2*R,3a*R**,10b*R**)-1-Methyl-5-tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (B6a)**

Prepared by the general method using ethyl (methylamino)acetate (**Ca**; 125 mg), and purified by column chromatography (PE–EtOAc, 6:1) to give a yellowish crystalline solid; yield: 172 mg (68%); mp 132–134 °C.

IR (KBr): 1030, 1092, 1167, 1261, 1335, 1352, 1448, 1599, 1728, 2798, 2812, 2858, 2937, 2985 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.47–1.60 and 1.76–2.07 (m, 6 H, H7 + H8 + H3), 2.44 (s, 3 H, $C_6H_4CH_3$), 2.56 (s, 3 H, NCH_3), 2.65–3.01 (m, 6 H, H6 + H9 + H2 + H3a + 1H in H4), 3.27 (d, *J* = 8.7 Hz, 1 H, H10b), 3.65 (d, *J* = 7.9 Hz, 1 H, H2), 4.07 (dd, *J* = 6.1, 12.7 Hz, 1 H, 1H in H4), 4.11 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 7.24 (d, *J* = 8.0 Hz, 2 H, $C_6H_4CH_3$), 7.53 (d, *J* = 8.0 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6 (CH_2CH_3), 21.8 ($C_6H_4CH_3$), 23.0 and 23.6 (C7 + C8), 25.6 and 25.7 (C6 + C9), 33.1 (C3), 35.9 (NCH_3), 37.2 (C3a), 52.0 (C4), 58.8 (C10b), 60.3 (CH_2CH_3), 66.4 (C2), 127.9 and 129.8 (2 × 2CH–$C_6H_4CH_3$), 130.1 (C), 132.5 (C), 133.4 (C), 133.5 (C), 136.7 (C), 144.0 (C), 173.3 (COOEt).

MS: *m/z* (%) = 474 (M^+, <5), 401 (80), 319 (10), 245 (100), 231 (10), 190 (15), 91 (15), 57 (15).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_4S_2^+$: 475.1725; found: 475.1741.

Ethyl (2*R,3a*R**,10b*R**)-1-Ethyl-5-tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (B6b)**

Prepared by the general method using ethyl (ethylamino)acetate (**Cb**; 140 mg), and purified by column chromatography (PE–EtOAc, 5:1) to give a colorless crystalline solid; yield: 200 mg (77%); mp 147–149 °C.

IR (KBr): 1028, 1099, 1169, 1342, 1450, 1599, 1730, 2846, 2945 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.2 Hz, 3 H, NCH_2CH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.41–1.58 and 1.73–2.00 (m, 6 H, H7 + H8 + H3), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.44–2.96 (m, 7 H, H6 + H9 + 1H in NCH_2CH_3 + H3a + 1H in H4), 3.11 (dd, *J* = 12.5, 7.5 Hz, 1 H, NCH_2CH_3), 3.20 (d, *J* = 9.2 Hz, 1 H, H10b), 3.80 (d, *J* = 7.7 Hz, 1 H, H2), 4.03–4.14 (m, 3 H, 1H in H4 + CH_2CH_3), 7.24 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.54 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (NCH_2CH_3), 14.6 (CH_2CH_3), 21.8 ($C_6H_4CH_3$), 22.9 and 23.6 (C7 + C8), 25.3 and 25.7 (C6 + C9), 33.7 (C3), 36.2 (C3a), 44.6 (NCH_2CH_3), 52.2 (C4), 58.4 (C10b), 60.2 (CH_2CH_3), 62.1 (C2), 127.9 and 129.7 (2 × 2CH–$C_6H_4CH_3$), 131.8 (C), 132.5 (C), 133.2 (C), 133.3 (C), 136.5 (C), 144.0 (C), 173.4 (COOEt).

MS: *m/z* (%) = 488 (M^+, <5), 411 (99), 333 (10), 259 (100), 231 (15), 190 (10), 91 (10), 56 (10).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_4S_2^+$: 489.1882; found: 489.1876.

Ethyl (2*R,3a*R**,10b*R**)-1-Benzyl-5-tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (B6c)**

Prepared by the general method using ethyl (benzylamino)acetate (**Cc**; 206 mg), and purified by column chromatography (PE–EtOAc, 12:1) to give a colorless crystalline solid; yield: 205 mg (70%); mp 168–170 °C.

IR (KBr): 1028, 1088, 1165, 1344, 1448, 1604, 1728, 2850, 2935 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.36–1.66 and 1.74–2.02 (m, 6 H, H7 + H8 + H3), 2.45 (s, 3 H, $C_6H_4CH_3$), 2.51–3.02 (m, 6 H, H6 + H9 + H3a + 1H in H4), 3.40–3.45 (m, 2 H, H2, H10b), 3.61 (d, *J* = 13.6 Hz, 1 H, $NCH_2C_6H_5$), 4.01–4.16 (m, 3 H, 1H in H4 + CH_2CH_3), 4.34 (d, *J* = 13.6 Hz, 1 H, $NCH_2C_6H_5$), 7.17–7.30 (m, 7 H, $C_6H_4CH_3$, $NCH_2C_6H_5$), 7.57 (d, *J* = 8.3 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_2CH_3), 21.8 ($C_6H_4CH_3$), 22.9 and 23.6 (C7 + C8), 25.4 and 25.7 (C6 + C9), 34.0 (C3), 36.7 (C3a), 52.2 (C4), 54.1 ($NCH_2C_6H_5$), 58.1 (C10b), 60.2 (CH_2CH_3), 61.9 (C2), 127.4 (CH–$NCH_2C_6H_5$), 127.9 (2 × CH–$C_6H_4CH_3$), 128.4 and 128.9 (2 × 2 CH–$NCH_2C_6H_5$), 129.8 (2 × CH–$C_6H_4CH_3$), 132.2 (C), 132.5 (C), 133.2 (C), 133.3 (C), 136.6 (C), 138.7 (C), 144.1 (C), 173.4 (COOEt).

MS: *m/z* (%) = 551 (M^+, <5), 477 (75), 395 (10), 322 (15), 321 (55), 231 (30), 190 (10), 91 (100).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{35}N_2O_4S_2^+$: 551.2038; found: 551.2033.

Ethyl (2*R,3a*R**,10b*R**)-1-Butyl-5-tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (B6d)**

Prepared by the general method using ethyl (butylamino)acetate (**Cd**; 170 mg), and purified by column chromatography (PE–EtOAc, 5:1) to give a yellowish crystalline solid; yield: 228 mg (83%); mp 136–138 °C.

IR (KBr): 1034, 1092, 1120, 1167, 1313, 1338, 1352, 1446, 1597, 1732, 2858, 2933, 2958, 2980 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.25–1.69 and 1.74–2.00 (m, 10 H, H7 + H8 + H3 + $NCH_2CH_2CH_2CH_3$ + $NCH_2CH_2CH_2CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.44–3.05 (m, 8 H, H6 + H9 + H3a + 1H in H4 + $NCH_2CH_2CH_2CH_3$), 3.18 (d, *J* = 9.2 Hz, 1 H, H10b), 3.76 (d, *J* = 7.7 Hz, 1 H, H2), 4.03–4.16 (m, 3 H, 1H in H4 + CH_2CH_3), 7.24 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.54 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 ($NCH_2CH_2CH_2CH_3$), 14.6 (CH_2CH_3), 20.8 ($NCH_2CH_2CH_2CH_3$), 21.7 ($C_6H_4CH_3$), 23.0 and 23.6 (C7 + C8), 25.3 and 25.7 (C6 + C9), 30.8 ($NCH_2CH_2CH_2CH_3$), 33.8 (C3), 36.3 (C3a), 50.3 ($NCH_2CH_2CH_2CH_3$), 52.2 (C4), 58.6 (C10b), 60.2 (CH_2CH_3), 62.5 (C2), 127.9 and 129.7 (2 × 2CH–$C_6H_4CH_3$), 132.0 (C), 132.5 (C), 133.1 (C), 133.3 (C), 136.6 (C), 144.0 (C), 173.5 (COOEt).

MS: *m/z* (%) = 516 (M^+,<5), 443 (100), 361 (10), 287 (80), 231 (20), 190 (15), 91 (10).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{37}N_2O_4S_2^+$: 517.2195; found: 517.2176.

Ethyl (2*R,3a*R**,10b*R**)-1-Isopropyl-5-tosyl-2,3,3a,4,5,6,7,8,9,10b-decahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (B6e)**

Prepared by the general method using ethyl (isopropylamino)acetate (**Ce**; 155 mg), and purified by column chromatography (PE–EtOAc, 6:1) to give a yellow crystalline solid; yield: 198 mg (74%); mp 144–146 °C.

IR (KBr): 1030, 1092, 1165, 1360, 1456, 1599, 1730, 2852, 2929, 2976 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 [d, *J* = 6.6 Hz, 3 H, $NCH(CH_3)_2$], 1.08 [d, *J* = 6.6 Hz, 3 H, $NCH(CH_3)_2$], 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.33–1.58 and 1.78–1.94 (m, 6 H, H7 + H8 + H3), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.50–2.92 (m, 6 H, H6 + H9 + H3a + 1H in H4), 3.12 (d, *J* = 7.8 Hz, 1 H, H10b), 3.36 [d, *J* = 6.4 Hz, 1 H, $NCH(CH_3)_2$], 3.75 (d, *J* = 7.5 Hz, 1 H, H2), 4.01–4.20 (m, 3 H, 1H in H4 + CH_2CH_3), 7.25 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$), 7.57 (d, *J* = 8.2 Hz, 2 H, $C_6H_4CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 18.4 [$NCH(CH_3)_2$], 21.7 ($C_6H_4CH_3$), 22.3 [$NCH(CH_3)_2$], 22.9 and 23.6 (C7 + C8), 25.1 and 25.7 (C6 + C9), 34.9 (C3), 37.8 (C3a), 48.5 [$NCH(CH_3)_2$], 51.7 (C4), 55.0

(C10b), 60.5 (2C, C2 + CH_2CH_3), 127.9 and 129.7 (2 × 2CH–$C_6H_4CH_3$), 132.7 (C), 132.9 (C), 133.3 (C), 133.7 (C), 136.6 (C), 144.0 (C), 175.8 (COOEt).

MS: *m/z* (%) = 502 (M^+, <5), 429 (100), 273 (95), 231 (55), 203 (10), 190 (15), 91 (25), 70 (25).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_4S_2^+$: 503.2038; found: 503.2033.

Acknowledgment

The authors are grateful to Masaryk University for its institutional support of this research. Our thanks also go to Marek Nečas for help with the X-ray crystal structure analysis of the prepared compounds.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561428.

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