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Indole-3-Pyruvic Acid Oxime ethers and Thieno Analogues by Heck Cyclisation. Application to the Synthesis of Thia-Tryptophans.

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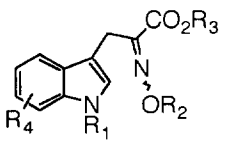
Abstract: *N*-allylation of *N*-BOC substituted *o*-iodo anilines (**14a-e**) and thienoamines (**16,18,20**) employing methyl or benzyl oxime ethers of ethyl (E)-2-oxo-5-bromo-3-pentenoate **2a**, followed by palladium-catalysed Heck cyclisation yielded oxime ethers of Bz-substituted ethyl indole-3-pyruvates (**15a-f**) and thienopyrroles (**17,19,21-23**). Attempted conversion of **2a** into the corresponding tosyl hydrazone or oxime resulted in formation of pyridazine (**10**) and oxazine (**13**) derivatives. The three possible isomers of thia-tryptophan were obtained as the ethyl esters from corresponding methyl oxime ethers by reduction of the oxime double bond. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Oximes and oxime ethers of substituted indole-3-pyruvic esters **1** have found use as synthetic intermediates in the synthesis of tryptophans[1], *N*-hydroxytryptophans[2] and related ß-carboline-[3], dioxopiperazine-[4] and indolactam V-derivatives.[5] The most frequently employed method for synthesis of these precursors involves attachment of the side chain in the 3-position by electrophilic attack of nitrosoacrylate ethyl ester generated *in situ* from ethyl bromopyruvate oxime (Gilchrist's reagent).[6] Availability of already suitably substituted indole derivatives, possessing enough electron density to be amenable to attack by an electrophile, are thus necessary.

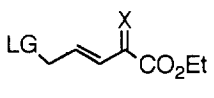


1

An alternative and - as yet - unexplored way for the synthesis of derivatives of **1**, is to construct the pyrrole part of the indole unit using *o*-halo-anilines and olefins containing an allylic leaving group as building blocks, utilising a Heck cyclisation[7] as the key step. Recent success in the construction of indole-3-acetic acids and their hetero analogues[8] by use of this methodology, prompted us to further explore its use in the construction of **1** and the corresponding thieno analogues. This approach would allow the introduction of different substituents on the benzene part of the indole ring, as well as assembly of isosteric analogues such as the corresponding thienopyrroles,[9] by use of properly substituted *o*-halo-(het)arylamines as starting materials.

RESULTS AND DISCUSSION

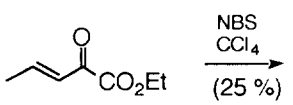
Synthesis of olefinic building blocks. Our initial strategy was to prepare allylic derivatives such as **2a** and **2b**, having leaving groups in the 5-position, for use as starting materials towards substituted indole- and thia-indole-3-pyruvic acid ethyl esters. Condensation between these compounds and hydroxylamine or alkoxyamines would then give the desired derivatives of **1**.



2

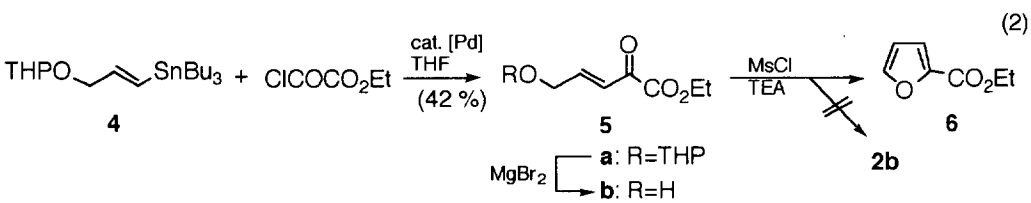
a: X=O, LG=Br
b: X=O, LG=OMs
c: X=N~OMe, LG=Br
d: X=N~OBn, LG=Br
e: X=$(OEt)_2$, LG=Br

For this purpose we first tried to use ethyl (E)-2-oxo-5-bromo-3-pentenoate (**2a**), which could be prepared by Wohl-Ziegler bromination of ethyl (E)-2-oxo-3-pentenoate (**3**), although in only 25% yield (scheme 1). Unfortunately **2a** was unexpectedly found to be sensitive to the basic reaction conditions employed in the allylation of *N*-BOC substituted *o*-iodo(het)arylamines. Several different attempts were carried out with variation in temperature (-70°C-room temperature), of solvent (DMF, THF) and base (cæsium- or potassium carbonate, tetrabutylammonium fluoride), all resulting either in no reaction or decomposition of **2a**.



3 (1)

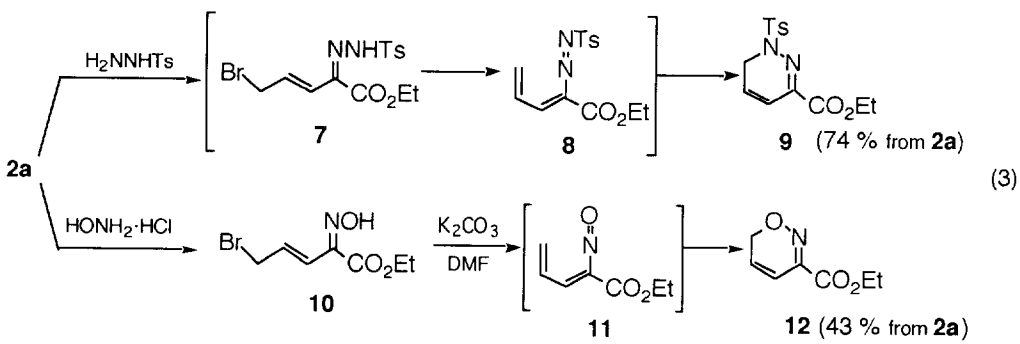
Another approach for the synthesis of the necessary allylic derivatives with a leaving group in the 5-position was then carried out (Scheme 2). Stille coupling of (E)-[3-[(tetrahydro-2H-pyran-2-yl)oxy]-1-propenyl]tributylstannane (**4**)[10] and ethyl oxalyl chloride gave ethyl (E)-2-oxo-5-[(tetrahydro-2H-pyran-2-yl)oxy]-3-pentenoate (**5a**).[11] Removal of the THP protective group using anhydrous magnesium bromide in diethyl ether[12] gave highly acid and base sensitive ethyl (E)-2-oxo-5-hydroxy-3-pentenoate (**5b**) together with minor amounts of ethyl 2-furancarboxylate (**6**). Attempted conversion into ethyl (E)-2-oxo-5-mesyloxy-3-pentenoate (**2b**) under standard conditions (TEA, MsCl) was unsuccessful, resulting only in formation of **6**.



(2)

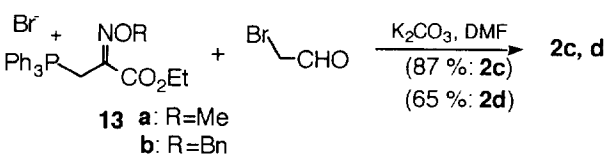
4 **5** **6** **2b**

However, conversion of **2a** to its ketal, ethyl (E)-2,2-diethoxy-5-bromo-3-pentenoate (**2e**), or the oxime ethers, ethyl (E)-2-[(E,Z)-methyloximino]-5-bromo-3-pentenoate (**2c**) (E:Z[13] 62:38) and ethyl (E)-2-[(E,Z)-benzyloximino]-5-bromo-3-pentenoate (**2d**) (E:Z[13] 73:27), by treatment with triethyl orthoformate (using Amberlyst 15 as catalyst) or methoxy- or benzyloxy amine hydrochloride respectively, resulted in increased stability towards base thus making these derivatives suitable for further synthetic steps. Furthermore, we made an interesting observation when attempting to convert **2a** in a similar way to the tosyl hydrazone or the oxime, through the reaction with tosyl hydrazine and hydroxylamine hydrochloride, respectively (scheme 3). Treatment of **2a** with tosyl hydrazine resulted in the formation of ethyl 1-(*p*-toluensulfonyl)-1,6-dihydro-pyridazine-3-carboxylate (**9**) in good yield. A similar reaction was found upon treatment with hydroxylamine hydrochloride. The product consisted of a mixture (3:1 mol:mol) of oxime **10** and ethyl 6H-1,2-oxazine-3-carboxylate (**12**), which was converted into pure **12** under basic conditions. We suggest that the first steps (**7**→**8** and **10**→**11**) in these reactions might be looked upon as vinylogous to corresponding reactions of the hydrazones[14] and the oxime[6] of ethyl bromopyruvate. The initially formed hydrazone **7** or oxime **10** eliminate HBr, to give the azodiene **8** and nitrosodiene[15] **11**, respectively, which rapidly undergo a subsequent six-electron electrocyclisation reaction[16] to give **9** and **12**, respectively. To the best of our knowledge, this reaction represents a novel entry to the pyridazine[17] and 1,2-oxazine skeleton and might show further synthetic potential, but it was not desirable with respect to our synthetic strategy.



(3)

A more general and higher-yielding route for the preparation of **2c** and **2d** is the Wittig reaction of [(2-carboethoxy-2-methyloximino)ethyl]triphenylphosphonium bromide (**13a**) and [(2-carboethoxy-2-benzyloximino)ethyl]triphenylphosphonium bromide (**13b**) with bromoacetaldehyde, giving **2c** (E:Z 92:8) and **2d** (E:Z 85:15) in 87% and 65% yield respectively (scheme 4).[18] Small amounts (~5%) of other isomers of **2c** or **2d**, with identical molecular weight, were also produced in this reaction.



(4)

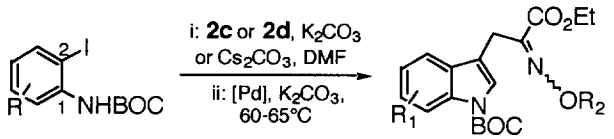
Allylation and palladium-catalysed Heck cyclisation (Scheme 5). Allylation of the *o*-iodo(het)arylamines **14a-e**, **16**, **18**, **20** with a slight excess (1.5 equiv.) of the allylic bromides **2c-e** and palladium-catalysed ring closure of the allylated products were carried out without isolation of intermediates using two different protocols. For *N*-BOC substituted anilines containing electron-withdrawing groups, or in which the *N*HBOC moiety is positioned at the 2-position of the thiophene ring, potassium carbonate in DMF was found to be a sufficiently strong base for the allylation to occur. In other cases, cæsium carbonate was used in order to obtain more facile allylation. We have previously noted that the use of cæsium carbonate as base in the palladium-catalysed Heck cyclisation gives relatively low yields,[19] and this base was therefore exchanged to potassium carbonate before cyclisation.

Substituted *o*-iodo-*N*-BOC-anilines and *o*-iodo-*N*-BOC-thiophenamines were used as aromatic coupling partners. They were chosen because of their ready availability via the modified Curtius reaction[20] starting from the carboxylic acid or, alternatively, direct introduction of the *N*-BOC-substituent on anilines[21] and *o*-lithiation procedures,[22] as well as the possibility of mild removal of the *N*-BOC-substituent[23] in the final indole or thienopyrrole. The new aniline, *N*-(*tert*-butoxycarbonyl)-2-iodo-3-nitroaniline (**14d**), was prepared in 88 % yield by treatment of the corresponding carboxylic acid with triethyl amine and diphenylphosphoryl azide in refluxing *tert*-butanol.

The ^{1}H-NMR spectra of the crude products indicated that the E:Z ratio at the oxime double bond of the oxime ethers used as allylating agents, and the indoles and thienopyrroles obtained therefrom, changed slightly in favour of the E isomer during allylation and ring closure. Thus, the use of the oxime ethers **2c** (E:Z 92:8) and **2d** (E:Z 85:15) - which were obtained from **13a-b** by the Wittig reaction - as starting materials, led to formation of the products **15a-d**, **17**, **19**, **21** (E:Z 96:4-93:7) and **15e-f** (E:Z 92:8-90:10), respectively. The minor Z-isomer of products **15a-e**, **17**, **19** and **21**, were found to elute faster than the E-isomer on TLC-plates (silica, EtOAc:*n*-heptane), but it was difficult to separate Z- and E-isomers. No separation of isomers was achieved for **15e**. The ^{1}H-NMR chemical shifts (Ar-$\underline{CH_2}$-C=N, N-O-$\underline{CH_2}$(3), $CO_2\underline{CH_2}$Me, $CO_2CH_2\underline{CH_3}$) for the Z-isomer were shifted upfield as compared to the E-isomer ($\Delta\delta$ (ppm): 0.10-0.20, 0.19-0.27, 0.08-0.15, 0.12-0.21 respectively) in all the *N*-BOC substituted indoles and thienopyrroles obtained.[24]

Treatment of the tautomeric thienopyrrole derivatives **22** or **23** under the slightly acidic conditions normally employed for conversion of ketals into corresponding oxo derivatives (wet acetone:PPTS or Amberlyst 15, wet THF:silica gel, wet acetic acid),[25] resulted in all cases as indicated by TLC, in the formation of enol ether **24**[26] together with small amounts of as yet unidentified materials. The formation of this compound might be due to its thermodynamic stability.[27]

Synthesis of Thia-tryptophans (Scheme 6). Analogues of tryptophan where the benzenoid part of the indole ring is substituted for heteroaromatics are of interest as potentially bioactive molecules. Hitherto, only two reports on the synthesis of thia-tryptophans have been published.[28] Here we report the synthesis of three positional isomers of the thia-tryptophans. All were obtained as the ethyl esters, with an additional *N*-BOC substituent attached to the 5,6-isomer **25** due to instability of the parent ring system. Reduction of the oxime ether function in thienopyrrole **17** using Al (Hg) in wet THF provided *N*-BOC-5,6-thia-(D,L)-tryptophan ethyl ester (**25**). Removal of the *N*-BOC substituents in thienopyrroles **19** and **21** using silica gel at reduced pressure[8,23] gave **26** and **27**, respectively. Similar reduction of these derivatives gave 4,5- and 6,7-thia-(D,L)-tryptophan ethyl esters (**28** and **29** respectively), as rapidly darkening oils.

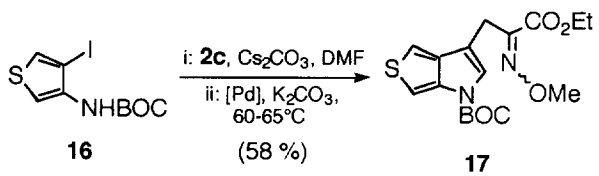


14

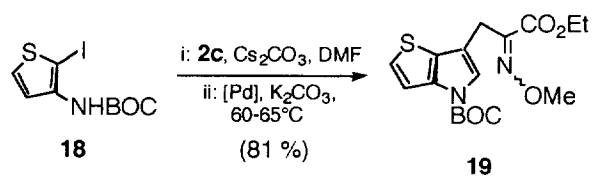
a: R=H
b: R=4-MeO
c: R=4-NO_2
d: R=3-NO_2
e: R=4-Br

15

a: R_1=H, R_2=Me (59 %)
b: R_1=5-MeO, R_2=Me (75 %)
c: R_1=5-Br, R_2=Me (77 %)
d: R_1=4-NO_2, R_2=Me (65 %)
e: R_1=H, R_2=Bn (62 %)
f: R_1=5-NO_2, R_2=Bn (77 %)

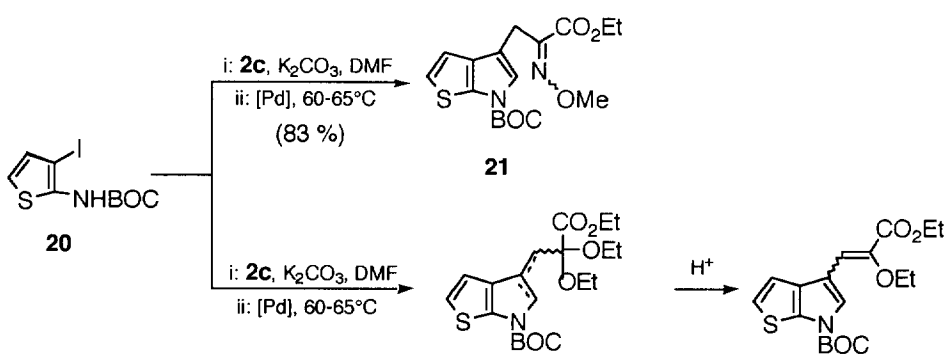


16 (58 %) **17**



18 (81 %) **19**

(5)

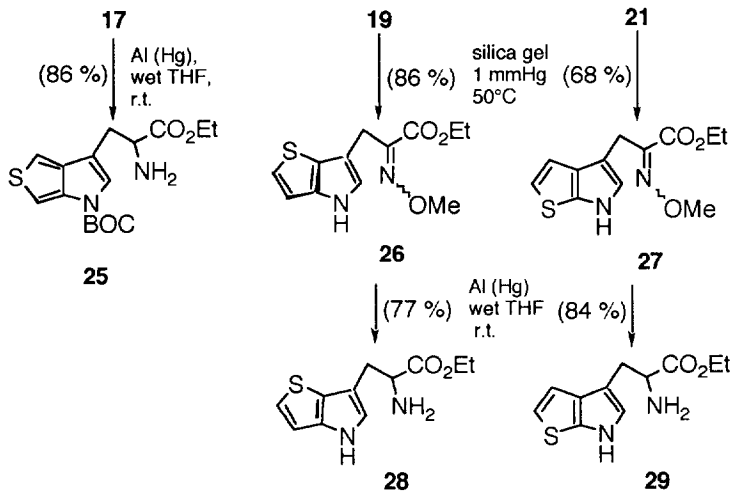


20

21

22 exo (70 %)
23 endo (20 %)

24



(6)

ACKNOWLEDGEMENT

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EXPERIMENTAL

All reactions were performed under argon atmosphere. The starting materials ethyl (E)-2-oxo-3-pentenoate (**3**),[29] [(2-carboethoxy-2-metyloximino)ethyl]triphenylphosphonium bromide (**13a**),[18] *N*-(*tert*-butoxycarbonyl)-2-iodo-4-methoxyaniline (**14b**),[30] *N*-(*tert*-butoxycarbonyl)-2-iodo-4-nitroaniline (**14c**),[8] *N*-(*tert*-butoxycarbonyl)-2-iodo-4-bromoaniline (**14e**),[8] *N*-(*tert*-butoxycarbonyl)-4-iodo-3-aminothiophene (**16**),[31] *N*-(*tert*-butoxycarbonyl)-2-iodo-3-aminothiophene (**18**),[8] *N*-(*tert*-butoxycarbonyl)-3-iodo-2-aminothiophene (**20**),[31] bromacetaldehyde[32] and 2-iodo-3-nitrobenzoic acid[33] were prepared according to literature procedures. All solvents and eluents were distilled before use. Anhydrous THF was distilled from sodium under nitrogen. Chromatographic purification of smaller amounts of crude products were performed on rotating silica gel / gypsum (Merk, 60 PF-254 with calcium sulphate) coated glass sheets, with coating layer of either 1, 2, or 4 mm using a TC Research 7924T chromatotron and is referred to as "purification on chromatotron (X mm, eluent)". Larger amounts were purified using flash column chromatography on silica gel (Matrex No. 85040), referred to as "purification by chromatography". TLC analyses were performed on silica coated aluminium plates (Merck 60 F254). The spots were visualized in UV light (254 nm), and by an anisaldehyde/sulfuric acid/ethanol-spray followed by heating. Gas chromatographic analyses were run on a Varian 3400 gas chromatograph, using an SPB-5 (Supelco) capillary column (30 m, 0.25 mm i.d., 0.25 μm stationary phase). ^{1}H NMR spectra were recorded on a Varian XL-300 NMR spectrometer, operating at 300 MHz (proton). ^{13}C NMR spectra were recorded on the same spectrometer at 75 MHz. Chemical shifts (δ) are reported in parts per million downfield from TMS. Mass spectra were obtained on a Jeol SX 102 spectrometer using electron impact ionization at 70 eV. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium (Mülheim, Germany). Uncorrected melting points were determined using a Wetzlar microscope.

Ethyl (E)-2-oxo-5-bromo-3-pentenoate (2a): A mixture of 16.0 g (113 mmol) of ethyl (E)-2-oxo-3-pentenoate (**3**), 65.0 g (365 mmol) of NBS and 0.50 g of AIBN in carbon tetrachloride (400 ml) was refluxed

for 5 h, with addition of extra 0.30 g of AIBN every 30 min. After cooling to room temperature the solid formed was removed by filtration and the filtrate washed with saturated $Na_2S_2O_3$, water and brine, followed by drying ($MgSO_4$) and evaporation. The crude product was then purified twice by chromatography (550 + 270 g silica gel, EtOAc/*n*-heptane 2:8) to give 6.35 g (25 %) of **2a** as an orange oil that darkened somewhat upon storage at 0 °C but showed no change on ^1H NMR or TLC for several month. ^1H NMR ($CDCl_3$) ∂ 7.19 (dt, J=15.5, 7.1 Hz, 1H), 6.89 (dt, J=15.5, 1.2 Hz, 1H), 4.36 (q, J=7.1 Hz, 2H), 4.09 (dd, J=7.1, 1.2 Hz, 2H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 182.3, 161.3, 145.5, 126.8, 62.7, 29.0, 14.0; MS m/z (%): 220 / 222 (M^+, 7), 147 / 149 (100), 141 (22), 127 (32), 119 / 121 (23), 68 (43); HRMS (CI-CH_4) observed: 222.9785 (M^++H). Calcd: 222.9794; Anal. Calcd for $C_7H_9BrO_3$: C 38.03, H 4.10. found: C 37.88, H 3.89.

Ethyl (E)-2-[(E,Z)-methyloximino]-5-bromo-3-pentenoate (2c):

From 2a: A mixture of 221 mg (1.00 mmol) of ethyl (E)-2-oxo-5-bromo-3-pentenoate (**2a**) and 84 mg (1.00 mmol) of methoxyamine hydrochloride was stirred in a mixture of chloroform and methanol (3:2, 5 ml) at room temperature for 5 h. Evaporation of the solvent followed by purification on chromatotron (1 mm, EtOAc/*n*-heptane 15:85) gave 177 mg (71 %) of **2c** (E:Z 62:38, as estimated from ^1H NMR) as a yellowish oil.

From 13a: To a mixture of 14.0 g (28.8 mmol) of [(2-carboethoxy-2-metyloximino)ethyl]triphenylphosphonium bromide (**13a**) and 4.78 g (34.5 mmol) of anhydrous finely divided potassium carbonate in DMF (150 ml), was added 34.5 ml (30 mmol, 1.0 M/*c*-hexane) of bromacetaldehyde solution. After rapid stirring for 3 h at room temperature, methylene chloride (250 ml) was added and the mixture filtered through celite. The solvent was removed by evaporation (water bath temperature 55 °C) and the residue purified by filtration through silica gel (100 g) using 600 ml EtOAc/*n*-heptane to give 6.29 g (87 %) of **2c** (E:Z 92:8, as estimated from ^1H NMR) as a yellowish oil that was contaminated with ~5 % of isomeric compounds with identical molecular weight, and ~5 % of unknown material (determined by GC-MS analyses). **E-2c**: ^1H NMR ($CDCl_3$) ∂ 6.96 (dt J=15.9, 7.6 Hz, 1H), 6.69 (dt, J=15.9, 1.0 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 4.09 (s, 3H), 4.04 (dd, J=7.6, 1.0 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 162.8, 145.8, 137.3, 119.3, 63.8, 62.0, 32.1, 14.2; MS m/z (%): 249 / 251 (M^+, 19), 221 / 223 (5), 204 / 206 (9), 176 / 178 (9), 170 (100), 142 (75), 98 (32), 82 (28), 66 (74); HRMS observed: 249.0001 (M^+). Calcd: 249.0001. **Z-2c**: ^1H NMR ($CDCl_3$) ∂ 6.32 (dt J=15.9, 1.0 Hz, 1H), 6.05 (dt, J=15.9, 7.6 Hz, 1H), 4.38 (q, J=7.1 Hz, 2H), 4.02 (dd, J=7.6, 1.0 Hz, 2H), 3.94 (s, 3H), 1.36 (t, J=7.1 Hz, 3H).

Ethyl (E)-2-[(E,Z)-Benzyloximino]-5-bromo-3-pentenoate (2d):

From 2a: The same procedure as above was used, employing benzyloxyamine hydrochloride to give 248 mg (76 %) of **2d** (E:Z 73:27, as estimated from ^1H NMR) as a yellowish oil.

Via 13b: A mixture of 6.11 g (31.3 mmol) of ethyl bromopyruvate and 5.00 g (31.3 mmol) of methoxyamine hydrochloride was stirred in a mixture of chloroform and methanol (3:2, 100 ml) at room temperature for 5 h. Dilution with methylene chloride (300 ml) followed by washing with water and brine, drying ($MgSO_4$), and evaporation of the solvent gave 7.87 g (84 %) of ethyl 2-benzyloximino-3-bromopropanoate as a yellowish oil. ^1H NMR ($CDCl_3$) ∂ 7.30-7.45 (m, 5H), 5.40 (s, 2H), 4.37 (q, J=7.1 Hz, 2H), 4.22 (s, 2H), 1.38 (t, J=7.1 Hz, 3H). To a solution of 7.77 g (25.9 mmol) of this oil in anhydrous THF (100 ml), 7.47 g (28.5 mmol) of triphenylphosphine was added. The mixture was refluxed for 30 min and then stirred at room temperature over night. Evaporation of the solvent provided a reddish glass that was stirred rapidly with 200 ml dry diethyl ether for 2 d. Decantation of the ether followed by drying of the residue at 1 mmHg gave 14.9 g (102 %) of [(2-carboethoxy-2-benzyloximino)ethyl]triphenylphosphonium bromide (**13b**) as a yellowish hygroscopic powder. ^1H NMR ($CDCl_3$) ∂ 7.05-7.80 (m, 20H), 5.05 (d, J=16.0 Hz, 2H), 5.04 (s, 2H), 4.08 (q, J=7.1 Hz, 2H), 1.11 (t, J=7.1 Hz, 3H). The same procedure as above was then used for

reaction of 12.1 g (21.5 mmol) of **13b** with bromacetaldehyde to give 4.55 g (65 %) of **2d** (E:Z 85:15, as estimated from ^{1}H NMR) as a yellowish oil that was contaminated with ~5 % of isomeric compounds with identical molecular weight, and ~5 % of unknown material (determined by GC-MS analyses). **E-2d:** ^{1}H NMR ($CDCl_3$) ∂ 7.30-7.40 (m, 5H), 6.95 (dt, J=15.9, 7.6 Hz, 1H), 6.74 (dt, J=15.9, 1.0 Hz, 1H), 5.32 (s, 2H), 4.34 (q, J=7.1 Hz, 2H), 4.02 (dd, J=7.6, 1.0 Hz, 2H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 162.8, 146.2, 137.4, 136.2, 128.6, 128.5, 128.4, 119.3, 78.4, 62.0, 32.1, 14.2; MS (CI-CH4) m/z (%): 326 / 328 (M^++H, 80), 280 / 282 (3), 246 (100), 156 (36), 91 (66); HRMS (CI-CH4) observed: 326.0389 (M^++H). Calcd: 326.0392. **Z-2d:** ^{1}H NMR ($CDCl_3$) ∂ 7.30-7.40 (m, 5H), 6.32 (dt, J=15.9, 1.0 Hz, 1H), 6.06 (dt, J=15.9, 7.5 Hz, 1H), 5.28 (s, 2H), 4.37 (q, J=7.1 Hz, 2H), 4.01 (dd, J=7.5, 1.0 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H).

Ethyl (E)-2,2-diethoxy-5-bromo-3-pentenoate (2e): A mixture of 442 mg (2.00 mmol) of ethyl (E)-2-oxo-5-bromo-3-pentenoate (**2a**) and 442 mg of Amberlyst 15 in triethyl orthoformate (5 ml) was stirred at 70 °C for 16 h. After cooling to room temperature the mixture was filtered and evaporated. The residue was purified on chromatotron (1 mm, diethyl ether/*n*-heptane 2:8) to give 133 mg (22 %) of **2e** as a yellowish oil contaminated with ~5 % (as estimated from ^{1}H NMR) of the starting material **2a**. ^{1}H NMR ($CDCl_3$) ∂ 6.27 (dt, J=15.4, 7.7 Hz, 1H), 5.70 (dt, J=15.4, 1.1 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.91 (dd, J=7.7, 1.1 Hz, 2H), 3.38-3.60 (m, 4H), 1.15-1.29 (m, 9H); ^{13}C NMR ($CDCl_3$) ∂ 168.4, 131.5, 99.0, 61.8, 58.5, 30.7, 15.1, 14.1; MS m/z (%): 265 / 267 (M^+-Et, 1), 249 / 251 (28), 221 / 223 (100), 193 / 195 (38), 165 / 167 (75), 147 / 149 (55), 85 (61), 68 (61).

Ethyl 1-(*p*-toluensulfonyl)-1,6-dihydro-pyridazine-3-carboxylate (9): To a solution of 221 mg (1.00 mmol) of ethyl (E)-2-oxo-5-bromo-3-pentenoate (**2a**) in a stirred mixture of chloroform and methanol (3:2, 5 ml) at room temperature, 186 mg (1.00 mmol) of *p*-toluene sulphonyl hydrazine was added in one portion. The mixture was stirred for another 2 h before dilution with diethyl ether (100 ml) and washing with water and brine, followed by drying ($MgSO_4$). The crude product obtained after evaporation of the solvent was purified on chromatotron (1 mm, EtOAc/*n*-heptane 3:7) to give 229 mg (74 %) of **9** as a yellow oil that slowly decomposed upon storage at 0 °C. ^{1}H NMR ($CDCl_3$) ∂ 7.84 (d, J=8.0 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 6.40 (dt, J=9.9, 1.6 Hz, 1H), 6.13 (dt, J=9.9, 7.3 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 4.14 (dd, J=4.3, 1.6 Hz, 2H), 2.42 (s, 3H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 162.4, 145.0, 141.6, 132.2, 129.8, 128.8, 127.2, 117.5, 61.7, 41.2, 21.7, 14.1; MS m/z (%): 308 (M^+, 49), 263 (9), 153 (80), 125 (27), 108 (34), 91 (100), 80 (98); HRMS observed: 308.0832 (M^+). Calcd: 308.0831; Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C 54.53, H 5.23, N 9.09. found: C 54.36, H 5.34, N 8.99.

Ethyl 6H-1,2-oxazine-3-carboxylate (12): To a solution of 400 mg (1.81 mmol) of ethyl (E)-2-oxo-5-bromo-3-pentenoate (**2a**) in a stirred mixture of chloroform and methanol (3:2, 10 ml) at room temperature, 126 mg (1.81 mmol) of hydroxylamine hydrochloride was added in one portion. The mixture was stirred for another 4 h before removal of the solvent by evaporation. The residue was purified on chromatotron (1 mm, EtOAc/*n*-heptane 3:7) to give 295 mg of a semi solid mixture of **12** and **10** (1:3 mol:mol, as estimated from ^{1}H NMR). **10:** ^{1}H NMR ($CDCl_3$) ∂ 9.88 (br.s, 1H), 7.17 (dt, J=15.9, 7.6 Hz, 1H), 6.78 (br.d, J=15.9 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 4.08 (dd, J=7.6, 1.0 Hz, 2H), 1.38 (t, J=7.1 Hz, 3H). To a solution of 165 mg of this mixture in DMF (5 ml) at room temperature, 150 mg of anhydrous finely divided potassium carbonate was added. After stirring for another 30 min., dilution with diethyl ether (100 ml), filtration through a short plug of silica gel and evaporation of the solvent, the residue was purified on chromatotron (1 mm, EtOAc/*n*-heptane 2:8) to give 67 mg (43 % from **2a**) of **12** as a yellowish oil. ^{1}H NMR ($CDCl_3$) ∂ 6.41 (dt, J=9.9, 1.7 Hz, 1H), 6.22 (dt, J=9.9, 4.2 Hz, 1H), 4.55 (dd, J=4.2, 1.7 Hz, 2H), 4.33 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 162.2, 150.6, 127.1, 114.2, 63.2, 62.2, 14.1; MS m/z (%): 155 (M^+, 66), 127 (9),

111 (100), 94 (75), 83 (93), 66 (50), 54 (47), 52 (39); HRMS observed: (M^+) 155.0586. Calcd: 155.0583; Anal. Calcd for $C_7H_9NO_3$: C 54.19, H 5.85, N 9.03. found: C 54.23, H 5.89, N 8.77.

N-(*Tert*-butoxycarbonyl)-2-iodoaniline (14a): A mixture of 4.96 g (20.0 mmol) of *o*-iodobenzoic acid, 3.05 ml (22 mmol) of TEA and 4.75 ml (22 mmol) of diphenylphosphoryl azide was heated at reflux in *tert*-butanol (150 ml) for 12 h, followed by evaporation of the solvent and partition of the residue between diethyl ether (250 ml) and 2 M NH_4Cl (200 ml). The ether phase was then washed with saturated $NaHCO_3$, dried ($MgSO_4$) and the solvent was removed by evaporation. Purification on chromatotron (4 mm, EtOAc/*n*-heptane 5:95) yielded 4.73 g (74 %) of **14a** as a colourless syrup. The ^1H[21,34] and ^{13}C[34] NMR-spectra were in accordance with those previously reported.

N-(*Tert*-butoxycarbonyl)-2-iodo-3-nitroaniline (14d): The same procedure as above was used employing 6.20 g (21.15 mmol) of 2-iodo-3-nitrobenzoic acid to give 6.75 g (88 %) of **14d** as yellow crystals. mp 81-83 °C; ^1H NMR ($CDCl_3$) ∂ 8.31 (dd, J=7.9, 1.8 Hz, 1H), 7.35-7.46 (m, 2H), 7.19 (br.s, 1H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$) ∂ 152.3, 141.3, 129.6, 122.8, 119.1, 82.0, 81.3, 28.2; MS m/z (%): 364 (M^+, 12), 308 (20), 264 (27), 57 (100); HRMS observed: 363.9916 (M^+). Calcd: 363.9919; Anal. Calcd for $C_{11}H_{13}IN_2O_4$: C 36.28, H 3.60, N 7.70. found: C 36.35, H 3.54, N 7.63.

General procedures for synthesis of the ethyl α-alkyloximino-β-aryl-propionates (15a-f, 17, 19, 21) and the ketals (22-23) by allylation and palladium-catalysed ring closure.

Method A: A total of 1.5 equiv. of ethyl (E)-2-[(E,Z)-methyloximino]-5-bromo-3-pentenoate (**2c**, E:Z 92:8) (for products **15a-d**, **17**, **19**, **21**), ethyl (E)-2-[(E,Z)-benzyloximino]-5-bromo-3-pentenoate (**2d**, E:Z 85:15) (for products **15e-f**) or ethyl (E)-2,2-diethoxy-5-bromo-3-pentenoate (**2e**) (for products **22-23**), was added in one portion to a stirred mixture of the *o*-iodo(het)arylamine (0.25 mmol / ml) and 4 equiv. of anhydrous finely divided potassium carbonate in DMF. The resultant mixture was stirred at room temperature until TLC indicated total allylation of the starting *o*-iodo(het)arylamine. Thereafter 0.1- and 0.05 equiv. of triphenylphosphine and palladium acetate respectively were added and ring closure was carried out at 60-65 °C for the time indicated. The mixture was then allowed to reach room temperature before dissolving in diethyl ether. The etheral solution was filtered through silica gel and evaporated, followed by purification on chromatotron (2 mm) using EtOAc/*n*-heptane 15:85 as eluent unless otherwise stated. The products **15a-f**, **17**, **19**, **21** were contaminated with 4-10 % of the corresponding Z-isomer as estimated from ^1H NMR.

Method B: As method A with the following exceptions: Allylation was carried out with 1.5 equiv. of cæsium carbonate as base at 0 °C followed by heating to room temperature for two hours. The base was then changed before cyclisation by diluting the mixture with diethyl ether, and filtering through a short plug of silica gel, followed by removal of the ether *in vacuo* and addition of 1.5 equiv. of potassium carbonate.

Ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-3-indolyl]propanoate (15a): The reaction was carried out on 319 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (**14a**) using method B. Ring closure was carried out in presence of 278 mg (1.00 mmol) of *n*-Bu_4NCl for 17 h to give 211 mg (59 %) of **15a** as a yellowish oil. ^1H NMR ($CDCl_3$) ∂ 8.10 (br.d, J=7.6 Hz, 1H), 7.63 (d, J=6.8 Hz, 1H), 7.43 (br.s, 1H), 7.21-7.35 (m, 2H), 4.30 (q, J=7.1 Hz, 2H), 4.13 (s, 3H), 3.98 (d, J=1.1 Hz, 2H), 1.67 (s, 9H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.2, 150.1, 149.7, 135.2, 130.2, 124.4, 124.3, 122.5, 119.2, 115.1, 114.6, 83.5, 63.4, 62.0, 28.2, 20.9, 14.2; MS m/z (%): 360 (M^+, 42), 304 (55), 273 (84), 260 (6), 229 (66), 155 (98), 130 (52), 57 (100); HRMS observed: 360.1694 (M^+). Calcd: 360.1685; Anal. Calcd for $C_{19}H_{24}N_2O_5$: C 63.32, H 6.71, N 7.77. found: C 63.22, H 6.75, N 7.85.

Ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-5-methoxy-3-indolyl]propanoate (15b): The reaction was carried out on 349 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodo-4-methoxyaniline (**14b**) using method B. Ring closure was carried out for 12 h to give 293 mg (75 %) of **15b** as a yellow oil. ^{1}H NMR ($CDCl_3$) ∂ 7.92-8.02 (br.s, 1H), 7.39 (br.s, 1H), 7.11 (d, J=2.5 Hz, 1H), 6.90 (dd, J=9.0, 2.5 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 4.13 (s, 3H), 3.94 (d, J=1.0 Hz, 2H), 3.87 (s, 3H), 1.64 (s, 9H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.2, 155.8, 150.0, 149.6, 131.0, 129.9, 125.0, 115.9, 114.3, 113.1, 101.9, 83.4, 63.4, 62.0, 55.6, 28.2, 21.0, 14.2; MS m/z (%): 390 (M^+, 48), 334 (90), 303 (99), 290 (24), 259 (64), 185 (100), 171 (15), 160 (74), 57 (56); HRMS observed: 390.1792 (M^+). Calcd: 390.1791; Anal. Calcd for $C_{20}H_{26}N_2O_6$: C 61.52, H 6.71, N 7.18. found: C 61.38, H 7.10, N 6.79.

Ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-5-bromo-3-indolyl]propanoate (15c): The reaction was carried out on 398 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodo-4-bromoaniline (**14e**) using method A. Allylation and ring closure was carried out for 30 and 4 h respectively to give 337 mg (77 %) of **15c** as a white powder. mp 84-86 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.97 (br.d, J=8.8 Hz, 1H), 7.76 (d, J=2.0 Hz, 1H), 7.42 (br.s, 1H), 7.39 (dd, J=8.8, 2.0 Hz, 1H), 4.32 (q, J=7.1 Hz, 2H), 4.16 (s, 3H), 3.92 (d, J=0.9 Hz, 2H), 1.64 (s, 9H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.1, 149.7, 149.3, 134.0, 131.9, 127.2, 125.5, 122.2, 116.6, 115.9, 114.0, 84.1, 63.4, 62.1, 28.2, 20.8, 14.2; MS m/z (%): 438 / 440 (M^+, 17), 382 / 384 (24), 351 / 353 (30), 338 / 340 (7), 307 / 309 (36), 233 / 235 (37), 228 (21), 208 / 210 (23), 57 (100); HRMS observed: 438.0794 (M^+). Calcd: 438.0790; Anal. Calcd for $C_{19}H_{23}BrN_2O_5$: C 51.95, H 5.28, N 6.38. found: C 51.88, H 5.32, N 6.32.

Ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-4-nitro-3-indolyl]propanoate (15d): The reaction was carried out on 364 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodo-3-nitroaniline (**14d**) using method A. Allylation and ring closure was carried out for 17 and 12 h respectively to give 263 mg (65 %) of **15d** as a yellow oil that slowly crystallised. mp 62-66 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.50 (d, J=8.3 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.42 (s, 1H), 7.38 (dd, partly unresolved, 1H), 4.30 (q, J=7.1 Hz, 2H), 4.06 (d, J=1.3 Hz, 2H), 4.04 (s, 3H), 1.66 (s, 9H), 1.30 (t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) ∂ 163.3, 150.3, 148.7, 143.6, 142.7, 137.6, 127.6, 123.5, 120.4, 119.6, 113.3, 85.0, 63.4, 62.1, 28.1, 23.2, 14.1; MS m/z (%): 405 (M^+, 14), 349 (14), 318 (5), 305 (3), 303 (3), 274 (20), 257 (6), 228 (4), 200 (16), 154 (9), 57 (100); HRMS observed: 405.1538 (M^+). Calcd: 405.1536; Anal. Calcd for $C_{19}H_{23}N_3O_7$: C 56.29, H 5.72, N 10.37. found: C 56.21, H 5.75, N 10.32.

Ethyl α-[(E)-benzyloximino]-β-[1-(*tert*-butoxycarbonyl)-3-indolyl]propanoate (15e): The reaction was carried out on 319 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (**14a**) using method B. Ring closure was carried out in presence of 278 mg (1.00 mmol) of *n*-Bu_4NCl for 12 h to give 272 mg (62 %) of **15e** as a yellowish oil. ^{1}H NMR ($CDCl_3$) ∂ 8.12 (br.d, unresolved, 1H), 7.60 (d, J=7.4 Hz, 1H), 7.15-7.47 (m, 8H), 5.39 (s, 2H), 4.32 (q, J=7.1 Hz, 2H), 4.02 (d, J=1.0 Hz, 2H), 1.67 (s, 9H), 1.34 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.3, 150.4, 149.6, 136.3, 135.2, 130.2, 128.6, 128.5, 128.4, 124.5, 124.3, 122.4, 119.4, 115.1, 114.5, 83.5, 78.0, 62.0, 28.2, 21.1, 14.1; MS m/z (%): 436 (M^+, 24), 380 (40), 363 (19), 336 (7), 319 (24), 289 (30), 273 (13), 245 (28), 229 (30), 155 (38), 130 (46), 91 (100), 57 (59); HRMS observed: 436.2001(M^+). Calcd: 436.1998; Anal. Calcd for $C_{25}H_{28}N_2O_5$: C 68.79, H 6.47, N 6.42. found: C 68.57, H 6.10, N 6.16.

Ethyl α-[(E)-benzyloximino]-β-[1-(*tert*-butoxycarbonyl)-5-nitro-3-indolyl]propanoate (15f): The reaction was carried out on 364 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodo-4-nitroaniline (**14c**) using method A. Allylation and ring closure was carried out for 2 and 12 h respectively to give 369 mg (77 %) of **15f** as yellow crystals. mp 115-117 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.58 (dd, J=1.8, 1.0 Hz, 1H), 8.19 (m, 2H), 7.56 (s, 1H),

7.30-7.40 (m, 5H), 5.40 (s, 2H), 4.32 (q, J=7.1 Hz, 2H), 4.02 (d, J=0.9 Hz, 2H), 1.68 (s, 9H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.1, 149.5, 148.8, 143.6, 138.3, 135.9, 130.1, 128.8, 128.6, 128.5, 127.4, 119.6, 116.0, 115.5, 115.3, 85.0, 78.4, 62.2, 28.1, 20.9, 14.2; MS m/z (%): 481 (M^+, 5), 425 (12), 408 (4), 381 (5), 364 (14), 334 (4), 318 (2), 290 (15), 274 (5), 91 (100), 57 (46); HRMS observed: 481.1858 (M^+). Calcd: 481.1849; Anal. Calcd for $C_{25}H_{27}N_3O_7$: C 62.36, H 5.65, N 8.73. found: C 62.01, H 5.61, N 8.65.

Ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-3-thieno[3,4-b]pyrrolyl]propanoate (17): The reaction was carried out on 325 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-4-iodo-3-aminothiophene (**16**) using method B. Ring closure was carried out for 72 h. Diethyl ether/*n*-heptane 2:8 was used as eluent to give 213 mg (58 %) of **17** as a colourless oil. ^{1}H NMR (DMSO-d6) ∂ 7.30 (bs, 1H), 7.13 (d, J=2.5 Hz, 1H), 6.9-7.3 (bs, 1H), 4.21 (q, J=7.1 Hz, 2H), 4.06 (s, 3H), 3.73 (s, 2H), 1.58 (s, 9H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO-d6) ∂ 162.5, 148.8, 148.2 (br.), 137.4 (br.), 129.7, 128.5, 111.6 (br.), 108.9, 101.9, 83.0 (br.), 63.1, 61.4, 27.6, 21.4, 13.9; MS m/z (%): 366 (M^+, 32), 310 (65), 279 (73), 266 (9), 235 (47), 189 (33), 161 (76), 136 (37), 57 (100); HRMS observed: 366.1242 (M^+). Calcd: 366.1250; Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C 55.72, H 6.05, N 7.65. found: C 55.61, H 6.08, N 7.69.

Ethyl α-[(E)-metyloximino]-β-[4-(*tert*-butoxycarbonyl)-6-thieno[3,2-b]pyrrolyl]propanoate (19): The reaction was carried out on 325 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-2-iodo-3-aminothiophene (**18**) using method B. Ring closure was carried out for 16 h to give 296 mg (81 %) of **19** as yellow crystals that rapidly darkened. mp 57-60 °C; ^{1}H NMR (DMSO-d6) ∂ 7.44 (d, J=5.2 Hz, 1H), 7.20-7.26 (m, 2H), 4.21 (q, J=7.1 Hz, 2H), 4.06 (s, 3H), 3.78 (s, 2H), 1.58 (s, 9H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO-d6) ∂ 162.4, 148.7, 147.8, 137.3, 126.5, 126.3, 122.0, 114.5, 114.2, 83.9, 63.0, 61.4, 27.5, 21.8, 13.9; MS m/z (%): 366 (M^+, 35), 310 (70), 279 (58), 266 (16), 235 (53), 189 (28), 161 (79), 136 (59), 57 (100); HRMS observed: 366.1248 (M^+). Calcd: 366.1250; Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C 55.72, H 6.05, N 7.65. found: C 55.84, H 6.10, N 7.58.

Ethyl α-[(E)-metyloximino]-β-[6-(*tert*-butoxycarbonyl)-4-thieno[2,3-b]pyrrolyl]propanoate (21): The reaction was carried out on 325 mg (1.00 mmol) of *N*-(*tert*-butoxycarbonyl)-3-iodo-2-aminothiophene (**20**) using method A. Allylation and ring closure was carried out for 3 and 12 h respectively to give 304 mg (83 %) of **21** as a yellow oil. ^{1}H NMR (DMSO-d6) ∂ 7.16-7.35 (m, 2H), 6.96 (d, J=5.4 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 4.06 (s, 3H), 3.83 (s, 2H), 1.60 (s, 9H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO-d6) ∂ 163.2, 150.0, 122.7 (br.), 121.2 (br.), 117.1 (br.), 115.0, 84.4 (br.), 63.3, 61.9, 28.1, 22.2, 14.2; MS m/z (%): 366 (M^+, 39), 310 (80), 279 (53), 266 (15), 235 (61), 189 (40), 161 (100), 136 (53), 57 (76); HRMS observed: 366.1249 (M^+). Calcd: 366.1250; Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C 55.72, H 6.05, N 7.65. found: C 55.58, H 5.96, N 7.61.

Ethyl α,α-dimethoxy-β-[6-(*tert*-butoxycarbonyl)-4-thieno[2,3-b]pyrrolyl]propanoate (23) and 4-[(carboethoxy-diethoxy)methylmethylene]-6-(*tert*-butoxycarbonyl)-4,5-dihydro-thieno[2,3-b]pyrrole (22): The reaction was carried out on 98 mg (0.30 mmol) of *N*-(*tert*-butoxycarbonyl)-3-iodo-2-aminothiophene (**20**) using method A. Allylation and ring closure was carried out for 5 + 5 h, respectively. Diethyl ether/*n*-heptane 3:7 was used as eluent to give 24 mg (20 %) of **23** together with 86 mg (70 %) of **22** as yellow oils. **22:** ^{1}H NMR ($CDCl_3$) ∂ 6.65-6.85 (m, 2H), 5.31 (m, 1H), 5.05 (dd, J=18.8, 3.0 Hz, 2H), 4.18-4.28 (m, 2H), 3.40-3.70 (m, 4H), 1.50-1.65 (3s, 4H, 3.5H, 1.5H), 1.22-1.35 (m, 9H); MS m/z (%): 411 (M^+, 6), 366 (4), 338 (27), 310 (12), 282 (100), 265 (6), 238 (10); HRMS observed: 411.1718 (M^+). Calcd: 411.1716. **23:** ^{1}H NMR ($CDCl_3$) ∂ 7.05-7.40 (br.s, 1H), 6.95 (s, 2H), 4.09 (q, J=7.1 Hz, 2H), 3.53-3.74 (m, 4H), 3.24 (d, J=0.9 Hz, 2H), 1.64 (s, 9H), 1.10-1.32 (m, 9H).

Ethyl α-(metyloximino)-β-(6-thieno[3,2-b]pyrrolyl)propanoate (26): A solution of 149 mg (0.407 mmol) of ethyl α-[(E)-metyloximino]-β-[4-(*tert*-butoxycarbonyl)-6-thieno[3,2-b]pyrrolyl]propanoate (**19**) in methylene chloride was evaporated onto 1.5 g of silica gel (Merck, 35-70 mesh). This gel was then evacuated (1 mmHg) at 50 °C using Kugelrohr equipment with protection from light for 24 h, followed by purification by chromatography using EtOAc/*n*-heptane 3:7 as eluent to give 93 mg (86 %) of **26** as a brownish oil. ^{1}H NMR ($CDCl_3$) ∂ 8.15 (br.s, 1H), 7.07 (dd, J=5.2, 1.3 Hz, 1H), 6.89 (d, J=5.2 Hz, 1H), 6.88 (m, 1H), 4.30 (q, J=7.1 Hz, 2H), 4.15 (s, 3H), 3.92 (d, J=0.7 Hz, 2H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.4, 150.3, 138.4, 123.9, 123.8, 121.8, 111.2, 110.3, 63.2, 61.9, 22.4, 14.2; MS m/z (%): 266 (M^+, 83), 235 (59), 221 (8), 208 (18), 189 (27), 161 (100), 136 (96); HRMS observed: 266.0733(M^+). Calcd: 266.0725; Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C 54.12, H 5.30, N 10.52. found: C 54.08, H 5.25, N 10.55.

Ethyl α-(metyloximino)-β-(4-thieno[2,3-b]pyrrolyl)propanoate (27): The same procedure as above was carried out on 168 mg of ethyl α-[(E)-metyloximino]-β-[6-(*tert*-butoxycarbonyl)-4-thieno[2,3-b]pyrrolyl]propanoate (**21**) to give 83 mg (68 %) of **27** as a colourless oil. ^{1}H NMR ($CDCl_3$) ∂ 8.18 (br.s, 1H), 6.99 (dd, J=5.3, 0.6 Hz, 1H), 6.86 (m, 1H), 6.79 (dd, J=5.3, 1.0 Hz, 1H), 4.29 (q, J=7.1 Hz, 2H), 4.11 (s, 3H), 3.94 (d, J=0.8 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 163.5, 151.0, 133.2, 131.0, 122.8, 117.7, 117.3, 110.1, 63.9, 61.8, 22.2, 14.2; MS m/z (%): 266 (M^+, 61), 235 (58), 221 (8), 208 (17), 189 (38), 161 (100), 136 (90); HRMS observed: 266.0721(M^+). Calcd: 266.0725; Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C 54.12, H 5.30, N 10.52. found: C 54.05, H 5.67, N 10.91.

1-(*Tert*-butoxycarbonyl)-5,6-thia-(D,L)-tryptophan ethyl ester (25): Al (Hg), prepared by treating an aluminium pellet (0.66 g) with 8 % NaOH for 3 min. followed by washing with water and amalgamation in 2 % $HgCl_2$ for 5 min., was added to a solution of 124 mg (0.338 mmol) of ethyl α-[(E)-metyloximino]-β-[1-(*tert*-butoxycarbonyl)-3-thieno[3,4-b]pyrrolyl]propanoate (**17**) in a mixture of THF and water (9:1, 20 ml). After rapid stirring for 48 h at room temperature the mixture was filtered through silica gel. The silica gel was then eluted with EtOAc (100 ml) and the combined organic phases evaporated. Purification on chromatotron (1 mm, diethyl ether/EtOAc 1:1) gave 98 mg (86 %) of **25** as a yellowish oil. ^{1}H NMR (DMSO-d6) ∂ 7.30-7.42 (br.s, 1H), 7.28 (d, J=2.6 Hz, 1H), 6.9-7.3 (br.s, 1H), 3.98-4.10 (m, 2H), 3.60-3.65 (m, 1H), 2.68-2.87 (m, 2H), 1.85 (br.s, 1.8H), 1.59 (br.s, 7.2H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO-d6) ∂ 174.8, 148.3 (br.), 137-139 (br.), 129.7, 114.2 (br.), 108.8, 101.5, 82.7 (br.), 60.0, 53.9, 31.1, 27.6, 13.9; MS m/z (%): 338 (M^+, 14), 282 (7), 265 (3), 238 (2), 236 (4), 209 (6), 165 (6), 136 (100), 57 (32); HRMS observed: 338.1304 (M^+). Calcd: 338.1300; Anal. Calcd for $C_{16}H_{22}N_2O_4S$: C 56.78, H 6.55, N 8.28. found: C 56.66, H 6.48, N 8.17.

4,5-Thia-(D,L)-tryptophan ethyl ester (28): This product was prepared as above using 73 mg (0.274 mmol) of ethyl α-(metyloximino)-β-(6-thieno[3,2-b]pyrrolyl)propanoate (**26**), with the exception that CH_2Cl_2/MeOH 9:1 was used as eluent in the purification to give 50 mg (77 %) of **28** as a brownish oil that rapidly darkened. ^{1}H NMR ($CDCl_3$) ∂ 8.51 (br.s, 1H), 7.07 (dd, J=5.2, 1.3 Hz, 1H), 6.90 (d, J=5.2 Hz, 1H), 6.81 (m, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.80 (dd, J=7.6, 4.8 Hz, 1H), 3.12 (ddd, J=14.4, 4.8, 0.9 Hz, 1H), 2.98 (ddd, J=14.4, 7.6, 0.7 Hz, 1H), 1.70 (br.s, 2H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 175.2, 138.8, 123.8, 123.6, 121.7, 111.6, 111.4, 61.1, 54.6, 32.0, 14.2; MS m/z (%): 238 (M^+, 21), 165 (9), 136 (100); HRMS observed: 238.0775 (M^+). Calcd: 238.0776; Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C 55.44, H 5.92, N 11.76. found: C 55.31, H 5.89, N 11.41.

6,7-Thia-(D,L)-tryptophan ethyl ester (29): This product was prepared as above using 76 mg (0.285 mmol) of ethyl α-(metyloximino)-β-(4-thieno[2,3-b]pyrrolyl)propanoate (**27**) to give 57 mg (84 %) of **29** as a

brownish oil that rapidly darkened. ^{1}H NMR ($CDCl_3$) ∂ 8.89 (br.s, 1H), 6.96 (d, J=5.2 Hz, 1H), 6.77-6.82 (m, 2H), 4.17 (q, J=7.1 Hz, 2H), 3.78 (dd, J=7.6, 4.8 Hz, 1H), 3.15 (dd, J=14.2, 4.8 Hz, 1H), 2.97 (dd, J=14.2, 7.6 Hz, 1H), 1.70 (br.s, 2H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) ∂ 175.3, 133.7, 130.9, 122.6, 118.0, 116.7, 111.3, 61.0, 55.1, 32.0, 14.2; MS m/z (%): 238 (M^+, 19), 165 (10), 136 (100); HRMS observed: 238.0775 (M^+). Calcd: 238.0776; Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C 55.44, H 5.92, N 11.76. found: C 55.25, H 5.76, N 11.39.

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