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Tetrahedron
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Tetrahedron 60 (2004) 9171–9177

2-(Arylsulfinylmethyl)oxazinanes: chiral carbonyl equivalents. Application to the asymmetric synthesis of 1,2,3,4-tetrahydro-β-carbolines

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Received 12 May 2004; revised 30 June 2004; accepted 23 July 2004

Available online 25 August 2004

Abstract—2-(*p*-Tolylsulfinylmethyl)oxazinane, a chiral carbonyl equivalent, has been synthesised and used for the diastereoselective synthesis of tetrahydro-β-carbolines including intermediates of yohimbine and herman alkaloids. A fair degree of diastereoselectivity, comparable with other approaches, has been achieved.

1. Introduction

The tetrahydroisoquinoline (THIQ) and tetrahydro-β-carboline (THBC) cores are structural motifs common to a diverse family of natural products, which display a variety of biological activities.[1] Most THBC and THIQ derivatives are optically active and have marked physiological activities[2] which are invariably different from those of their antipodes. The development of methods for enantioselective or diastereoselective synthesis of optically active 1-substituted THBCs is an important area in synthetic organic chemistry. The Pictet–Spengler reaction,[3] employing reaction of the biogenic amines with carbonyl substrates, is certainly one of the most powerful methods for the direct synthesis of THBC and THIQ derivatives.[4] Many other traditional synthetic methods are based on procedures that employ a stoichiometric amount of chiral building blocks, auxiliaries or reagents, catalytic asymmetric syntheses, catalytic asymmetric hydrogenation etc.[5] The chiral formamidine approach developed by Meyers et al.[6] has been extensively employed in the synthesis of both THBC and THIQ systems with high enantioselectivity. The use of a stereogenic sulfur centre of a chiral sulfoxide to achieve stereocontrol in asymmetric syntheses has been amply demonstrated.[7] Use of chiral acetylenic sulfoxides in the enantioselective synthesis of THBC and THIQ alkaloids through a tandem Michael addition/acid induced cyclisation reaction sequence has also been reported.[8] Chiral vinyl sulfoxides have been implemented,[9] via an intramolecular asymmetric conjugate addition of a nitrogen nucleophile to synthesise alkaloid systems. Since not many sulfoxide derivatives of the latter type are available, their use in asymmetric synthesis of THBCs and THIQs has been limited.

Using an unconventional approach we have been engaged in designing and mimicking[10] the reactivity pattern of a folate cofactor and investigating its use in the development of various types of synthetic strategies. Recently we reported[11] that simple and C-2 functionalised oxazinanes embodying a masked carbonyl substrate can be convincingly employed to synthesise otherwise inaccessible THBCs in a highly distereoselective manner and have thus been regarded as carbonyl equivalents. This has successfully addressed the problems associated with the direct use of carbonyl substrates (especially aliphatic carbonyls), in the diversification at the C-1 of THBCs, an attribute of potential utility in the total synthesis of indole alkaloids. These findings gave us additional impetus in developing optically active oxazinanes (chiral carbonyl equivalents)[12] with a possibility of further C-2 (at the oxidation level of the carbonyl) elaboration for exploration in asymmetric synthesis of THBCs and related systems. We now present a full account of our investigations on the synthesis of a new, stereochemically homogenous chiral oxazinane and its use as a two carbon synthon for enantio- and diastereoselective

Keywords: 2-(*p*-Tolylsulfinylmethyl)oxazinane; Carbonyl equivalents; Oxazinanes; Yohimbine alkaloids; Diastereoselective synthesis.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.062

synthesis of THBCs, which can be converted into yohimbine and herman alkaloids.

2. Results and discussion

2.1. Synthesis of chiral carbonyl equivalent

The reaction of C-2 metallated (*n*-BuLi/THF) 2,4,4,6-tetramethyl-5,6-dihydro-(4H)-1,3-oxazine **1**[13,14]with (−)-(*S*)-menthyl *p*-toluenesulfinate[15] at −78 °C (Scheme 1) afforded 2-arylsulfinylmethyl oxazine **2** as a mixture of its diastereomers[16] in 85% overall yield, after crystallisation from hot hexane. On the basis of the fact that such Anderson type reactions proceed with inversion[17] of configuration at the sulfinyl sulfur atom, the absolute configuration (*R*) can be assigned at the sulfinyl sulfur of compound **2**. The assignments of all the protons have been made on the basis of NOE connectivity while the carbons have been distinguished by the HMQC spectrum. To further widen the synthetic scope, **2** was metallated and quenched with MeI to obtain further elaborated oxazine **4** which after reduction could be used to obtain C-1 elaborated THBCs.

2.2. Synthesis of THBCs

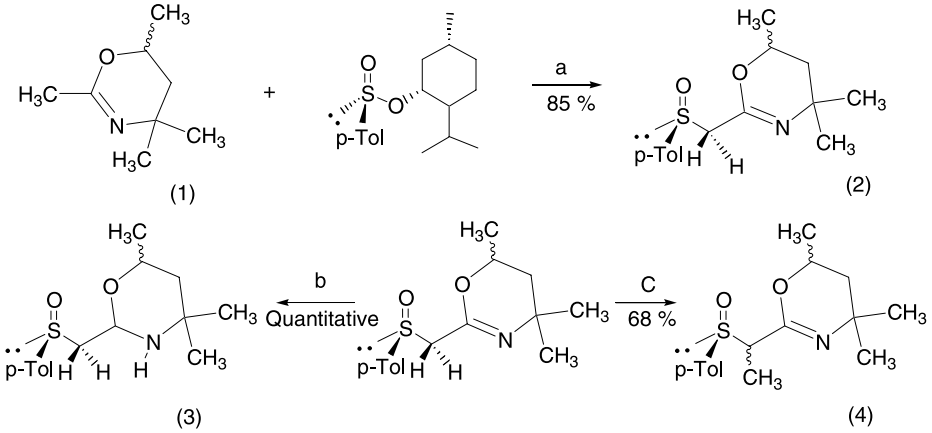
Acid catalysed reactions of **3** were performed with tryptamine and tryptophan derivatives **5a–d** to obtain THBCs which could be converted into the alkaloidal targets (Scheme 2). The chemical yields and the extent of stereoselectivity was comparable with the known syntheses.[8]

If a stoichiometric mixture of tryptamine **5a** and **3** in anhydrous MeCN/AcOH (10:1) solution is combined at ambient temperature, the following sequence takes place: formation of iminium intermediate **6** (tautomeric equilibrated, hydrogen bonded), spontaneous in situ conversion into a spiroindolenine[19] through acid induced intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety and subsequent rearrangement-deprotonation. This furnishes THBCs **7a** and **8a** in a 70:30 (1*R*/1*S*) diastereomeric ratio (^{1}H NMR spectroscopy correlation),[20] out of which **7a** could be isolated in 40% yield. This sequence establishes the crucial carbon–nitrogen and carbon–carbon bond formations in a one-pot reaction and creates a new chiral centre at C-1 of the alkaloid system.

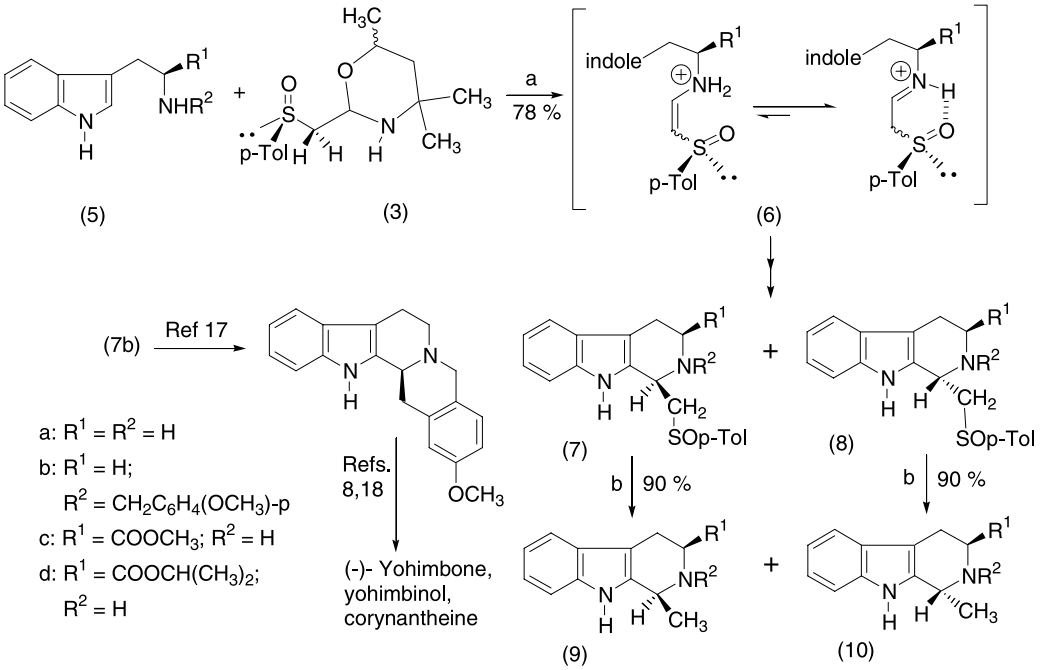
Similarly, secondary amine **5b**, which was prepared from tryptamine through reductive amination with *p*-methoxy benzaldehyde, reacts with **3** in MeCN/AcOH (10:1) at reflux temperature, yielding a mixture of two products, isolated by flash chromatography. The higher R_f component was minor and the lower one was the major component. These were assigned as **7b** and **8b**, respectively in 80% overall isolated yield and in a 30:70 (1*R*/1*S*) diastereomeric ratio. The NMR spectra and optical rotations were compared with the corresponding authentic data[17] and were thus assigned the appropriate absolute configuration at C-1. The THBC **7b** has also been converted into the homochiral pentacyclic intermediate **11**, which is a known precursor[18] of the pentacyclic yohimbine alkaloids (yohimbinol and corynantheine). Yohimbine alkaloids have a range of interesting biological properties and are used clinically in conventional medicines and folklore treatments. One interesting outcome of this methodology is reversal of the stereochemical bias in comparison with the chiral acetylenic approach. Switching from the chiral acetylenic sulfoxides to the oxazinane **3**, the stereochemical outcome of the reaction alters from **7a/8a** (30:70) and **7b/8b** (70:30) in the former method to **7a/8a** (70:30) and **7b/8b** (30:70) in the present approach.

Desulfurisation of the major component **8b** was conducted using Raney Ni and proceeded quantitatively to yield **10b**. The optical rotation of this enantiomer was found to be $[\alpha]_D^{21} = +25.0$ (*c* 0.126, CH_2Cl_2). On the basis of the correct spectral data and the fact that the starting **8b** is the 1*S* isomer, it can be assigned 1*R* configuration at C-1. Likewise, the minor component, **7b**, was also desulfurised under similar conditions and the product **9b** was assigned 1*S* configuration at C-1 {$[\alpha]_D^{21} = -24.0$ (*c* 0.126, CH_2Cl_2)}.

Similar reactions of a stoichiometric mixture of (L)-tryptophan methyl ester **5c** with **3** in anhydrous MeCN/AcOH (10:1) at ambient temperature furnished a mixture of THBCs, **7c** and **8c** (*cis*/*trans*: 33:66) in 76% isolated yield. *trans*-selectivity was favoured when the reaction was run at low temperature. The *cis* and *trans* isomers were distinguished as reported from the ^{13}C chemical shifts of the C-1 (*cis*: downfield, *trans*: upfield)[21] and also from the benzylic



Scheme 1. (a) *n*-BuLi, −78 °C, THF. (b) $NaBH_4$, THF/EtOH (1:1), −45 °C. (c) NaH, MeI, THF, 0 °C.



Scheme 2. (a) CH_3CN/AcOH (10:1). (b) Raney Ni, MeOH, 0 °C.

carbons (*trans*: upfield, *cis*: downfield),[19] which are easily distinguishable from rest of the signals (ca. 70 ppm). Also, both **7c** and **8c** were desulfurised using Raney Ni at 0 °C in methanol to obtain the corresponding known compounds[22] **9c** and 1**0c**, to further correlate the *cis* and *trans* stereochemistry. Likewise, reaction of tryptophan isopropyl ester **5d** with **3** under a similar set of conditions, yielded the THBCs **7d** and **8d** *cis*/*trans* diastereomers in 78% yield and similar diastereomeric ratio (Table 1). **7d** and **8d** were also desulfurised to obtain **9d** and **10d** to correlate the stereochemistry.

In view of the facile debenzylation[22] of **10b** and **9b**, and facile removal of the C-3 ester functions in **9d** and **10d** following the method of Yamada,[23] the above protocol constitutes a formal synthesis of optically pure eleagnine,[20] a herman alkaloid of known absolute configuration.

3. Conclusions

2-(*p*-Tolylsulfinylmethyl)oxazinane, a chiral carbonyl equivalent, has been synthesised and used for the diastereoselective synthesis of tetrahydro-β-carbolines including an intermediate of yohimbine alkaloids. The transformations depicted in Scheme 2 showed a fair degree of diastereoselectivity comparable with the reported methods,[8] when the chiral oxazinanes are employed as inductors. Also, precursors for the synthesis of optically pure eleagnine, a herman alkaloid have been synthesised. In addition, this strategy has scope for asymmetric synthesis of many more C-1 substituted THBCs and related compounds.

4. Experimental

4.1. General

All melting points are uncorrected. IR sectra were recorded on Shimadzu DR-8001 FT and Pye Unicam SP 3-300 spectrophotometer. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were run on Bruker AC 200 instrument using TMS as the internal standard. Mass (70 eV) spectra were performed on Shimadzu GCMS QP 2000 spectrometer. Elemental analyses of the samples were performed on and Perkin–Elmer 2400 CHN elemental analyser, respectively.

Table 1. Diastereocontrol in the reactions of **2** with tryptamine derivatives

Sr. no.	THBCs (**7**/**8**)	Reaction temperature	Diastereomeric ratio[a] of THBCs (**7**:**8**)	Reaction time (h)	Isolable yield (%)
1	$R^1=R^2=H$	rt	2.33:1 (1*R*:1*S*)[b]	12	40 (1*R*)
		Reflux	Decomposition	—	—
2	$R^1=H$	rt	Very slow reaction	—	—
	$R^2=CH_2C_6H_5(OCH_3)p$	Reflux	1:2.33 (1*R*:1*S*)[b]	24	80
3	$R^1=COOCH_3$ $R^2=H$	rt	1:2 (*c*/*t*)[a]	30	72
		Reflux	1:1.2 (*c*/*t*)[a]	10	78
4	$R^1=COOCH(CH_3)_2$	rt	1:2 (*c*/*t*)[c]	36	70
	$R^2=H$	Reflux	1:1.2 (*c*/*t*)[c]	12	75

[a] ±3% as determined from the integration of the C-3 ester signals in the ^1H NMR spectrum.
[b] Compared with the reported data.[12]
[c] Identified from the chemical shift of C-1 H signals.

TLC was performed on aluminium sheets coated with Silica gel 60 F_{254} (Merck). Optical rotations were measured using a Jasco DIP-360 digital polarimeter. All solvents MeCN (P_2O_5), THF (Na-benzophenone ketyl), hexane (sodium) and ethyl acetate (anhydrous K_2CO_3) were dried and distilled before use. Column chromatography was performed on silica gel (60–120 mesh).

L-Tryptophan methyl/isopropyl esters and 4-methoxy-benzyl tryptamine were prepared following the reported/modified procedures.[22] *p*-Toluene sulfinic acid, sodium salt hydrate (97%) and (1*R*,2*S*, 5$_R$)-(−)-menthol were purchased from Aldrich. (−)-(*S*)-Menthyl (*p*-tolunesulfinate) was synthesised following the reported procedure.[15]

4.1.1. Formation of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine (2). A two necked round bottom flask (250 mL) equipped with a magnetic stirring bar, and pressure equalising additional funnel (75 mL) topped with rubber septum and a nitrogen inlet tube was evacuated and flushed with nitrogen, at least thrice in succession. Anhydrous THF (100 mL) and 2,4,4,6-tetramethyl-5,6-dihydro-(4H)-1,3-oxazine (14.1 g, 0.1 mol) was added using a hypodermic syringe through the rubber septum. The stirred solution was cooled (−78 °C) and *n*-BuLi in hexane (50 mL, 2.2 N) was injected into the addition funnel and added dropwise over a period of 1 h into the flask. After approximately 1 h, and after the addition of *n*-BuLi, a yellow precipitate was formed (indicative of the complete anion formation) and a solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (14.7 g, 0.05 mol) in dry THF (60 mL) was injected into the addition funnel and slowly added to the reaction mixture over 1 h. After this addition, the reaction mixture was stirred at the same low temperature (−78 °C) for 1.5 h. The reaction was then quenched with saturated ammonium chloride solution (50 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and evaporated in vacuo. The oily residue was dissolved in hot hexane and was allowed to crystallise at −5 °C. After the first crop, the mother liquor was concentrated and allowed once again to crystallise at −5 °C. This operation was repeated three times, and finally the product was crystallised once from hot hexane.

Yield: 84%; white amorphous solid, mp 54 °C; ν_{max} (KBr) 1597 (C=N), 1218 (C–O), 1041 (S=O) cm^{-1}. δ_H (200 MHz $CDCl_3$)† 1.03 (3H, s, Me), 1.06 (3H, s, Me), 1.10 (3H, s, Me), 1.13 (3H, s, Me), 1.17 (3H, d, *J*=6.1 Hz, Me), 1.23 (3H, d, *J*=6.1 Hz, C*H*$_2$), 1.40 (1H, m, C(5)*H*H), 1.65 (1H, m, C(5)H*H*), 2.40 (3H, s, Me), 3.43 (1H, distorted d, *J*=12.7 Hz, –C*H*HSO), 3.60 (2H, m, C*H*$_2$SO), 3.83 (1H, distorted d, *J*=12.7 Hz, CH*H*SO), 4.06 (1H, m, C(6)*H*), 7.29 (4H, d, *J*=8.0 Hz, Ph), 7.57 (4H, d, *J*=8.0 Hz, Ph); δ_C (50 MHz $CDCl_3$)†: δ 21.0, 21.3, 29.2, 29.4, 31.2, 41.3, 41.5, 50.4, 62.4, 62.7, 68.6, 124.7, 129.6, 139.2, 139.3, 141.9, 152.0. *m*/*z* 279 (M$^+$); [Found: C, 64.54; H, 7.58; N 4.98. $C_{15}H_{21}NO_2S$ requires C, 64.51; H, 7.52; N, 5.01].

4.1.2. Reduction of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine. Formation of 2-(arylsulfinylmethyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine (3). A solution of 2-(arylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4H)-1,3-oxazine (5 g, 0.017 mol) in a mixture of ethyl alcohol (95%) and THF (1:1 v/v, 60 mL) was taken in a round bottom flask (100 mL) and cooled to −45 °C. Hydrochloric acid (9 N) was added to this magnetically stirred solution until pH 7 was obtained. Sodium borohydride solution was prepared separately by dissolving sodium borohydride (0.681 g, 0.017 mol) in a minimum amount of water (1–2 mL) containing a drop of aqueous sodium hydroxide (40%) solution. The sodium borohydride solution and the 9 N hydrochloric solution were introduced to the stirred solution of dihydrooxazine alternatively, so that pH 7–8 was maintained throughout the course of reaction. After the addition of the borohydride solution was complete, the solution was stirred at the same low temperature (−45 °C) for an additional 1 h. During this period, pH 7 was maintained by the occasional addition of 9 N hydrochloric acid. The contents were then poured into water (approx. 50 mL) and made basic by the addition of aqueous sodium hydroxide solution (40%) (care was taken not to raise the temperature above 10 °C during this addition). Oil globules/turbidity appeared upon basification and the solution was extracted with ethyl acetate (2× 30 mL). The combined organic extracts were washed with saturated sodium chloride solution (50 mL) and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to obtain the crude tetrahydrooxazine, which was purified using column chromatography employing a mixture of hexane and ethyl acetate (1:1, v/v) as the eluent.

Yield: quantitative; colourless oil at rt; ν_{max} ($CHCl_3$) 3390 (N–H), 1230 (C–O), 1045 (S=O) cm^{-1}. δ_H (200 MHz $CDCl_3$)† 1.10 (3H, s, Me), 1.43 (3H, s, Me), 1.20 (1H, m, C(5)*H*H), 1.40 (1H, dd, *J*=6.0, 2.2 Hz, C(5)H*H*), 1.47 (1H, dd, *J*=6.0, 2.2 Hz, C(5)*H*H), 2.40 (3H, s, Me), 2.75 (1H, dd, *J*=8.4, 6.1 Hz, C*H*HSO), 2.81 (1H, dd, *J*=8.4, 6.1 Hz, CH*H*SO), 3.09 (1H, t, *J*=13.2 Hz, C*H*HSO), 3.11 (1H, t, *J*=13.2 Hz, CH*H*SO), 3.85 (1H, m, C(6)*H*), 4.62 (1H, dd, *J*=6.1, 3.8 Hz, C(2)*H*), 4.66 (1H, dd, *J*=6.1, 3.8 Hz, C(2)*H*), 7.42 (4H, d, *J*=8.1 Hz, Ph), 7.43 (4H, d, *J*=8.1 Hz, Ph); δ_C (50 MHz $CDCl_3$)† 21.4, 22.1, 23.3, 23.7, 32.6, 45.0, 45.3, 49.2, 49.5, 62.2, 63.3, 69.2, 69.3, 78.3, 79.4, 124.3, 129.9, 141.0, 141.5. δ_C (50 MHz $CDCl_3$, DEPT-135) 21.4, 22.1, 23.3, 23.7, 32.6, 45.0 (−ve), 45.3 (−ve), 49.2, 49.5, 62.2 (−ve), 63.3 (−ve), 69.2, 69.3, 78.3, 79.4, 124.3, 129.9. *m*/*z* 281 (M$^+$); [Found: C, 63.99; H, 8.20; N, 4.95. $C_{15}H_{23}NO_2S$ requires C, 64.05; H, 8.18; N, 4.98].

4.1.3. Synthesis of oxazine 4. Dry THF (25 mL) was distilled directly from Na-benzophenone ketyl into a round bottom flask (50 mL), containing sodium hydride (0.90 g, 3.75 mmol), thoroughly prewashed with anhydrous hexane and dried. The flask was stoppered with a septum cap, flushed with nitrogen and cooled in ice, **2** (1.0 g, 3.5 mmol) dissolved in anhydrous THF (10 mL) was added dropwise and the colourless solution was stirred (0.5 h) at 0 °C. To this solution methyl iodide (1.0 mL, 16 mmol) was added dropwise and the reaction stirred for an additional 2 h at rt. The reaction was then quenched with saturated ammonium chloride solution (50 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2× 50 mL). The combined organic extracts were dried

† Extra signals appear owing to diastereomers.

(anhydrous sodium sulphate) and evaporated in vacuo. The oily residue was purified by column chromatography using ethyl acetate, hexane and their mixtures as eluents to obtain the pure product.

Yield: 74%; viscous oil; ν_{max} (KBr) 1590 (C=N), 1220 (C–O), 1035 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 0.95 (3H, d, $J=8.0$ Hz, Me), 1.20 (9H, m, 3×Me), 1.63 (2H, m, CH_2), 2.40 (3H, s, PhMe), 3.25 (0.6H, q, $J=8.0$ Hz, C*H*Me), 3.58 (0.4H, q, $J=8.0$ Hz, C*H*Me), 4.02 (1H, m, C*H*), 7.27 (2H, m, Ph), 7.53 (2H, m, Ph); δ_C (50 MHz $CDCl_3$) 21.0, 21.3, 29.1, 29.3, 29.5, 31.1, 31.3, 41.5, 41.7, 41.9, 41.9, 50.1, 50.2, 50.3, 63.9, 64.3, 66.7, 66.9, 68.2, 96.0, 125.3, 125.6, 130.5, 130.7, 138.8, 141.5. *m/z* 293 (M^+); [Found: C, 65.50; H, 7.81; N, 4.82 $C_{16}H_{23}NO_2S$ requires C, 65.52; H, 7.84; N, 4.77].

4.2. General procedure for the reaction of 2-(arylsulfinyl methyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2 with L-tryptophan methyl/ isopropyl ester or N_b-4-methoxy benzyl tryptamine or tryptamine

2-(Arylsulfinylmethyl)-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2 (2.29 mmol), the appropriate tryptophan ester/ tryptamine derivative (2.29 mmol) and acetic acid (catalytic) in anhydrous acetonitrile (30 mL) were stirred at rt/ refluxed at 80 °C till the reaction completed (TLC). The reaction was basified with cold aqueous sodium carbonate (5%) solution and extracted with ethyl acetate (3×50 mL). The extract was washed once with cold water (50 mL) and dried (anhydrous Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) using hexanes, ethyl acetate or their mixtures as eluents.

The reaction of L-tryptamine with oxazinanes provided the following product.

4.2.1. (1*R*,S$_R$)-1-(*p*-Tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (7a).[20] Yield: 33%; white solid, mp 158–160 °C; ν_{max} (KBr) 3280 (N–H), 1028 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.41 (3H, s, Me), 2.76 (2H, m, NCH_2), 2.82 (1H, br, D_2O exchangeable, NH), 3.02 (1H, dd, $J=13.6$, 4.9 Hz, C*H*HSO), 3.20 (2H, m, $PhCH_2$), 3.40 (1H, dd, $J=13.6$, 4.9 Hz, CH*H*SO), 4.80 (1H, dd, $J=4.9$, 4.3 Hz, CH), 7.29 (4H, m, Ph), 7.48 (4H, 2×d $J=8.0$ Hz, ArH), 9.60 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 22.2, 42.5, 50.0, 63.8, 108.9, 111.4, 118.1, 119.2, 121.9, 124.0, 126.9, 130.2, 133.4, 135.5, 140.2; [Found: C, 70.26; H, 6.30; N, 8.48 $C_{19}H_{20}N_2OS$ requires C, 70.34; H, 6.12; N, 8.63].

The reaction of N_b-4-methoxy benzyl tryptamine with oxazinanes furnished the following products.

4.2.2. (1*R*,S$_R$)-N-(*p*-Methoxybenzyl)-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (7b). Yield: 24%; white solid, mp 157 °C; ν_{max} (KBr) 3280 (N–H), 1029 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.41 (3H, s, Me), 2.53 (1H, m, NCH_2CHH), 2.90 (3H, m, NCH_2CHH), 3.19 (1H, dd, $J=8.6$, 2.7 Hz, C*H*HSO), 3.33 (2H, m, CH_2Ph), 3.52 (dd, $J=8.6$, 2.7 Hz, CH*H*SO), 3.79 (3H, s, OMe), 4.06 (1H, dd, $J=8.6$, 2.7 Hz, CH), 6.90 (4H, 2×d, $J=8.5$ Hz, Ph), 7.16 (4H, m, Ph), 7.43 (4H, 2×d, $J=8.3$ Hz, Ph), 8.39 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 18.3, 21.3, 45.4, 51.2, 55.1, 56.4, 58.6, 107.8, 111.3, 113.6, 118.0, 119.0, 121.5, 124.2, 129.5, 129.9. 130.7, 132.7, 136.0, 138.5, 141.5 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 18.3 (−ve), 21.3, 45.4 (−ve), 51.2, 55.2, 56.4 (−ve), 58.6 (−ve), 111.3, 113.6, 118.0, 119.0, 121.5, 124.2, 129.5, 129.9. *m/z* 444 (M^+); [Found: C, 72.98; H, 6.41; N, 6.28 $C_{27}H_{28}N_2O_2S$ requires C, 72.97; H, 6.30; N, 6.30]; $[\alpha]_D=+211.57$ (*c* 0.272, CH_2Cl_2).

4.2.3. (1*S*,S$_R$)-N-(*p*-Methoxybenzyl)-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (8b). Yield: 56%; white solid, mp 82 °C; ν_{max} (KBr) 3265 (N–H), 1032 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.40 (3H, s, Me), 2.55 (1H, m, NCH_2CHH), 3.00 (3H, m, NCH_2CHH), 3.19 (2H, m, CH_2SO), 3.81 (3H, s, OMe), 3.86 (2H, m, CH_2Ph), 4.48 (1H, br t, $J=6.0$ Hz, C(1)H), 7.00 (4H, 2×d, $J=8.5$ Hz, Ph), 7.14 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.6$ Hz, Ph), 9.28 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 17.2, 21.3, 43.5, 53.2, 55.1, 56.8, 63.2, 107.8, 111.3, 113.7, 117.9, 119.0, 121.5, 124.0, 126.9, 129.6, 130.0, 132.4, 136.2, 140.7, 141.5, 158.8. *m/z* 427 (M^+-OH), 291 ($M^+-CH_2SOC_6H_4Me$); [Found C, 72.85; H, 6.29; N, 6.42 $C_{27}H_{28}N_2O_2S$ requires C, 72.97; H, 6.30; N, 6.30]; $[\alpha]_D^{21}=+138.57$ (*c* 0.221, CH_2Cl_2).

Following the above procedure the reaction of L-tryptophan methyl ester with oxazinanes provided the following products.

4.2.4. (*cis*, S$_R$)-Methyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (7c). Yield: 35%; yellow viscous oil; ν_{max} ($CHCl_3$) 3430 (N–H), 1720 (C–O), 1030 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.91 (1H, br, D_2O exchangeable, NH), 2.41 (3H, s, C_6H_4Me), 3.07 (3H, m, C(4)H_2 and H_B of ABX of CH_2SO), 3.72 (3H, m, C(3)H and H_A of ABX CH_2SO), 3.76 (3H, s, OMe), 4.26 (1H, dd, $J=9.0$, 2 Hz, C(1)H), 7.23 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.1$ Hz, Ph), 10.38 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 25.5, 48.2, 52.2, 56.6, 57.8, 107.3, 111.6, 117.9, 119.2, 121.8, 124.3, 126.7, 130.3, 132.4, 136.0, 136.7, 142.0, 173.2; δ_C (50 MHz $CDCl_3$, DEPT-135) 21.4, 25.5 (−ve), 48.2, 52.2, 56.6, 57.8 (−ve), 111.6, 117.9, 119.2, 121.8, 124.3, 130.3. *m/z* 382 (M^+); [Found: C, 65.78; H, 5.84; N, 7.29 $C_{21}H_{22}O_3N_2S$ requires C, 65.96; H, 5.75; N, 7.32]; $[\alpha]_D=+253.97$ (*c* 0.175, $CHCl_3$).

4.2.5. (*trans*, S$_R$)-Methyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (8c). Yield: 43%; white solid, mp 215 °C; ν_{max} (KBr) 3210 (N–H), 1740 (C–O), 1045 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.85 (1H, br, D_2O exchangeable, NH), 2.41 (3H, s, C_6H_4Me), 3.05 (3H, m, C(4)H_2 and H_B of ABX of CH_2SO), 3.28 (1H, dd, $J=13.4$, 6.8 Hz, H_A of ABX of CH_2SO), 3.76 (3H, s, OMe), 3.85 (1H, dd, $J=7.2$, 5.3 Hz, C(3)H), 5.01 (1H, dd, $J=13.3$, 8.5 Hz, C(1)H), 7.26 (4H, m, Ph), 7.42 (4H, 2×d, $J=8.1$ Hz, Ph), 9.55 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 25.2, 47.2, 52.2, 53.1, 64.2, 107.2, 111.4, 118.0, 119.3, 122.0, 124.0, 126.7, 130.2, 132.8, 136.2, 140.2, 142.0, 173.8. *m/z* 365 (M^+-OH^-), 229 ($M^+-CH_2SOC_6H_4CH_3$); [Found: C,

65.86; H, 5.78; N, 7.36 $C_{21}H_{22}O_3N_2S$ requires C, 65.96; H, 5.75; N, 7.32]; $[\alpha]^{21}=+698.39$ (*c* 0.112, $CHCl_3$).

The reaction of L-trptophan isopropyl ester with oxazinanes furnished the following products.

4.2.6. (*cis*, S_R)-Isopropyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (7d). Yield: 34.5%; yellow viscous oil; ν_{max} ($CHCl_3$) 3380 (N–H), 1725 (C–O), 1030 (S–O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.27 (6H, 2×d, *J*=6.2 Hz, $CH(Me)_2$), 2.16 (1H, br, D_2O exchangeable, NH), 2.43 (3H, s, C_6H_4Me), 2.85 (3H, m, C(4)H and H_B of ABX of CH_2SO), 3.60 (2H, m, C(3)H and H_A of ABX of CH_2SO), 4.18 (1H, br d, *J*=9.0 Hz, C(1)H), 5.09 (1H,heptet, *J*=6.2 Hz, $CH(Me)_2$), 7.26 (4H, m, Ph), 7.48 (4H, 2×d, *J*=8.1 Hz, Ph), 10.33 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.3, 21.7, 25.5, 48.1, 56.7, 57.8, 68.7, 107.4, 111.6, 112.0, 117.9, 119.1, 121.7, 124.3, 126.7, 130.2, 132.6, 135.8, 136.7, 141.9, 172.4; *m/z* 410 (M^+); [Found: C, 67.42; H, 6.35; N, 6.74 $C_{23}H_{26}N_2O_3S$ requires C, 67.31; H, 6.34; N, 6.82]; $[\alpha]_D=+212.19$ (*c* 0.250, $CHCl_3$).

4.2.7. (*trans*, S_R)-Isopropyl-1-(*p*-tolylsulfinylmethyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (8d). Yield: 40.5%; white solid, mp 225 °C; ν_{max} (KBr) 3300 (N–H), 1734 (C–O), 1027 (S=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.28 (6H, 2×d, *J*=6.9 Hz, $CH(Me)_2$), 1.94 (1H, br, D_2O exchangeable, NH), 2.86 (1H, dd, *J*= 15.2, 8.2 Hz, H_A of ABX of $C(4)H_2$), 3.07 (2H,m, H_B of ABX of $C(4)H_2$ and H_A of ABX of CH_2SO), 3.28 (1H, dd, *J*=8.2, 4.9 Hz, H_B of ABX of CH_2SO), 3.77 (1H, dd, *J*= 8.2, 4.9 Hz, C(3)H), 5.02 (1H, br t, *J*=5.6 Hz, C(1)H), 5.11 (1H, heptet, *J*=6.9 Hz, $CH(Me)_2$), 7.25 (4H, m, Ph), 7.45 (4H, 2×d, *J*=8.1 Hz, Ph), 9.53 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.3, 21.7, 25.4, 47.1, 53.1, 64.3, 68.6, 107.2, 111.3, 117.9, 119.1, 121.8, 123.9, 126.7, 130.1, 132.9, 136.2, 140.3, 141.8, 172.8; *m/z* 393 (M^+-OH^-), 257 ($M^+-CH_2SOC_6H_4Me$); [Found: C, 67.32; H, 6.42; N, 6.83 $C_{23}H_{26}N_2O_3S$ requires C, 67.31; H, 6.34; N, 6.82]; $[\alpha]_D=+646.03$ (*c* 0.166, $CHCl_3$).

4.3. Desulfurisation of 7/8. General procedure

To an ice cooled solution of the appropriate **7** or **8** (1.5 mol) in methanol (30 mL) was added Raney nickel (excess). This mixture was stirred at 0 °C under a nitrogen atmosphere till the reaction completed (TLC), was then filtered through a bed of celite and the residue evaporated. The crude product was purified by column chromatography on silica gel (60–120 mesh) using hexane, ethyl acetate and their mixtures as eluents.

4.3.1. (1*S*)-N-(*p*-Methoxybenzyl)-1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (9b). Yield: quantitative; viscous oil; ν_{max} ($CHCl_3$) 3285 (N–H) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.44 (3H, d, *J*=6.6 Hz, Me), 2.67 (1H, m, PhC*H*H), 2.86 (2H, m, PhCH*H* and NC*H*H) 3.14 (1H, m, NCH*H*), 3.75 (2H, ABq, *J*=13.3 Hz, CH_2Ph), 3.80, (3H, s, OMe), 3.86 (1H, m, C(1)H), 7.14 (4H, 2×d, *J*=8.5 Hz, Ph), 7.17 (2H, m, Ph), 7.28 (1H, m, Ph), 7.46 (1H, m, Ph), 7.68 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 19.3, 19.4, 45.3, 52.0, 55.2, 56.6, 107.6, 110.7, 113.7, 118.1, 119.3, 121.4, 127.3, 130.0, 135.9, 136.1, 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 19.3, 19.4 (−ve), 45.3 (−ve), 52.0, 55.2, 56.6 (−ve), 110.7, 113.7, 118.1, 119.3, 121.4, 130.0; *m/z* 306 (M^+); [Found: C, 78.45; H, 7.25; N, 9.19 $C_{20}H_{22}N_2O$ requires C, 78.43; H, 7.18; N, 9.15]; $[\alpha]_D=-24.0$ (*c* 0.154, CH_2Cl_2).

4.3.2. (1*R*)-N-(*p*-Methoxybenzyl)-1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]indole (10b). Yield: quantitative; viscous oil; ν_{max} ($CHCl_3$) 3280 (N–H) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.44 (3H, d, *J*=6.7 Hz, Me), 2.62 (m, 1H, PhC*H*H), 2.85 (2H, m, PhCH*H* and NC*H*H), 3.19 (1H, m, NCH*H*), 3.70 (2H, ABq, *J*=13.3 Hz, CH_2Ph), 3.82 (3H, s, OMe), 3.89 (1H, m, C(1)H), 7.10 (4H, 2×d, *J*=8.5 Hz, Ph), 7.06 (2H, m, Ph), 7.29 (1H, m, Ph), 7.48 (1H, m, Ph), 7.66 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 19.21 19.2, 45.4, 51.9, 55.2, 56.6, 107.7, 110.6, 113.6, 118.0, 119.3, 121.4, 127.3, 129.9, 131.0, 135.9, 136.1, 158.7; δ_C (50 MHz $CDCl_3$, DEPT-135) 19.2, 19.2 (−ve), 45.4 (−ve), 51.9, 55.2, 56.6, 110.6, 113.6, 118.0, 119.3, 121.4, 129.9; [Found: C, 78.40; H, 7.29; N, 9.09 $C_{20}H_{22}N_2O$ requires C, 78.43; H, 7.18; N, 9.15]; $[\alpha]^{21}=+25.0$ (*c* 0.126, CH_2Cl_2).

4.3.3. (1*S*,3*S*) Methyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (9c).[22] Yield: 72%; viscous liquid; ν_{max} 3400 (N–H), 1725 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.46 (3H d, *J*=6.5 Hz, Me), 1.89 (1H, br, D_2O exchangeable, NH), 3.15 (2H, m, $C(4)H_2$), 3.73 (3H, s, OMe), 4.02 (1H, m, C(3)H), 4.42 (1H, br, C(1)H), 7.10 (2H, m, Ph), 7.34 (1H, m, Ph), 7.52 (1H, m, Ph), 7.88 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.2, 24.8, 45.8, 52.2, 52.3, 106.4, 110.8, 118.1, 119.6, 121.9, 127.0, 136.0, 173.5; *m/z* 244 (M^+); [Found: C, 68.39; H, 6.23; N, 11.34 $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.55; N, 11.47].

4.3.4. (1*R*,3*S*) Methyl 1-methyl 1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (10c).[22] Yield: 75%; viscous liquid; ν_{max} ($CHCl_3$) 3405 (N–H), 1745 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.49 (3H, d, *J*=6.7 Hz, Me), 1.92 (1H, br, D_2O exchangeable, NH), 2.90 (2H, m, $C(4)H_2$), 3.82 (3H, s, OMe), 3.90 (1H, m, C(3)H), 4.30 (1H, br, C(1)H), 7.14 (2H, m, Ph), 7.40 (2H, m, Ph), 7.83 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 20.3, 25.7, 48.2, 52.1, 56.3, 107.3, 110.7, 119.5, 119.6, 121.8, 127.0, 136.0, 173.3; *m/z* 244 (M^+); [Found: C, 68.41; H, 6.24; N, 11.43 $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.55; N, 11.47].

4.3.5. (1*S*,3*S*)-Isopropyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (9d). Yield: 89%; viscous liquid, ν_{max} ($CHCl_3$) 3405 (N–H), 1735 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.22 (6H, 2×d, *J*=6.1 Hz, 2×Me), 1.47 (3H, d, *J*=6.3 Hz, CH_3), 2.64 (1H, br, D_2O exchangeable, NH), 2.99 (2H, m, $C(4)H_2$), 3.99 (1H, dd, *J*= 7.6, 5.2 Hz, C(3)H), 4.44 (1H, q, *J*=6.3 Hz, C(1)H), 5.15 (1H, heptet, *J*=6.1 Hz, $CH(Me)_2$), 7.13 (2H, m, Ph), 7.29 (1H, m, Ph), 7.52 (1H, m, Ph), 7.95 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 21.4, 21.7, 25.0, 45.9, 52.3, 68.6, 106.4, 110.8, 118.0, 119.4, 121.6, 127.0, 136.0, 172.9; *m/z* 272 (M^+); [Found: C, 70.62; H, 7.41; N,19.15 $C_{16}H_{20}N_2O_2$ requires C, 70.59; H, 7.35; N, 10.30].

4.3.6. (1*R*,3*S*)-Isopropyl 1-methyl-1,2,3,4-tetrahydro-9H-pyrido [3,4-*b*]-indole-3-carboxylate (10d). Yield:

94%; viscous liquid, ν_{max} ($CHCl_3$) 3400 (N–H), 1725 (C=O) cm^{-1}; δ_H (200 MHz $CDCl_3$) 1.22 (6H, m, 2×Me), 1.40 (3H, d, J=6.3 Hz, Me), 1.67 (1H, br, D_2O exchangeable, NH), 2.68 (1H, m, C(4)*H*H), 2.98 (1H, m, C(4)H*H*), 3.65 (1H, dd, J=11.1, 4.3 Hz, C(3)H), 4.15 (1H, q, J=6.4 Hz, C(1)H), 5.03 (1H, heptet, J=6.3 Hz, C*H*$(Me)_2$), 7.09 (2H, m, Ph), 7.19 (1H, m, Ph), 7.38 (1H, d, J=7.1 Hz, Ph), 7.72 (1H, br, D_2O exchangeable, NH); δ_C (50 MHz $CDCl_3$) 20.2, 21.7, 25.8, 48.3, 56.6, 68.6, 107.4, 110.8, 118.0, 119.5, 121.7, 127.2, 136.0, 172.5; *m/z* 272 (M^+); [Found: C, 70.60; H, 7.39; N, 10.20 $C_{16}H_{20}N_2O_2$ requires C, 70.59; H, 7.35; N, 10.30].

Acknowledgements

The authors thank CSIR, New Delhi, for the grant [(1653)/00-EMR-II]. KS thanks Prof. A.W.M. Lee for supplying spectral and physical data of some THBCs for comparison purpose.

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