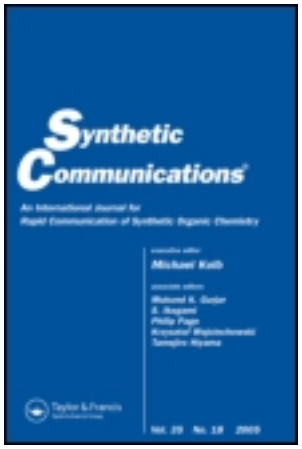

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Diastereoselective Synthesis of trans-Fused Pyrrolo[3,4-b]quinolines Through Intramolecular Imino Diels-Alder Reaction

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Available online: 02 Jan 2012

To cite this article: Mathesan Jayagobi & Raghavachary Raghunathan (2012): Novel Diastereoselective Synthesis of trans-Fused Pyrrolo[3,4-b]quinolines Through Intramolecular Imino Diels-Alder Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:19, 2917-2930

To link to this article: http://dx.doi.org/10.1080/00397911.2011.572218

Synthetic Communications®, 42: 2917–2930, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.572218

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NOVEL DIASTEREOSELECTIVE SYNTHESIS OF *TRANS*-FUSED PYRROLO[3,4-*b*]QUINOLINES THROUGH INTRAMOLECULAR IMINO DIELS–ALDER REACTION

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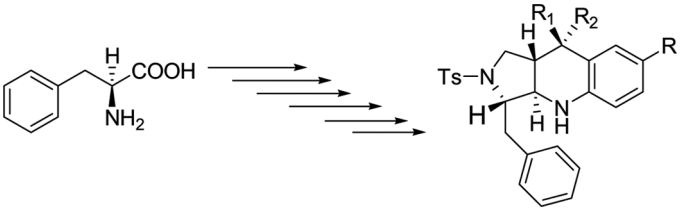
GRAPHICAL ABSTRACT



Abstract *Synthesis of a series of 1aR,2S,4aS-hexahydropyrrolo[3,4-*b*]quinolines has been achieved by the intramolecular cyclization reaction of aldimines derived from aromatic amines and (*S*)-2-(*N*-(3-methylbut-2-enyl)-*N*-tosyamino)-3-methylpropanal/(*S*)-2-(*N*-(3-methylbut-2-enyl)-*N*-tosyamino)-3-phenylpropanal in acetonitrile with $InCl_3$ as a catalyst, in excellent yields and in short duration of time, under mild conditions.*

Keywords Arylamines; diastereoselectivity; hexahydropyrrolo[3,4-*b*]quinolines; imino Diels–Alder reaction; indium trichloride

INTRODUCTION

The development of methodology for the synthesis of enantiomerically pure compounds has become a core area of research in organic chemistry because of increasing demand for these compounds by the pharmaceutical industry. Because naturally occurring chiral compounds are often too expensive for use as starting materials, a more economical approach is to employ substoichiometric amounts of chiral compounds in catalytic enantioselective processes, which produce large quantities of optically pure compounds.[1] The stereoselective synthesis of partially unsaturated *N*-heterocycles such as tetrahydroquinolines are important for pharmacological research.[2] Quinoline ring systems are widely distributed in nature, and synthesis of quinoline ring systems could be achieved by various methods. However,

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for asymmetric synthesis of quinoline derivatives, only limited methods are available.[3] Tetrahydroquinolines exhibit a wide range of biological activities.[4–7] Pyrrolidines and hexahydropyrroloquinolines have also been shown to possess various types of bioactivities.[8,9]

Tetrahydroquinoline derivatives have been synthesized by various methods in recent years,[10] of which the imino Diels–Alder (IMDA) reaction provides a rapid means of constructing such molecules with control of regio- and stereo selectivity. Imines, which serve as dienophiles in this reaction, can be synthesized from a variety of aldehydes and ketones.[11]

Although IMDA reaction is catalyzed by many reagents,[12] $InCl_3$ is the reagent of choice for catalyzing this reaction because it is a mild and water-tolerant Lewis acid imparting high regio- and chemoselectivity.[13] Unlike intermolecular Diels–Alder reaction of aza dienes generated from the reactions of arylaldehydes with arylamines, there are only a few reports available for the IMDA reaction of dienes generated from allyl tethered aliphatic aldehyde with arylamines.[14]

In continuation of our research interest in the IMDA reaction, we herein describe a simple method for the synthesis of hexahydropyrrolo[3,4-*b*] quinolines from aromatic amines and *N*-allyl derivatives of chiral aldehydes via intramolecular [4 + 2] cyclization of imines catalyzed by $InCl_3$.[15]

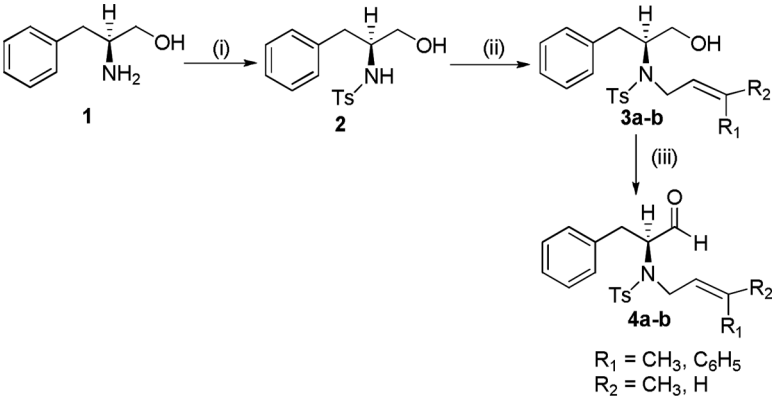
RESULTS AND DISCUSSION

We started with a known simple chiral substrate for the synthesis of hexahydropyrrolo[3,4-*b*]quinolines. Thus, starting from (*S*)-phenyl alanine **1**, chiral alkenyl aldehydes **4a** and **4b** were synthesized and imine dienophiles, generated from the reactions of aldehydes **4** with various arylamines **5a–e**, were trapped intramolecularly to yield a variety of enantiomerically pure hexahydropyrrolo[3,4-*b*]quinolines **6a–j**.

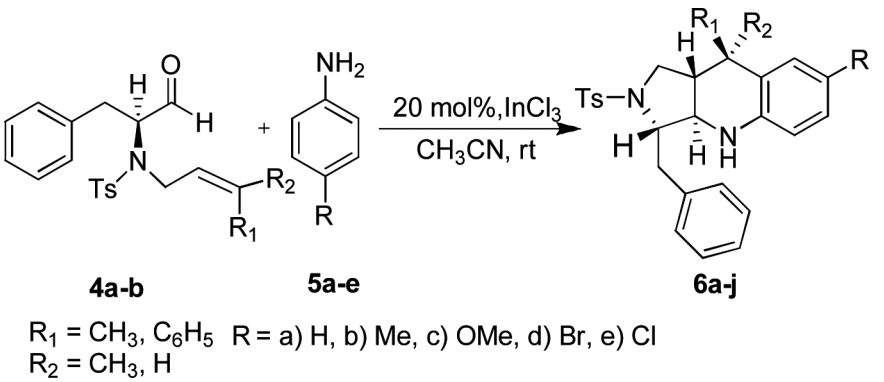
Synthesis of Enantiomerically Pure *N*-Alkenyl Aldehyde

(S)-Phenyl alanine was converted to its ethylester hydrochloride by treatment with excess of thionyl chloride in dry ethanol. The hydrochloride salt of the ester was then reduced by sodium borohydride in aqueous ethanolic solution to obtain the amino alcohol **1** in good yield $\{[\alpha] = -24.1$ (*c* 1, EtOH)$\}$.[16] The amino group of the alcohol was protected using using *p*-toluenesulfonyl chloride to afford compound **2** in good yield. Compound **2** was characterized by spectroscopic data.

The *N*-sulfonyl chiral alcohol **2** was then subjected to *N*-prenylation using prenyl bromide with anhydrous potassium carbonate in dry acetone to obtain the *N*-prenylated alcohol **3a** in good yield. The alkenyl alcohol was then oxidized quantitatively to the alkenyl aldehyde, (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal, by stirring the suspension of IBX (iodoxybenzoic acid) in dimethylsulfoxide (DMSO) with the alcohol for 4 h (Scheme 2). The structure of alkenyl aldehyde **4a** was confirmed on the basis of spectroscopic data. The same methodology was followed for the synthesis of **4b** by using cinnamyl bromide. The N-substituted cinnamyl alcohol **3b** was oxidized quantitatively to the alkenyl aldehyde, (*S*)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropanal **(4b)** by using IBX in DMSO as an oxidizing agent (Scheme 1).[17]



Scheme 1. Synthesis of *N*-alkenyl aldehydes. *Reagents and conditions*: (i) TBAB, 10% NaOH/benzene, tosyl chloride, 0 °C–rt; 8 h, 90%; (ii) prenyl bromide/cinnamyl bromide, K_2CO_3/acetone, 12 h, 90%; and (iii) iodoxybenzoic acid, DMSO, 4 h, 98%.



Scheme 2. Synthesis of enantiopure hexahydropyrrolo[3,4-*b*]quinolines.

Synthesis of Enantiopure Hexahydropyrrolo[3,4-*b*]quinolines

The aldehyde **4a**, when reacted with aromatic amines (**5a–e**) in the presence of 20 mol% indium trichloride in acetonitrile at room temperature, generated the imines, which then cyclized with olefines intramolecularly in a one-pot reaction to yield a series of pyrroloquinoline derivatives, with the *trans* isomer as the major product. The same reaction was extended to the aldehyde **4b** with aromatic amines **(5a–e)** to yield a series of novel pyrroloquinolines (Scheme 2).

We have tried the same reaction with various other Lewis acids, but the yield of the products obtained was moderate, and it took a long time for completion of the reaction (Table 1). We have found $InCl_3$ to be the best catalyst for the reaction in terms of yield and reaction time, and 20 mol% was found to be the optimum concentration for carrying out the reaction with high efficiency (Table 2).

Table 1. Influence of Lewis acids on the reaction of **6a** with **5a**

Entry	Lewis acid	Reaction time	Overall yield (%)
1	$BF_3 \cdot OEt_2$	3 h	62
2	$Yb(OTf)_3$	1.5 h	78
3	$Sc(OTf)_3$	1 h	72
4	$InCl_3$	10 min	93

Table 2. Study of molar ratio of $InCl_3$ on the reaction of **6a** with **5a**

Entry	$InCl_3$ (mol%)	Overall yield (%)
1	5	30
2	10	55
3	15	67
4	20	93

The structures of the cycloadducts were confirmed by spectroscopic data. All the cycloadducts were obtained as a single diastereomer, and the specific rotation values were found to be constant after repeated crystallizations. In all cases, only the *trans*-isomer was obtained as the major product and characterized on the basis of detailed 2D NMR studies (Table 3). The cycloadduct **6a** as typical example of the series with optical rotation $+6.79^{o}$ (*c* 1, $CHCl_3$) showed infrared (IR) absorption stretching bands at 3391 cm^{-1} due to a NH group and at 1160.0 and 1344.7 cm^{-1} due to the presence of a sulfonyl group.

The ^1H NMR spectrum of the compound **6a** exhibited singlets at δ 1.07 and 1.12 due to the geminal methyl protons. The ring junction proton Ha appeared as a doublet of triplet at δ 1.30 (dt, 1Ha, $J = 6.00$, 12.00 Hz). A sharp singlet was exhibited at δ 2.39 due the aromatic methyl protons and a broad singlet at δ 2.69 for NH. The -NCH_2 protons exhibited a triplet δ 3.28 ($J = 12.0$ Hz) and a doublet of triplet appeared at δ 3.47 (dt, 1H, $J = 3.00$, 6.00). A doublet of doublet was observed at

Table 3. $InCl_3$-catalyzed synthesis of hexahydropyrrolo[3,4-*b*]quinoline derivatives

Entry	R	R_1	R_2	Compound	Time (min)	Yield (%)
1	H	Me	Me	6a	10	93
2	Me	Me	Me	6b	15	87
3	Ome	Me	Me	6c	17	89
4	Br	Me	Me	6d	17	96
5	Cl	Me	Me	6e	15	97
6	H	H	Ph	6f	10	97
7	Me	H	Ph	6g	12	92
8	OMe	H	Ph	6h	12	90
9	Br	H	Ph	6i	12	95
10	Cl	H	Ph	6j	10	98

δ 3.68 (dd, 1H, $J = 9.00$, 12.00 Hz), and the benzyl methylene protons resonated as a doublet of doublet at δ 2.86 (dd, 1H, $J = 12.00$, 12.00 Hz) and δ 3.68 (dd, 1H, $J = 3.00$, 6.00, 12.00 Hz). The ring junction proton Hb exhibited a doublet of doublet at δ 3.21 (dd, 1Hb, $J = 3.00$, 6.00, 12.00 Hz). The ring junction proton showed a doublet of triplet at δ 1.30 (dt, 1Ha, $J = 6.00$, 12.00 Hz) for the Ha proton and doublet of doublet at δ 3.21 (dd, 1Hb, $J = 3.00$, 6.00, 12.00 Hz) for the Hb proton. The *trans*-fusion of the two rings is ascertained by the large coupling constant exhibited by Ha and Hb protons ($J = 12.00$ Hz) The aromatic protons resonated as multiplets in the range δ 5.92–7.81.

Further ^{13}C NMR spectrum of the compound **6a** showed signals at 21.54, 27.02, 28.60, 34.04, 42.27, 47.92, 49.25, 57.72, 66.85, 115.65, 118.78, 126.86, 127.14, 127.42, 128.97, 129.56, 129.90, 130.63, 134.53, 137.01, 143.05, and 143.77 ppm.

The molecular ion peak for the compound **6a** appeared at m/z 446.32 (M^+) in mass spectrum. Further, the products were confirmed through elemental analysis.

Moreover, the structure and stereochemistry of the cycloadducts **6f** and **6g** were established by single-crystal x-ray diffraction analysis.[18] The *trans*-stereochemistry of the products was assigned based on the values of the coupling constants of the protons in the ^1H NMR spectra and also by direct comparison with literature data wherever available.[19] The *trans*-fusion at the ring junction was further confirmed by the absence of a nuclear Overhauser effect (NOE) between H_a and H_b.

CONCLUSION

The chiral N-alkenyl aldehydes were successfully subjected to intramolecular cycloaddition reaction with various aromatic amines to obtain a series of enantiopure hexahydropyrrolo[3,4-*b*]quinolines. The cycloaddition reactions were found to be stereoselective and gave *trans*-fused cycloadducts. The reaction was effectively catalyzed by $InCl_3$, which resulted in good yield of the products with high stereoselectivity.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-8300 series Fourier transform (FT)–IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 300-MHz instruments in $CDCl_3$ solvent with tetramethylsilane (TMS) as standard. Mass spectra were recorded on a JEOL-DX303 HF mass spectrophotometer. Elemental analysis was carried out by Perkin-Elmer CHNS 2400 instrument. Single-crystal x-ray diffraction analysis was performed by Bruker SMART APEX CCD area-detecter diffractometer and Bruker SMART APEXII CCD area-detector diffracrometer.

Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reaction was done using thin-layer chromatography (TLC) developed on glass plates coated with silica gel-G (ACME) of 25 mm thick and visualized with iodine.

Preparation of (*S*)-2-Amino-3-phenylpropan-1-ol

(*S*)-2-amino-3-phenylpropan-1-ol was prepared in two stages from (*S*)-phenyl alanine.

Stage 1: Preparation of (*S*)-phenylalanine ethyl ester hydrochloride. To a stirred, ice-cold suspension of (*S*)-phenyl alanine (30 g, 0.182 mol) in absolute ethanol (800 mL), thionyl chloride (32.5 g, 0.273 mol) was added dropwise, and the reaction mixture was heated at reflux for 3.5 h. The pale yellow solution was allowed to stand overnight at room temperature, and the ethanol was evaporated in vacuo to obtain a colorless solid. The vacuum-dried (*S*)-phenylalanine ethyl ester hydrochloride was washed with dry diethyl ether, filtered, and dried in vacuo. The solid thus obtained was used as such in the next step.

Stage 2: Preparation of (*S*)-phenylalaninol from (*S*)-phenylalanine ethyl ester hydrochloride. A solution of (*S*)-phenylalanine ethyl ester hydrochloride (40 g, 0.176 mol) in 50% aqueous ethanol (400 mL) was added dropwise to solution of sodium borohydride (28 g, 0.736 mol) in 50% aqueous ethanol (400 mL), and the resulting mixture was refluxed for 4.5 h. Ethanol was evaporated in vacuum. The aqueous solution thus obtained was the extracted with ethyl acetate. The extract was washed with saturated brine solution and dried over anhydrous sodium hydroxide. Evaporation of the ethyl acetate under reduced pressure afforded (*S*)-phenyl alaninol **3** as a pale yellow solid. Pale yellow solid, 72% (19.16 g); $[\alpha]_D^{26} = -24.2$ (c 1, EtOH); mp: 85–87 °C; IR (KBr): 2990 and 3452 cm^{-1}.

Synthesis of (*S*)-3-Phenyl-2-(tosylamino)propan-1-ol, 2

Half a portion of 19.06 g (0.1 mol) *p*-toluenesulfonyl chloride was added to a solution of 15.10 g (0.1 mol) of (*S*)-2-amino-3-phynylpropan-1-ol in 100 mL benzene at 0 °C. The reaction mixture was stirred vigorously, and after 10 min, 30 mL of benzene was added, followed by the remaining portion of *p*-toluenesulfonyl chloride and a catalytic amount (500 mg) of the phase-transfer catalyst, tetrabutylammonium bromide (TBAB). To this stirred mixture, a 25% solution of sodium hydroxide (0.1 mol) was added dropwise using an additional funnel, resulting in a thick flocculation. The temperature of the reaction mixture was raised to room temperature once the addition of sodium hydroxide was complete. After 8–10 h, the reaction mixture was diluted with 100 mL of water. It was then extracted with 100 mL of benzene and washed with brine solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuum to yield crude *N*-sulfonylated-(*S*)-phenyl alaninol. The pure **4** was obtained by column chromatography using a 9:1 mixture of hexane–ethyl acetate. Colorless solid, 89% (27.18 g); $[\alpha]_D^{34} = -24.36°$ (*c* 1, $CHCl_3$); mp: 76–78 °C; IR (KBr): 1339, 1163, 3100 and 3452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 1H, OH), 2.40 (s, 3H, Ar-CH_3), 2.66 (dd, 1H, $J = 6.0$, 15.0 Hz), 2.77 (dd, 1H, $J = 6.0$, 15.0 Hz), 3.39–6.65 (m, 3H), 5.06 (d, 1H, $J = 6.0$ Hz, including NH), 6.95–7.59 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.09, 36.32, 55.22, 62.58, 125.24, 125.57, 127.21, 127.72, 128.25, 135.32, 135.43 and 141.95 ppm; MS *m/z*, 305.31 (M^+). Anal. calcd. for $C_{16}H_{19}NO_3S$: C, 62.93, H, 6.27, N, 4.59%. Found: C, 62.83, H, 6.21, N, 4.63%.

Synthesis of (*S*)-2-(*N*-(3-Methyl but-2-enyl)-*N*-tosylamino)-3-phenylparopan-1-ol, 3a / (*S*)-2-(*N*-Cinnamyl-*n*-tosylamino)-3-phenylparopan-1-ol, 3b

To a solution of 20 mmol of (*S*)-3-phenyl-2-(tosylamino)propan-1-ol in 100 mL of dry acetone under a nitrogen atmosphere was added 60 mmol of potassium carbonate. To this stirred solution, 20 mmol of prenyl/cinnamyl bromide in 50 mL of dry acetone was added. The stirring was continued for 8–10 h. After completion of the reaction, the solid was filtered off. The residue was washed several times with acetone, and the filtrate was concentrated in vacuum and extracted with dichloromehane (100 mL) and water (100 mL). The organic extract was washed with brine solution and concentrated under reduced pressure. The crude product was subjected to column chromatography with hexane–ethylacetate mixture (9:1) to obtain pure *N*-allylated (*S*)-3-phenyl-2-(tosylamino) propan-1-ol, **3a**.

Compound 3b. Colorless oil, 80% (5.52 g); $[\alpha]_D^{34} = -29.96^\circ$ (*c* 1, $CHCl_3$); IR (KBr): 1330, 1169, 1600 and 3546 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.68 (s, 6H), 2.39 (s, 3H), 2.17 (bs, 1H, OH), 2.65–2.78 (m, 2H), 3.54–3.67 (m, 2H), 3.86 (d, 2H, $J = 6.0$ Hz), 4.03–4.13 (m, 1H), 5.16 (dd, 1H, $J = 3.0$, 9.0 Hz), 7.03–7.61 (m, 9ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.83, 19.44, 23.10, 34.32, 40.52, 59.65, 60.62, 119.54, 124.49, 125.16, 126.51, 126.97, 127.49, 133.37, 135.80, 135.91 and 141.09 ppm; MS *m/z*: 373.90 (M^+). Anal. calcd. for $C_{21}H_{27}NO_3S$; C, 67.53; H, 7.29; N,3.75%; Found: C, 67.44; H, 7.71; N, 3.69%.

(*S*)-2-(*N*-Cinnamyl-*N*-tosylamino)-3-phenylparopan-1-ol, 3b. Colorless solid, 80% (5.52 g); $[\alpha]_D^{34} = 29.96^\circ$ (*c* 1, $CHCl_3$); mp: 89–91; IR (KBr): 1330, 1169, 1600 and 3546 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (bs, 1H, OH), 2.35 (s, 3H), 2.76 (dq, 2H, $J = 6.0$, 12.0 Hz), 3.58–3.74 (m, 2H), 3.97–4.21 (m, 3H), 6.05–6.15 (m, 1H), 6.52 (d, 1H, $J = 15.0$ Hz), 7.01–7.60 (m, 14ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.49, 36.51, 46.98, 61.90, 62.69, 126.53, 126.61, 127.36, 127.94, 128.30, 128.62, 129.10, 129.64, 132.94, 136.29, 137.78, 137.85 and 143.34 ppm; MS *m/z*: 421.72 (M^+). Anal. calcd. for $C_{25}H_{27}NO_3S$: C, 71.23; H, 6.46; N, 3.32%. Found: C, 71.12; H, 6.35; N, 3.34%.

Synthesis of (*S*)-2-(*N*-(3-Methyl but-2-enyl)-*N*-tosylamino)-3-phenyl Propanal, 4a

To a stirred solution of IBX (2.94 g, 0.010 mmol), dissolved in DMSO (10 mL) was added 2.07 g (0.006 mmol) of (*S*)-2-(N-allyl-N-tosylamino)-3-phenylpropan-1-ol, 5. After 2 h of vigorous stirring, the reaction mixture was diluted with water, and the precipitate that formed was filtered and washed with ethyl acetate (2×20 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off at reduced pressure to obtain a brown crude aldehyde in quantitative yield. It was subjected to column chromatography (silica gel, 100–200 mesh) using a hexane–ethyl acetate mixture (9:1) to obtain pure (*S*)-2-(*N*-(3-methyl but-2-enyl)-*N*-tosylamino)-3-phenylpropanal **4a**. Yellow oil, 90% (1.86 g); $[\alpha]_D^{34} = -14.78^\circ$ (*c* 1, $CHCl_3$); IR (KBr): 1335, 1161 and 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 3H), 1.55 (s, 3H), 2.30 (s, 3H), 2.60 (dd, 1H, $J = 6.0$, 15.0 Hz), 3.68

(d, 2H, $J = 6.0$ Hz), 4.35 (dd, 1H, $J = 6.0$, 6.0 Hz), 3.95 (dd, 1H, $J = 6.0$, 9.0 Hz), 6.95–7.41 (m, 9ArH), 9.56 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.89, 20.45, 24.68, 31.84, 42.77, 66.12, 118.29, 125.55, 126.23, 127.57, 127.99, 128.63, 136.21, 136.44, 137.75, 142.44 and 197.86 ppm; MS m/z: 371.47 (M^+). Anal. calcd. for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78; N, 3.77%. Found: C, 67.93; H, 6.83; N, 3.65%.

Synthesis of (S)-2-(*N*-Cinnamyl-*N*-tosylamino)-3-phenylpropanal, 4b

To a stirred solution of IBX (2.94 g, 0.010 mmol) dissolved in DMSO (10 mL) was added 2.07 g (0.006 mmol) of (S)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropan-1-ol. After 2 h of vigorous stirring, the reaction mixture was diluted with water, and the precipitate that formed was filtered and washed with ethyl acetate (20 mL). The filtrate was then extracted with ethyl acetate (2×20 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off at reduced pressure to get a brown crude aldehyde in quantitative yield. It was subjected to column chromatography (silica gel, 100–200 mesh) using a hexane–ethyl acetate mixture (9:1) to obtain pure (S)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropanal **4b**. Yellow semisolid, 90% (1.86 g); $[\alpha]_D^{34} = -4.99°$ (c 1, $CHCl_3$); mp: 94–96 °C; IR (KBr): 1335, 1161 and 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H), 2.82 (dd, 1H, $J = 9.0$, 12.0 Hz), 3.41 (dd, 1H, $J = 6.0$, 12.0 Hz), 3.84 (dd, 1H, $J = 9.0$ 15.0 Hz), 3.97 (dd, 1H, $J = 9.0$, 15.0 Hz), 4.52 (dd, 1H, 6.0, 6.0 Hz), 5.94–5.98 (m, 1H), 6.34 (d, 1H, $J = 15.0$ Hz), 7.06–77.56 (m, 14ArH, 9.70 (s, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.50, 0.90, 33.47, 48.6, 67.45, 124.05, 126.58, 126.73, 127.44, 128.26, 128.64, 128.67, 129.11, 129.75, 135.21, 135.77, 137.20, 143.73 and 198.73 ppm; MS m/z: 419.19 (M^+). Anal. calcd. for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34%. Found: C, 71.45; H, 5.89; N, 3.42%.

Synthesis of Enantiopure *trans*-2-Benzyl-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*b*]quinolines, 6a–j

$InCl_3$ (20 mol%) was added to a mixture of (*N*-(3-methylbut-2-enyl)-*N*-tosylamino)-3-phenyl propanal **4a** (1 mmol), arylamine **5a** (1 mmol), and acetonitrile (20 mL). The reaction mixture was stirred at room temperature for 10 min. On completion of the reaction as indicated by TLC, the mixture was quenched with water and extracted with ethyl acetate; the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was chromatographed with silica gel (100–200 mesh) hexane–ethylacetate (9:1) to afford the cycloadducts **6a–e**, (1aR,2S,4aR)-2-benzyl-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*b*] quinolines.

(1aR,2S,4aS)-*trans*-2-Benzyl-5,5-dimthyl-3-tosyl pyrrolo[3,4-b]quinoline, 6a. Brown viscous oil, 93% (0.415 g); $[\alpha]_D^{34} = +7.19°$ (c 1, $CHCl_3$); IR (KBr): 3338, 1339 and 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.30 (dt, Ha, $J = 3.0$, 12.0 Hz, CHa), 2.39 (s, 3H, Ar-CH_3), 2.69 (bs, NH), 2.86 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.18–3.32 (m, 2H, CH, including CHb), 3.46 (dt, 1H, $J = 3.0$, 6.0 Hz, CH), 3.68 (dd, 1H, $J = 9.0$, 12.0 Hz, CH), 3.80 (dd, 1H, $J = 3.0$, 6.0, 12.0 Hz, CH), 5.92–7.82 (m, 13ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.54, 27.02, 28.60, 34.04, 42.27, 47.92, 49.25, 57.72, 66.85, 115.65,

118.78, 126.86, 127.14, 127.42, 128.42, 128.97, 129.56, 129.90, 130.63, 134.53, 137.01, 142.95, 143.05 and 143.77 ppm; MS m/z: 446.32 (M^+). Anal. calcd. for $C_{27}H_{30}N_2O_2S$: C, 72.61; H, 6.77; N, 6.27%. Found: C, 72.70; H, 6.68; N, 6.18%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-5,5-dimethyl-7-methyl-3-tosyl-pyrrolo[3,4-*b*]quinoline, 6b. Colorless semisolid, 90% (0.414 g); $[\alpha]_D^{34} = +3.79°$ (c 1, $CHCl_3$); mp: 142–145 °C; IR (KBr): 3338, 1339 and 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.30 (dt, Ha, $J = 3.0$, 12.0 Hz, CH), 2.14 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.60 (bs, NH), 2.86 (dd, 1H, $J = 12.0$, 12.0 Hz,CH), 3.15–3.31 (m, 2H, CH, including CHb), 3.44–3.52 (m, 1H, CH), 3.67 (dd, 1H, $J = 6.0$, 12.0 Hz, CH), 3.78 (dd, 1H, $J = 6.0$, 12.0 Hz, CH), 5.92–7.82 (m, 12ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.54, 21.25, 27.06, 28.71, 34.04, 42.33, 47.95, 49.41, 57.95, 66.89, 115.73, 127.05, 127.11, 127.44, 127.58, 128.01, 128.96, 129.57, 129.89, 130.65, 134.57, 137.05, 140.66 and 143.74 ppm; MS m/z: 460.10 (M^+). Anal. calcd. for $C_{28}H_{32}N_2O_2S$: C, 73.01; H, 7.00; N, 6.08%. Found: C, 73.12; H, 6.89; N, 6.20%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-7-methoxy-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*b*]quinoline, 6c. Yellow fluffy solid, 88% (0.418 g); $[\alpha]_D^{34} = +3.39°$ (c 1, $CHCl_3$); mp: 107–109 °C; IR (KBr): 3334, 1339 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.30 (dt, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.40 (s, 3H, Ar-CH_3), 2.69 (bs, NH), 2.86 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.15–3.31 (m, 2H, CH, including CHb), 3.50 (dt, 1H, $J = 3.0$, 6.0 Hz, CH), 3.65–3.71 (m, 1H, CH), 3.66 (s, 3H, OCH_3), 3.78 (dd, 1H, $J = 3.0$, 6.0, 12.0 Hz, CH), 5.92–7.82 (m, 12ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.55, 27.00, 28.80, 34.36, 42.26, 47.96, 49.25, 55.74, 58.14, 66.85, 112.58, 112.64, 116.48, 127.10, 127.44, 128.71, 128.95, 129.58, 129.91, 132.07, 134.59, 136.96, 13.06, 143.75 and 152.89 ppm; MS m/z: 476.91 (M^+). Anal. calcd. for $C_{28}H_{32}N_2O_3S$: C, 70.56; H, 6.77; N, 5.88%. Found: C, 70.76; H, 6.68; N, 5.96%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-7-bromo-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*b*]quinoline, 6d. Yellow viscous liquid, 98% (0.512 g); $[\alpha]_D^{34} = -24.56°$ (c 1, $CHCl_3$); IR (KBr): 3336, 1347 and 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.07 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.26 (dt, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.39 (s, 3H, Ar-CH_3), 2.70 (bs, NH), 2.85 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.15–3.28 (m, 2H,CH, including CHb), 3.44–3.51 (m, 1H, CH) 3.67 (dd, 1H, $J = 6.0$, 12.0 Hz, CH), 3.79 (dd, 1H, $J = 3.0$, 12.0 Hz, CH), 5.79–7.81(m, 12ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.59, 26.94, 28.48, 34.28, 42.20, 47.80, 48.89, 57.66, 66.71,110.45, 116.75, 117.22, 127.25, 127.42, 129.05, 129.40, 129.55, 129.63, 129.97, 131.97, 132.76, 134.50, 136.93, 142.13 and 143.90 ppm; MS m/z: 526.01 (M^+). Anal. calcd. for $C_{27}H_{29}BrN_2O_2S$: C, 61.71; H, 5.56; N, 5.33%. Found: C, 61.79; H, 5.47; N, 5.47%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-7-chloro-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*b*]quinoline, 6e. Yellow viscous liquid, 96% (0.450 g); $[\alpha]_D^{34} = -60.12°$ (c 1, $CHCl_3$); IR (KBr): 3336, 1342 and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.08 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.28 (dt, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.40 (s, 3H, Ar-CH_3), 2.67 (bs, NH), 2.85 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.16–3.30 (m, 2H, CH, including CHb), 3.44–3.52 (m, 1H, CH) 3.67 (dd, 1H, $J = 9.0$, 12.0 Hz, CH), 3.80 (dd, 1H, $J = 3.0$, 12.0 Hz, CH), 5.83–7.81 (m, 12ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.58,

26.92, 28.49, 34.29, 42.23, 47.80, 48.93, 57.77, 66.72, 116.77, 123.32, 126.52, 126.79, 127.24, 127.43, 129.05, 129.5, 129.96, 132.26, 134.54, 136.96, 141.65 and 143.88 ppm; MS m/z: 481.72 (M^+). Anal. calcd. for $C_{27}H_{29}ClN_2O_2S$: C, 67.41; H, 6.08; N, 5.82%. Found: C, 67.32; H, 5.96; N, 5.74%.

Synthesis of Enantiopure *trans*-2-Benzyl-5-phenyl-3-tosyl-pyrrolo[3,4-*b*]quinolines, 6f–j

$InCl_3$ (20 mol%) was added to a mixture of (*N*-cinnamyl-*N*-tosylamino)-3-phenyl propanal **4b** (1 mmol), arylamine **5a** (1 mmol), and acetonitrile (20 mL). The reaction mixture was stirred at room temperature for 10 min. On completion of the reaction as indicated by TLC, the mixture was quenched with water and extracted with ethyl acetate; the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was chromatographed with silica gel (100–200 mesh) hexane–ethylacetate (9:1) to afford the cycloadducts **6f–j**, (1aR,2S,4aR)-2-benzyl-5-phenyl-3-tosyl-pyrrolo[3,4-*b*]quinolines.

(1aR,2 s,4aS)-*trans*-2-Benzyl-5-phenyl-3-tosyl-pyrrolo[3,4-*b*]quinoline, 6f. White solid, 97% (0.480 g); $[\alpha]_D^{32} = -1.19°$ (*c* 1, $CHCl_3$); mp: 202–204 °C; IR (KBr): 3328, 1340 and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (dq, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.40 (s, 3H, Ar-CH_3), 2.75 (bs, NH), 2.88 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.07 (t, Hb, $J = 12.0$ Hz, CHb), 3.28 (dd, 1H, $J = 9.0$, 12.0 Hz, CH), 3.48–3.57 (m, 1H, CH), 3.74–3.79 (m, 1H, Ch), 6.01 (d, 1H, $J = 9.0$ Hz, CH), 6.45–7.63 (m, 18ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.54, 42.23, 47.10, 47.47, 51.64, 62.38, 66.61, 115.62, 118.95, 124.75, 127.06, 127.21, 127.30, 127.38, 128.21, 128.64, 129.01, 129.58, 129.85, 129.99, 134.32, 136.91, 142.76, 143.64 and 144.52 ppm; MS m/z: 494.28 (M^+). Anal. calcd. for $C_{31}H_{30}N_2O_2S$: C, 75.27; H, 6.11; N, 5.66%. Found: C, 75.36; H, 6.02; N, 5.72%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-5-phenyl-7-methyl-3-tosyl-pyrrolo[3,4-*b*] quinoline, 6g. White solid, 92% (0.466 g); $[\alpha]_D^{32} = -1.19°$ (*c* 1, $CHCl_3$); mp: 216–218 °C; IR (KBr): 3334, 1342 and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.51 (dq, Ha, $J = 6.0$, 12.0 Hz, CH), 1.97 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 2.64 (bs, NH), 2.87 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.06 (t, Hb, $J = 12.0$ Hz, CHb), 3.24 (dd, 1H, $J = 9.0$, 9.0 Hz, CH), 3.43 (t, 1H, $J = 9.0$ Hz, CH), 3.47–3.56 (m, 1H, CH), 3.70–3.77 (m, 2H,CH_2), 5.95 (d, 1H, $J = 9.0$ Hz, CH), 6.26–7.62 (m, 17ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.23, 21.55, 42.27, 47.39, 47.53, 51.70, 62.61, 66.66, 115.73, 142.72, 127.01, 127.19, 127.39, 128.00, 128.24, 128.36, 128.63, 129.01, 129.60, 129.86, 130.27, 134.35, 136.96, 142.20, 142.94 and 143.61 ppm; MS m/z: 508.03 (M^+). Anal. calcd. for $C_{32}H_{32}N_2O_2S$: C, 75.56; H, 6.34; N, 5.51%. Found: C, 75.42; H, 6.26; N, 5.43%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-5-phenyl-7-methoxy-3-tosyl-pyrrolo[3,4-*b*] quinoline, 6h. White solid, 95% (0.506 g); $[\alpha]_D^{32} = -0.99°$ (*c* 1, $CHCl_3$); mp: 192–194 °C; IR (KBr): 3334, 1340 and 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.54 (dq, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.40 (s, 3H, Ar-CH_3), 2.61 (bs, NH), 2.87 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.07 (t, Hb, $J = 12.0$ Hz, CHb), 3.23 (dd, 1H, $J = 9.0$, 12.0 Hz), 3.42–3.56 (m, 1H, CH), 3.48 (s, 3H, OCH_3), 3.71–3.78 (m, 2H,

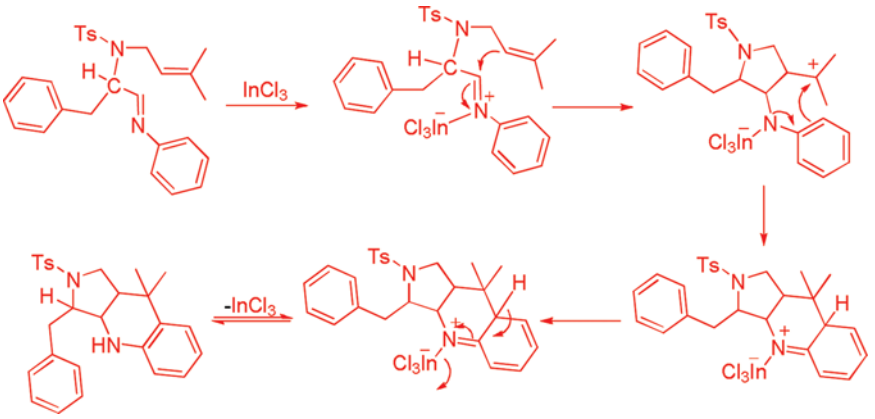


Figure 1. Mechanism of indium trichloride–catalyzed reaction. (Figure is provided in color online.)

CH2), 5.99 (d, 1H, $J = 9.0$ Hz, CH), 6.03–7.63 (m, 17ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.34, 42.20, 47.26, 47.85, 51.79, 55.38, 62.82, 66.65, 113.37, 115.46, 116.54, 125.99, 127.12, 127.17, 127.38, 128.20, 128.66, 128.99, 129.58, 129.86, 134.43, 137.10, 138.47, 142.65, 143.59 and 152.89 ppm; MS m/z: 524.26 (M^+). Anal. calcd. for $C_{32}H_{32}N_2O_3S$: C, 73.25; H, 6.15; N, 5.34%. Found: C, 73.33; H, 6.07; N, 5.43%.

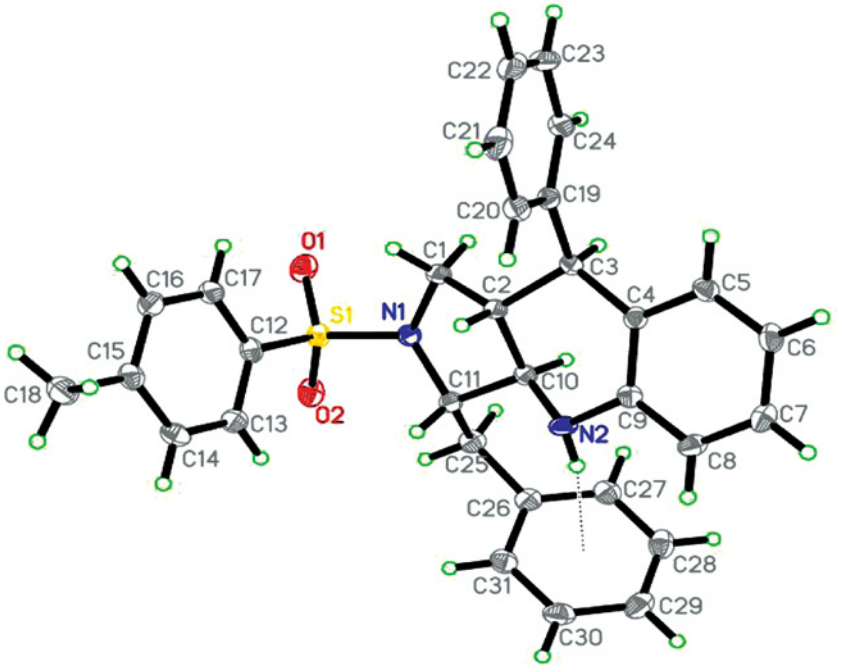


Figure 2. ORTEP diagram of **6f**. (Figure is provided in color online.)

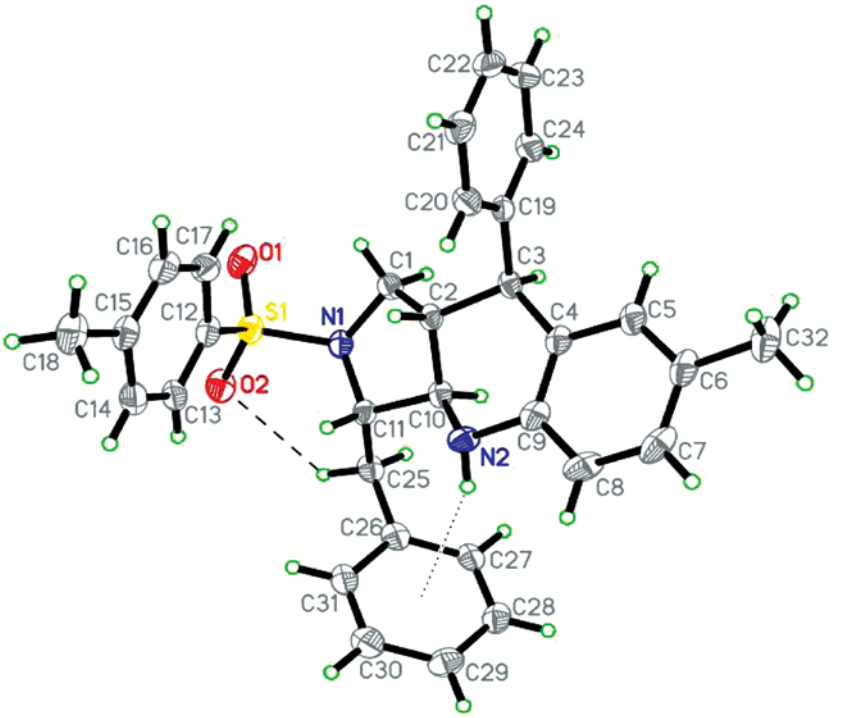


Figure 3. ORTEP diagram of **6g**. (Figure is provided in color online.)

(1aR,2 s,4aS)-*trans*-2-Benzyl-7-bromo-5-phenyl-3-tosyl-pyrrolo[3,4-*b*] quinoline, 6i. White solid, 95% (0.543 g); $[\alpha]_D^{33} = -2.39°$ (*c* 1, $CHCl_3$); mp: 221–223 °C; IR (KBr): 3330, 1344 and 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.51 (dq, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.41 (s, 3H, Ar-CH_3), 2.71 (bs, NH), 2.85 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.05 (t, Hb, $J = 12.0$ Hz, CHb), 3.25 (dd, 1H, $J = 9.0$, 12.0 Hz, CH), 3.44 (d, 1H, $J = 6.0$, 12.0 Hz,CH), 3.47–3.54 (m, 1H, CH), 3.69–3.74 (m, 1H, CH), 5.87 (d, 1H, $J = 9.0$ Hz, CH), 6.53–7.63 (m, 17ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.55, 42.18, 46.79, 47.26, 51.43, 62.31, 66.45, 110.69, 117.13, 126.80, 127.27, 127.35, 127.38, 128.08, 128.85, 129.05, 129.52, 129.87, 130.10, 132.34, 134.26, 136.81, 141.83, 143.61 and 143.71 ppm; MS *m/z*: 572.79 (M^+). Anal. calcd. for $C_{31}H_{29}BrN_2O_2S$: C, 64.92; H, 5.10; N, 4.88%. Found: C, 64.80; H, 5.21; N, 5.01%.

(1aR,2 s,4aS)-*trans*-2-Benzyl-7-chloro-5-phenyl-3-tosyl-pyrrolo[3,4-*b*] quinoline, 6j. White solid, 98% (0.517 g); $[\alpha]_D^{34} = -29.76°$ (*c* 1, $CHCl_3$); mp: 245–247 °C; IR (KBr): 3336, 1343 and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.52 (dq, Ha, $J = 6.0$, 12.0 Hz, CHa), 2.41 (s, 3H, CH_3), 2.71 (bs, NH), 2.86 (dd, 1H, $J = 12.0$, 12.0 Hz, CH), 3.05 (t, Hb, $J = 12.0$ Hz, CHb), 3.26 (t, 1H, $J = 9.0$ Hz, CH), 3.42 (t, 1H, $J = 6.0$ Hz, CH), 3.46–3.55 (m, 1H, CH), 3.68–3.79 (m, 2H, CH), 5.92 (d, 1H, $J = 9.0$ Hz, CH), 6.40–7.63 (m, 17ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.55, 42.21, 46.84, 47.35, 51.48, 62.45, 66.49, 116.71, 123.58, 126.34, 127.29,

127.39, 128.12, 128.87, 129.07, 129.51, 129.55, 129.89, 134.35, 136.87, 141.90, 143.16 and 143.73 ppm; MS m/z: 529.01 (M^+). Anal. calcd. for $C_{31}H_{29}ClN_2O_2S$: C, 70.37; H, 5.52; N, 5.29%. Found: C, 70.49; H, 5.60; N, 5.21%.

ACKNOWLEDGMENT

M. J. and R. R. thank the University Grants Commission, New Delhi, for financial support.

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