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Diastereoselective synthesis of *cis*-fused pyrano[4,5-*c*]pyrrole derivatives via microwave-accelerated intramolecular Knoevenagal hetero Diels–Alder reaction

Mathesan Jayagobi, Raghavachary Raghunathan *

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India

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ABSTRACT

The synthesis of enantiomerically pure pyrano[4,5-*c*]pyrroles has been accomplished by the intramolecular hetero Diels–Alder reaction of enantiomerically pure *N*-allyltetheredalkenyl aldehydes with various 1,3-diones. The reaction led to the formation of *cis*-fused enantiomerically pure pyrano[4,5-*c*]pyrroles in excellent yield under mild conditions and the products were characterized by spectroscopic data.

1. Introduction

One of the more important objectives in organic synthesis is the development of highly efficient synthetic procedures towards complex molecules. The hetero-Diels–Alder reaction represents one of the more effective methods for the synthesis of heterocyclic compounds, especially for natural product synthesis.[1,2] In recent years, intramolecular hetero-Diels–Alder (IMHDA) reactions have been widely used in organic synthesis, because of their economical and stereocontrolled nature.[3] These reactions allow the formation of two or more rings in a single operation, avoiding sequential chemical transformations. Amongst these reactions, hetero Diels–Alder reactions provide a means for the synthesis of pyran moieties,[4] since many natural products, such as carbohydrates, talaromycins, milbemycins, avermectins, pheromones and iridoids, contain a pyran skeleton[5a–e] and possess interesting biological activities with potential medical applications,[6a,6b] This wide range of interesting activities and properties has prompted studies into the development of a convenient and efficient methodology for synthesizing polyheterocycles with pyranopyrrole moieties. The domino hetero-Diels–Alder reaction is one of the most important methods for the construction of heterocyclic compounds.[7a–h] Herein we propose to utilise the hetero Diels–Alder reaction as a tool for the diastereoselective construction of pyranopyrroles, which are structurally related to natural products. Symmetrical 1,3-diones have been subjected to intramolecular cycloaddition reaction as heterodienes for the synthesis of complex polycyclic heterocycles.[8] A number of reports are available for the synthesis of pyrans and their benzopyrans analogues but there is no literature available on pyranopyrrole derivatives.[9a–g]

Over the course of our investigation directed towards the synthesis of pyrrole derivatives, we herein report a new diastereoselective route for the synthesis of pyranopyrrole derivatives based on the tandem Knoevenagel IMHDA reaction. Domino hetero Diels–Alder reactions have been well exploited by Tietze for the synthesis of polycyclic compounds.[10a,b] Herein we have used a chiral *N*-alkenyl aldehyde[11] for the first time in an intramolecular hetero Diels–Alder reaction for the synthesis of enantiomerically pure pyranopyrrole derivatives in a stereoselective manner.

2. Results and discussion

2.1. Synthesis of enantiopure alkenyl aldehyde

Phenyl alaninol **1** upon treatment with *p*-toluenesulfonyl chloride under phase transfer catalyst conditions gave *N*-sulphonyl alaninol **2** in good yield[12] (Scheme 1). 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 solvent to obtain the *N*-prenyl alcohol **3a** in good yield. The structure of chiral *N*-prenyl-*N*-tosyl alcohol **3a** was established on the basis of its spectroscopic data. The alkenyl alcohol was oxidized quantitatively to the alkenyl aldehyde, (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal by stirring the suspension of **3a** with 2-iodoxybenzoic acid in DMSO with 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 the alkenyl aldehyde, (*S*)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropanal **4b** in quantitative yield by using cinnamyl

* Corresponding author. Tel.: +91 44 22202811; fax: +91 4422300488.
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).

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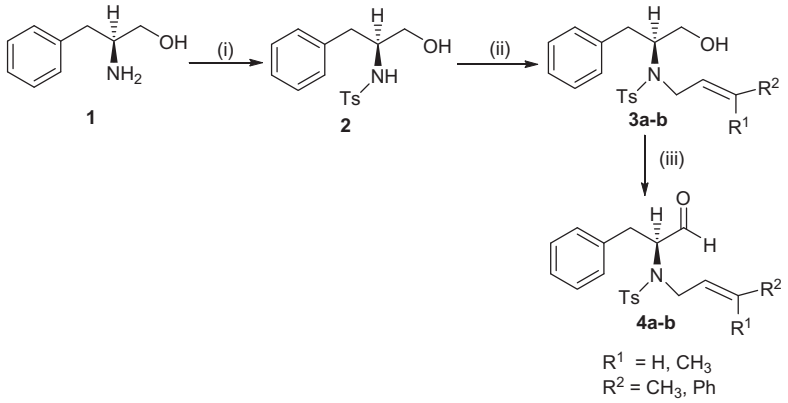
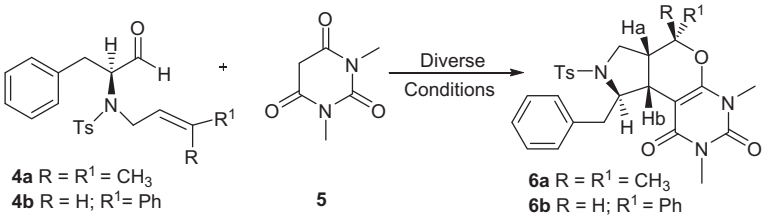


Scheme 1. Regents and conditions: (i) TBAB, 10% NaOH/benzene, tosyl chloride **2**, 0 °C to rt; 8 h, 90%; (ii) prenyl bromide/cinnamyl bromide, K_2CO_3/acetone, 12 h, 90%; (iii) iodoxybenzoic acid, DMSO, 4 h, 98%.



Scheme 2. Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

bromide (Scheme 2). The structure of alkenyl aldehyde **4b** was confirmed on the basis of the spectroscopic data.[12]

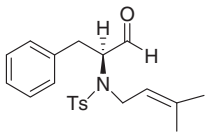
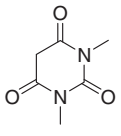
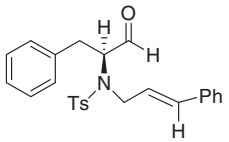
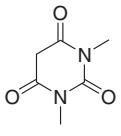
Thus, starting from a chiral substrate (*S*)-phenyl alanine, strategically positioned chiral alkenyl aldehydes **4a**–**b** were synthesized. Dienes generated from the reaction of aldehydes **4a**–**b** with various 1,3-diones, were trapped by the dienophile to yield a variety of enantiomerically pure pyrano[4,5-*c*]pyrroles.

2.2. Synthesis of enantiopure pyrano[4,5-*c*]pyrroles

An equimolar mixture of (*S*)-2-(*N*-(3-methylbut-2-enyl)-*N*-tosylamino)-3-phenylpropanal **4a** and barbituric acid **5** in presence of EDDA when refluxed, in toluene furnished a [4+2] cycloadduct, *cis*-[4b*R*,5*S*,7a*R*]-2-benzyl-1,3,8,8-tetramethyl-6-tosylpyrrolo[3,4-*c*]pyrano[5,6-*b*]pyrimidine-2,4-dione **6a**. The *cis*-isomer was found to be the major product with an overall yield of 64% (Scheme 2). The structure of the product was assigned on the basis of spectroscopic studies. Similarly, the reaction of **4b** with barbituric acid **5** (Scheme 2) was carried out under the optimized reaction conditions to give the product **6b** and the results are summarized in Table 1, The structures of the products were confirmed by spectroscopic techniques.

The ^{1}H NMR spectrum of compound **6b** exhibited a distorted doublet of triplets at δ 2.00 (dt, 1Ha, J = 3.00, 6.00, 12.00 Hz) and one doublet at δ 2.70 (d, 1H, J = 6.0 Hz). The *N*–CH_2 protons of the pyrrolidine ring were observed as multiplets in the range 3.02–3.12 (2H), two doublet of doublets at δ 3.32 (dd, 1H, J = 6.0, 12.0 Hz) and a doublet of doublets at δ 3.50 (dd, 1H, J = 9.0, 9.0 Hz). One triplet at δ 4.33 (t, 1H, J = 3.00 Hz) appeared for –*N*CH proton. Particularly diagnostic were the Ha and Hb protons situated at the ring junctions showing doublets of triplets at δ 2.00 (J = 6.0, 12.0 Hz) and δ 2.70 (J = 6.0), respectively. Furthermore

Table 1
Reaction times and yields of the products in domino reactions of **4a**–**b** with **5** under various conditions

Entry	Aldehydes	1,3-Diones	Conditions	Time	Products	Yield (%)
1		 **5**	Method A Method B	6 h 2 min	**8a** **8a**	64 80
2		 **5**	Method A Method B	6 h 2 min	**8b** **8b**	67 80

Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

the *cis*-annulation of the pyrrolo-pyrano rings was determined by the small value of the coupling constant (6.0 Hz).

The off-resonance decoupled ^{13}C NMR spectrum also confirmed the proposed structure for **6b** (vide experimental). The mass spectrum of compound **6b** showed the molecular ion peak at *m*/*z* 369.1 (M^+) and the compound gave satisfactory elemental analysis. Moreover, the structure of compound **6b** was unambiguously established by its single crystal X-ray diffraction analysis (Fig. 1).[13] The structure of the *cis*-product was determined on the basis of detailed 2D NMR studies.

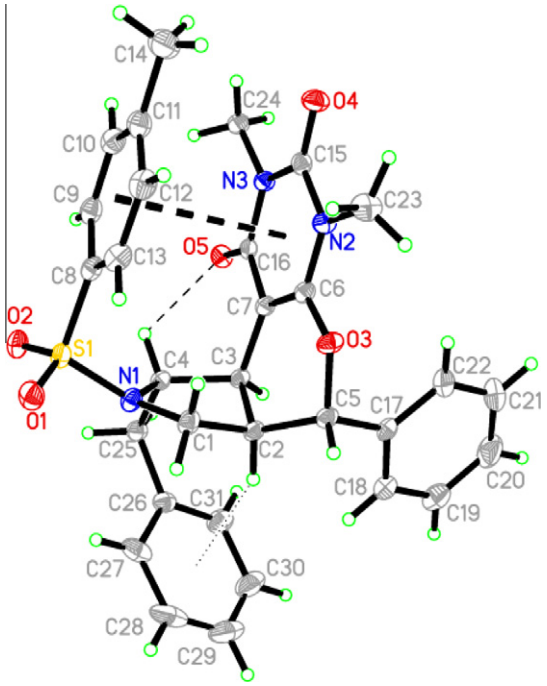


Figure 1. ORTEP diagram of **6b**.

In an attempt to improve the reaction yields we carried out the reaction under microwave conditions.[14a–f] We observed that the reaction in toluene under microwave irradiation gave a better yield of the product **6a** (80%) and was found to be totally stereoselective to give only one diastereomer. Encouraged by these findings, we expanded the scope of the hetero-Diels–Alder reaction by reacting **4b** with barbituric acid **5** (Scheme 2) under microwave conditions and we observed there was an improvement in the yield of the product **6b**; the results are summarized in Table 1.

Having optimized the reaction conditions for the stereoselective synthesis of pyrano[4,5-*c*]pyrrole derivatives, we conducted the intramolecular Knoevenagel hetero-Diels–Alder reaction by employing various symmetrical diones, dimedones, dioxinones and indane-1,3-diones with aldehydes **4a** and **4b** (Schemes 2 and 3). The results are summarized in Table 2. The intramolecular Knoevenagel hetero-Diels–Alder reaction of **4a** and **4b** with indane-1,3-dione in refluxing toluene was completed in 6 h (Scheme 3). As observed previously, we readily isolated the expected *cis* pyrano[4,5-*c*]pyrrole derivatives in good yield by changing from toluene/reflux conditions to microwave irradiation (Scheme 4).

The intramolecular cycloaddition of the heterodiene occurred with complete facial selectivity providing the pyranopyrrole derivatives with high diastereoselectivity. The stereochemistry observed can be explained by considering that the dienophile approaches the diene in an *exo* mode with respect to the diene. The stereochemistry observed is also consistent with this observation. Although two different transition states **A** and **B** are possible (Fig. 2), transition state **B** would be less favourable due to electronic repulsions between the lone pair on the oxygen atom at the carbonyl group and the aromatic ring of the phenyl substituent.

3. Conclusion

In conclusion, the chiral alkenyl aldehyde synthesized from (*S*)-phenyl alanine was successfully subjected to an intramolecular domino Knoevenagal hetero Diels–Alder reaction with various 1,3-diones to give chiral pyrano[4,5-*c*]pyrroles. The cycloaddition reactions were found to be stereoselective and gave *cis*-fused cycloadducts. We have accomplished the synthesis of novel polycyclic heterocyclic ring systems containing pyrano fused pyrimidine, indanone, cyclohexanone and dioxinone derivatives under mild condition enroute to diverse set of natural products. We have shown that use of microwave irradiation improved the yield of the products.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU IR-8300 series FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on BRUKER 300 MHz instruments in $CDCl_3$ solvent with TMS as standard. Mass spectra were recorded on JEOL-DX303 HF mass spectrometer. Elemental analysis was carried out on a Perkin–Elmer CHNS 2400 instrument. Single crystal X-ray diffraction analysis was performed on Bruker SMART APEX CCD area-detecter diffractometer and Bruker SMART APEXII CCD area-detector diffractometer. A microwave synthesizer Chem Discover benchmate microwave 300 W, $P = 100$, $T = 110$ °C, 20 MHz) was used for all the reactions.

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

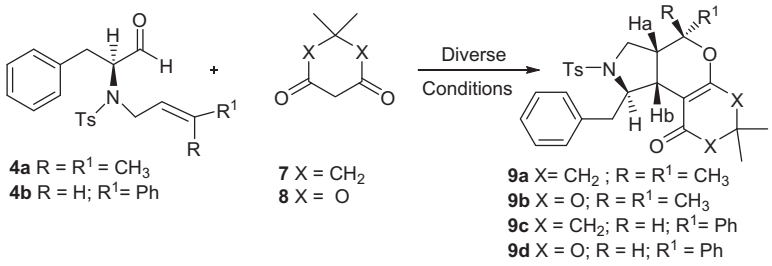
4.2. Synthesis of (*S*)-3-phenyl-2-(tosylamino)propan-1-ol 2

The compound was prepared as per the procedure reported by us previously.[12]

4.3. Synthesis of compound 3b

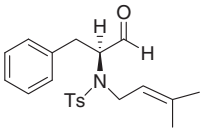
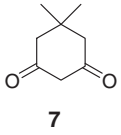
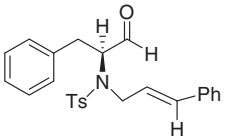
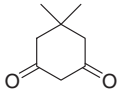
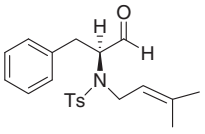
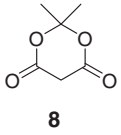
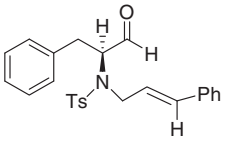
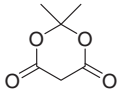
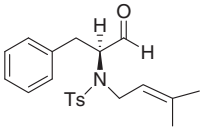
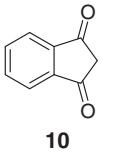
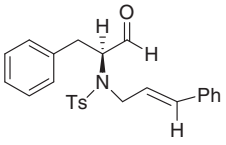
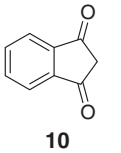
4.3.1. Synthesis of (*S*)-2-(*N*-(3-methyl but-2-enyl)-*N*-tosylamino)-3-phenylparopan-1-ol (3a) and (*S*)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylparopan-1-ol 3b

To a solution of 20 mmol of (*S*)-3-phenyl-2-(tosylamino)propan-1-ol in dry acetone (100 mL) under a nitrogen atmosphere were added potassium carbonate (60 mmol) and prenyl/cinnamyl bromide (20 mmol) in 50 mL of dry acetone. The mixture was stirred for 8–10 h and after completion of the reaction, the solid was filtered off. The residue was washed several times with acetone and the filtrate was concentrated in vacuo and extracted with dichloromethane (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 a hexane–ethylacetate mixture (9:1) to obtain pure N-allylated (*S*)-3-phenyl-2-(tosylamino)propan-1-ol, **3a**. Colourless oil, 80% (5.52 g); $[\alpha]_D^{34} = -30.0$ (*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 (br s, 1H, OH), 2.65–2.78 (m, 2H),

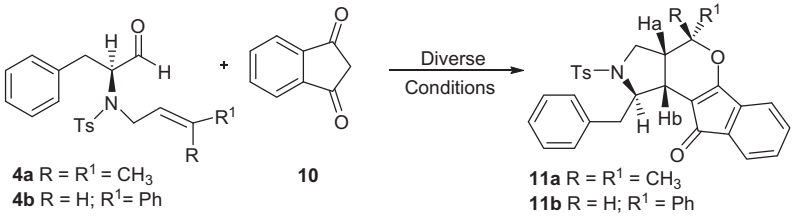


Scheme 3. Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

Table 2
Reaction time and yields of the products in domino reactions of **4a**–**b** with various symmetrical 1,3-diones under various conditions

Entry	Aldehydes	1,3-Diones	Conditions	Time	Products	Yield (%)
1		 **7**	Method A Method B	6 h 2 min	**8a** **8a**	63 75
		 **7**	Method A Method B	6 h 2 min	**8b** **8b**	72 84
		 **8**	Method A Method B	6 h 2 min	**8a** **8a**	64 80
2		 **8**	Method A Method B	6 h 2 min	**8a** **8a**	64 80
		 **10**	Method A Method B	8 h 2.5 min	**8a** **8a**	58 68
		 **10**	Method A Method B	8 h 2.5 min	**8a** **8a**	63 72

Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.



Scheme 4. Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

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, 9H, ArH); ^{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, 67.64; H, 7.38; N, 3.69.

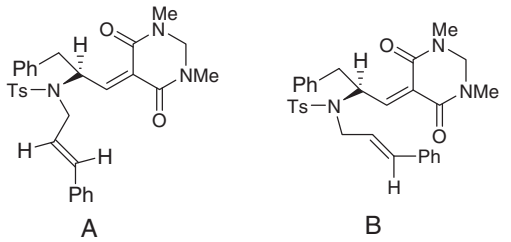


Figure 2.

4.3.2. (*S*)-2-(*N*-Cinnamyl-*N*-tosylamino)-3-phenylparopan-1-ol 3b

Colourless solid, 80% (5.52 g); $[\alpha]_D^{34} = -30.0$ (*c* 1, $CHCl_3$); mp: 89–91 °C; IR (KBr): 1330, 1169, 1600 and 3546 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (br s, 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, 14H, ArH); ^{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, 71.32; H, 6.55; N, 3.24.

4.4. Synthesis of compound 4a

4.4.1. Synthesis of (*S*)-2-(*N*-(3-methyl but-2-enyl)-*N*-tosylamino)-3-phenyl propanal 4a

To a stirred solution of 2-iodoxybenzoic acid (2.94 g, 0.010 mmol), dissolved in dimethyl sulfoxide (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 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 coloured crude product. This was subjected to column chromatography (silica gel, 100–200 mesh) using 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); $[\alpha]_D^{34} = -14.8$ (*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, 9H, ArH), 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, 6.87; N, 3.65.

4.4.2. Synthesis of (*S*)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropanal 4b

To a stirred solution of 2-iodoxybenzoic acid (2.94 g, 0.010 mmol), dissolved in dimethylsulfoxide (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 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 give a brown coloured crude product. This was subjected to column chromatography (silica gel, 100–200 mesh) using a hexane–ethyl acetate mixture (9:1) to give pure (*S*)-2-(*N*-cinnamyl-*N*-tosylamino)-3-phenylpropanal **4b**. Yellow solid, 90% (1.86 g); $[\alpha]_D^{34} = -5.0$ (*c* 1, $CHCl_3$); mp: 94–96 °C; IR (KBr): 1335, 1161 and 1735 cm^{-1}; ^1H 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, *J* = 6.0, 6.0 Hz), 5.94–5.98 (m, 1H), 6.34 (d, 1H, *J* = 15.0 Hz), 7.06–7.56 (m, 14H, ArH, 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, 71.69; H, 5.08; N, 3.42.

4.5. Synthesis of enantiopure *cis*-fused pyrano[4,5-c]pyrroles

Method A: To a refluxing solution of 1,3-diones (1 mmol) in 10 mL of dry toluene, the aldehyde **4a**/**4b** (1 mmol) was added and the reaction mixture was refluxed until the disappearance of the starting material as evidenced by thin layer chromatography. After the completion of the reaction as evidenced by TLC, the reaction mixture was concentrated under reduced pressure. The residue was extracted with dichloromethane (2 × 20 mL) and water (2 × 20 mL). The organic layer was washed with brine solution (2 × 20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was then subjected to column chromatography (silica gel, 100–200 mesh) with hexane–ethylacetate (7.5:2.5) to obtain the cycloadducts.

Method B: A solution of 1,3-diones (1 mmol) and the corresponding aldehyde (1 mmol) in dry toluene (2 ml) without base was irradiated under microwaves (MODEL = Chem Discover bench mate microwave, 300 W, *P* = 100, *T* = 110 °C, 20 MHz) until the thin layer chromatography showed the disappearance of the starting material. The reaction mixture was concentrated under reduced pressure, after which the residue was extracted with dichloromethane (2 × 20 mL) and water (2 × 20 mL). The organic layer was washed with brine solution (2 × 20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was then subjected to column chromatography (silica gel, 100–200 mesh) with hexane–ethylacetate (7.5:2.5) to give the cycloadducts.

Following the general procedure (Methods A and B), the reactions of 1,3-diones (1 mmol) with various chiral alkenyl aldehydes afforded chiral pyrrolo[3,4-*c*]pyrano derivatives.

4.5.1. (4b*R*,5*S*,7a*R*)-*cis*-5-Benzyl-1,3,8,8-tetramethyl-6-tosyl-pyrrolo[3,4-*c*]pyrano [5,6-*b*]primidin-2,4-dione 6a

White solid, 64% (0.320 g); $[\alpha]_D^{34} = +18.4$ (*c* 1, $CHCl_3$); mp: 202–204 °C; IR (KBr): 1695, 1647, 1342, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (s, 3H), 1.08 (dt, Ha, *J* = 6.0, 12.0 Hz), 1.21 (s, 3H), 2.29 (t, 1H, *J* = 12.0 Hz), 2.40 (s, 3H), 2.53 (dd, 1H, *J* = 9.0, 12.0 Hz), 3.21 (s, 3H), 3.33 (s, 3H), 3.47 (dd, 1H, *J* = 3.0, 12.0 Hz), 4.01 (dd, *J* = 3.0, 12.0 Hz), 4.17 (td, 1H, *J* = 3.0, 6.0 Hz), 7.19–7.74 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.35, 20.23, 26.63, 27.02, 27.80, 34.49, 38.22, 47.33, 47.87, 62.22, 81.49, 86.56, 124.85, 125.97, 126.49, 126.52, 130.30, 133.88, 136.42, 142.27, 149.48, 154.46 and 160.37 ppm; MS *m*/*z*: 509.18 (M^+). Anal. Calcd for $C_{27}H_{31}N_3O_5S$: C, 63.03; H, 6.13; N, 8.25. Found: C, 63.17; H, 6.18; N, 8.31.

4.5.2. (4b*R*,5*S*,7a*R*)-*cis*-5-Benzyl-1,3-dimethyl-8-phenyl-6-tosyl-pyrrolo[3,4-*c*]pyrano [5,6-*b*]primidin-2,4-dione 6b

White solid, 68% (0.370 g); $[\alpha]_D^{34} = +4.4$ (*c* 1, $CHCl_3$); mp: 174–176 °C; IR (KBr): 1695, 1628, 1340 and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.00 (distorted, dt, 6.0, 12.0 Hz), 2.40 (s, 3H), 2.70 (d, 1H, *J* = 6.0 Hz), 3.02–3.12 (m, 2H), 3.19 (s, 3H), 3.21 (s, 3H), 3.32 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.50 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.33 (t, 1H, *J* = 3.0 Hz), 5.12 (d, 1H, *J* = 3.0 Hz), 6.75–7.64 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.64, 27.70, 28.28, 34.67, 42.11, 49.52, 64.38, 87.05, 124.90, 126.89, 127.41, 128.44, 128.62, 128.85, 128.87, 130.45, 133.54, 136.26, 137.63, 143.93, 150.24, 153.75 and 162.18 ppm; MS *m*/*z*: 557.12 (M^+). Anal. Calcd for

$C_{31}H_{31}N_3O_5S$: C, 66.77; H, 5.60; N, 7.54. Found: C, 66.87; H, 5.49; N, 7.48.

4.5.3. (1b*R*,2*S*,4a*R*)-*cis*-2-Benzyl-5,5,8,8-tetramethyl-3-tosyl pyrrolo[3,4-*c*]pyrano [5,6-*b*] cyclohexan-1-one (9a)

White solid, 63% (0.306 g); $[\alpha]_D^{34} = +32.2$ (*c* 1, $CHCl_3$); mp: 163–165 °C; IR (KBr): 1619, 1342 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.72 (s, 3H), 0.78 (dt, Ha, *J* = 6.0, 12.0 Hz), 0.90 (s, 3H), 1.96–2.21 (m, 5H), 3.28 (t, 1H, *J* = 12.0 Hz), 2.39 (s, 3H), 3.39 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.53 (dd, 1H, *J* = 3.0, 6.0, 12.0 Hz), 3.88 (d, 1H, *J* = 3.0, 9.0 Hz), 4.09 (td, 1H, *J* = 3.0, 6.0 Hz), 7.15–.73 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.47, 21.49, 26.61, 28.46, 29.16, 31.68, 36.01, 40.15, 42.92, 48.77, 49.53, 51.17, 63.53, 79.53, 111.26, 126.10, 127.34, 127.79, 129.64, 131.59, 135.40, 138.13, 143.42, 169.63 and 196.35 ppm; MS *m*/*z*: 495.79 (M^+). Anal. Calcd for $C_{29}H_{35}NO_4S$: C, 70.36; H, 7.15; N, 2.84. Found: C, 70.48; H, 7.21; N, 2.79.

4.5.4. (1b*R*,4*S*,4a*R*)-*cis*-4-Benzyl-8,8-dimethyl-5-phenyl-3-tosyl pyrrolo[3,4-*c*]pyrano [5,6-*b*] cyclohexan-1-one (9b)

White solid, 70% (0.372 g); $[\alpha]_D^{34} = -0.2$ (*c* 1, $CHCl_3$); mp: 186–188 °C; IR (KBr): 1629, 1341 and 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.83 (s, 3H), 0.85 (s, 3H), 1.93–2.07 (m, 5H), 2.43 (s, 3H), 2.64 (dd, 1Ha, *J* = 3.0, 6.0 Hz), 3.02–3.10 (m, 1H, Hb), 3.29–3.38 (m, 2H), 3.97 (td, 1H, *J* = 3.0, 6.0 Hz), 4.84 (d, 1H, *J* = 3.0 Hz), 6.86–7.72 (m 14H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.53, 26.93, 29.46, 32.25, 34.33, 38.19, 41.13, 42.48, 49.68, 50.89, 64.71, 75.02, 110.63. 125.53, 126.51, 127.77, 128.14, 128.47, 129.67, 130.82, 134.65, 137.69, 138.10, 143.08, 168.36 and 197.64 ppm; MS *m*/*z*: 541.62 (M^+). Anal. Calcd for $C_{33}H_{35}NO_4S$: C, 73.17; H, 6.51; N, 2.59. Found: C, 73.28; H, 6.49; N, 2.64.

4.5.5. (1b*R*,2*S*,4a*R*)-*cis*-2-Benzyl-5,5,8,8-tetramethyl-3-tosyl-pyrrolo[3,4-*c*]pyrano [5,6-*b*]dioxin-1-one (9c)

Colourless solid, 63% (0.309 g); $[\alpha]_D^{34} = +18.3$ (*c* 1, $CHCl_3$); mp: 163–165 °C; IR (KBr): 1621, 1342 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.72 (s, 3H), 0.78 (dt, Ha, *J* = 6.0, 12.0 Hz), 0.90 (s, 3H), 1.46 (s, 6H), 1.96–2.21 (m, 1H), 3.28 (t, 1H, *J* = 12.0 Hz), 2.39 (s, 3H), 3.39 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.53 (dd, 1H, *J* = 3.0, 6.0, 12.0 Hz), 3.88 (d, 1H, *J* = 3.0, 9.0 Hz), 4.09 (td, 1H, *J* = 3.0, 6.0 Hz), 7.15–.73 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.47, 21.49, 26.61, 28.46, 29.16, 31.65, 36.11, 40.15, 42.87, 48.77, 49.53, 51.32, 63.53, 79.63, 110.92, 126.10, 127.17, 127.84, 129.64, 131.56, 135.42, 138.14, 143.41, 152.34 and 169.01 ppm; MS *m*/*z*: 497.38 (M^+). Anal. Calcd for $C_{27}H_{31}NO_6S$: C, 65.17; H, 6.28; N, 2.81. Found: C, 65.28; H, 6.32; N, 2.79.

4.5.6. (1b*R*,2*S*,4a*R*)-*cis*-2-Benzyl-8,8-dimethyl-5-phenyl-3-tosyl pyrrolo[3,4-*b*]pyrano [5,6-*b*]dioxin-1-one (9d)

Colourless solid, 63% (0.342 g); $[\alpha]_D^{34} = +4.7$ (*c* 1, $CHCl_3$); mp: 203–205 °C; IR (KBr): 1629, 1341 and 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.83 (s, 3H), 0.85 (s, 3H), 1.54 (s, 6H), 1.93–2.07 (m, 2H), 2.43 (s, 3H), 2.64 (dd, 1Ha, *J* = 3.0, 6.0 Hz), 3.02–3.10 (m, 1H, Hb), 3.29–3.38 (m, 2H), 3.97 (td, 1H, *J* = 3.0, 6.0 Hz), 4.84 (d, 1H, *J* = 3.0 Hz), 6.86–7.72 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.53, 24.34, 26.90, 29.54, 32.21, 34.33, 38.21, 41.15, 42.50 49.68, 50.86, 64.69, 75.02, 110.63, 125.53, 126.51, 127.77, 128.14, 128.47, 129.67, 130.80, 134.65, 137.69, 138.10, 143.08, 154.19 and 167.09 ppm; MS *m*/*z*: 545.51 (M^+). Anal. Calcd for $C_{31}H_{31}NO_6S$: C, 68.24; H, 5.73; N, 2.57. Found: C, 68.34; H, 5.81; N, 2.64.

4.5.7. (1b*R*,4*S*,4a*R*)-*cis*-2-Benzyl-5,5-dimethyl-3-tosyl-pyrrolo[3,4-*c*]pyrano[5,6-*b*]indan-1-one (11a)

White solid, 68% (0.335 g); $[\alpha]_D^{28} = +6.6$ (*c* 1, $CHCl_3$); mp: 201–203 °C; IR (KBr): 1619, 1339 and 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (s, 3H), 1.08 (dt, 1Ha, *J* = 6.0, 12.0 Hz), 1.20 (s, 3H), 2.30 (t, 1H, *J* = 12.0 Hz), 2.52 (dd, 1H, *J* = 9.0, 12.0 Hz), 3.40 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.56 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.89 (dd, 1H, *J* = 3.0, 12.0 Hz), 4.10 (td, *J* = 3.0, 6.0 Hz), 7.16–7.74 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.26, 26.86, 28.47, 76.14, 104.32, 125.02, 125.54, 126.81, 127.98, 128.46, 128.52, 130.31, 131.16, 131.18, 134.92, 135.71, 135.82, 141.69, 169.36 and 190.62 ppm; MS *m*/*z*: 499.80 (M^+). Anal. Calcd for $C_{30}H_{29}NO_4S$: C, 72.12; H, 5.85; N, 2.80. Found: C, 72.26; H, 5.79; N, 2.73.

4.5.8. (1b*R*,4*S*,4a*R*)-*cis*-2-Benzyl-5-phenyl-3-tosyl-pyrrolo[3,4-*c*]pyrano[5,6-*b*]indan-1-one (11b)

Yellow solid, 58% (0.315 g); $[\alpha]_D^{34} = +19.0$ (*c* 1, $CHCl_3$); mp: 211–213 °C; IR (KBr): 1612, 1343 and 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.97 (s, 3H), 2.14–2.23 (m, 1H), 254 (d, 1H, *J* = 6.0 Hz), 3.02 (t, 1H, *J* = 9.0 Hz), 3.08 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.55 (dd, 1H, *J* = 6.0, 9.0 Hz), 4.40–4.43 (m, 1H), 5.22 (d, 1H, *J* = 3.0 Hz), 6.86–7.59 (m, 18H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.77, 31.38, 37.44, 40.32, 47.6, 61.55, 76.13, 104.35, 115.96, 119.21, 123.12, 125.00, 125.56, 126.63, 126.70, 127.00, 127.63, 128.46, 128.51, 130.30, 131.12, 131.19, 134.79, 135.75, 135.85, 170.16 and 190.64 ppm; MS *m*/*z*: 547.03 (M^+). Anal. Calcd for $C_{34}H_{29}NO_4S$: C, 74.56; H, 5.34; N, 2.56. Found: C, 74.63; H, 5.31; N, 2.62.

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