JOC The Journal of Organic Chemistry
Note
pubs.acs.org/joc

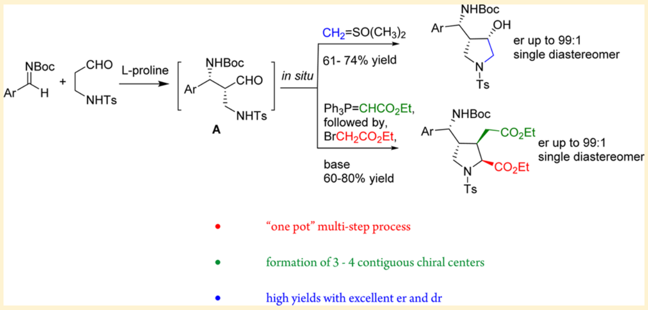
Proline-Catalyzed Sequential *syn*-Mannich and [4 + 1]-Annulation Cascade Reactions To Form Densely Functionalized Pyrrolidines

Ravindra D. Aher, B. Senthil Kumar, and Arumugam Sudalai*

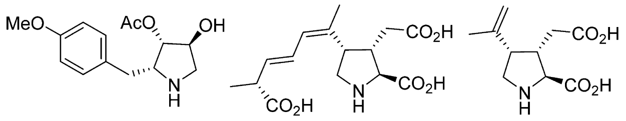
Chemical Engineering & Process Development Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, Maharashtra, India 411008

Ⓢ *Supporting Information*

ABSTRACT: A highly efficient one-pot [4 + 1]-annulation process for the asymmetric synthesis of densely functionalized pyrrolidine derivatives is described. The in situ generated *syn*-Mannich adduct obtained via proline catalysis acts as a four-atom component, and Corey's sulfur ylide or ethyl bromoacetate acts as a one-atom carbon source to construct pyrrolidine units in a highly enantio- and diastereoselective manner.



The derivatives of functionalized pyrrolidines are structural components of many bioactive natural products[1] and pharmaceutically important substances.[2] Figure 1 shows some of the examples of bioactive natural products containing densely substituted pyrrolidine units. In particular, anisomycin **1** is a basic antibiotic,[2f] while domoic acid **2** and kainic acid **3** are potent neuroexcitatory amino acids.[2g] Due to their biological importance and structural complexity, several methods for construction of pyrrolidine units have been reported recently, which mainly include [3 + 2]-cycloadditions of azomethine ylides with alkenes or nitrones with cyclopropanes,[3] transition-metal-catalyzed carboamination, hydroamination or allylic amination protocol,[4] intramolecular cyclization of epoxy and halogenated sulfones under basic conditions,[5] acid-catalyzed cyclization of vinylsilanes,[6] intramolecular carbolithiation of homoallylic amines,[7] radical cyclizations,[8] catalytic intramolecular hydroamination of alkenylamines,[9] manipulations of sugars from the chiral pool resources,[10] various metal-catalyzed cyclizations,[11] ring-closing metathesis of allylic amines,[12] and 5-*endo-trig* cyclization of *N*-allylic-substituted α-amino nitriles.[13] In recent years, proline-catalyzed sequential reactions have gained more applicability for the asymmetric synthesis of structurally diverse molecular architectures.[14]

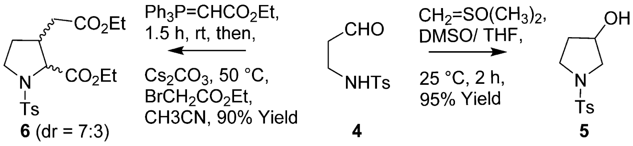


anisomycin (1) domoic acid (2) kainic acid (3)

Figure 1. Bioactive pyrrolidine-containing natural products.

Although many strategies for the synthesis of substituted pyrrolidines have been described, a transition-metal-free [4 + 1]-annulation strategy with well-defined stereochemistry and derivatizable functional groups has not been reported. Thus, we envisioned that a new synthesis of pyrrolidines via a [4 + 1]-annulation approach should be feasible by employing β-amino aldehyde[15] **4** as a four-atom precursor and sulfur ylide or ethyl bromoacetate as a one-carbon source (Scheme 1).

Scheme 1. Reaction of β-Amino Aldehydes with Sulfur Ylide and Wittig Olefination/N-Alkylation/Michael Reaction



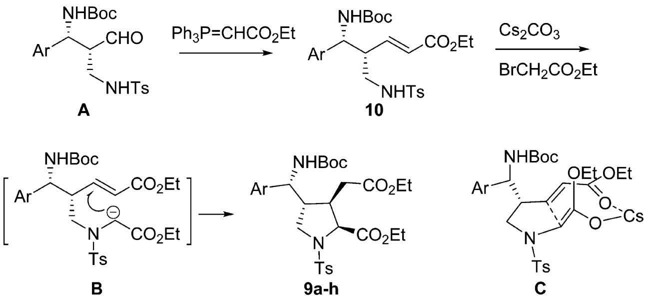
Accordingly, when β-amino aldehyde **4** was treated with $CH_2{=}SOMe_2$ (Corey's ylide)[16] in DMSO/THF at 25 °C, the desired hydroxypyrrolidine derivative **5** was obtained in 95% yield. Additionally, when **4** was treated with $Ph_3P{=}CHCO_2Et$ for 1.5 h at 25 °C followed by addition of ethyl bromoacetate in the presence of Cs_2CO_3 at 50 °C for 6 h, the corresponding pyrrolidine dicarboxylate derivative **6** was obtained in 90% yield with moderate diastereoselectivity (dr = 7:3).

Encouraged by initial results, we became interested in investigating the feasibility of this new diastereoselective [4 + 1]-annulation strategy with chiral Mannich aldehydes **A**[17] or δ,δ'-diamino α,β-unsaturated esters **10** (Scheme 2)[18] and $CH_2{=}SOMe_2$ or ethyl bromoacetate, respectively, which can furnish chiral-substituted pyrrolidines. In this communication, we describe a one-pot *sequential* [4 + 1]-annulation approach

Received: December 20, 2014
Published: January 16, 2015

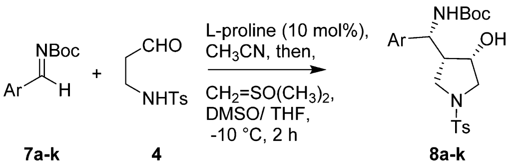
DOI: 10.1021/jo5028886
J. Org. Chem. 2015, 80, 2024−2031

Scheme 2. Probable Mechanistic Pathway for Pyrrolidine Carboxylate Formation



involving the reaction of in situ generated *syn*-Mannich aldehydes **A** with sulfur ylide or δ,δ'-diamino α,β-unsaturated ester **10** formed in situ with ethyl bromoacetate that provides for the construction of densely substituted pyrrolidine units **8** and **9** in a highly enantio- and diastereoselective manner (Tables 1 and 2).

Table 1. L-Proline-Catalyzed Sequential *syn*-Mannich/Corey−Chaykovsky Reaction for the Synthesis of Hydroxypyrrolidines 8a−k[a]

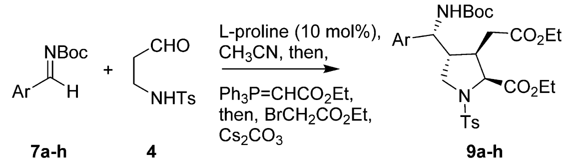


	imines 7a−k	products 8a−k[b]	
entry	Ar	yield (%)[c]	ee (%)[d]
1	phenyl (**7a**)	72	99
2	4-Cl-ph (**7b**)	66	96
3	4-CF_3-ph (**7c**)	70	95
4	4-tolyl (**7d**)	70	94
5	2-naph (**7e**)	63[e]	99
6	4-Br-ph (**7f**)	61[e]	98
7	4-F-ph (**7g**)	66[e]	94
8	furyl (**7h**)	64	90
9	4-SMe-ph (**7i**)	65	88
10	thienyl (**7j**)	63	86
11	*p*-anisyl (**7k**)	74	99

[a] Imine (2.5 mmol), aldehyde (2.75 mmol), L-proline (10 mol %), $CH_2{=}SOMe_2$ (3.75 mmol), DMSO/THF (1:1), −10 °C, 2 h. [b] Single diastereoisomer (dr >99:1) was obtained. [c] Isolated yield with respect to imine. [d] Percent enantioselectivity was determined from chiral HPLC analysis. [e] Corresponding oxazolidinones were isolated by using 7.5 mmol of ylide for 12 h at 25 °C.

Thus, β-amino aldehyde **4** was treated with aryl imine **7a** as a model substrate under List protocol[17] that produced the corresponding chiral *syn*-Mannich aldehyde **A** in situ. This was followed by the addition of a solution of $CH_2{=}SOMe_2$ in DMSO/THF (1.5 equiv) at 25 °C, which gave the desired chiral hydroxypyrrolidine **8a** in 68% yield with 92% ee and moderate diastereoselectivity (dr = 4:1). An improvement in diastereoselectivity (dr = 9:1) was realized by performing the reaction at 0 °C for 2 h. Finally, when the addition of ylide was conducted at −10 °C, **8a** was indeed obtained in 72% yield with 99% ee and >99 dr (Table 1, entry 1). However, further lowering of temperature for the annulation protocol had a deleterious effect on the yield (60%). Use of other solvents such as THF, $CHCl_3$, and DMF for the tandem protocol resulted in a sluggish reaction with low product yields. With these optimized reaction conditions (Table 1, footnote *a*), we next examined the scope of the annulation protocol. Substrates having fluoro, chloro, bromo, methoxy, methyl, trifluoromethyl, and thiomethyl groups on the aromatic nucleus and heteroaromatic compounds such as thiophenyl and furfuryl were well-tolerated under the reaction conditions (Table 1, entries 2−11).

Table 2. L-Proline-Catalyzed Sequential *syn*-Mannich/Wittig Olefination/N-Alkylation/Michael Addition Reaction for Synthesis of Pyrrolidine Carboxylate 9a−h[a]



	imines 7a−h	product 9a−h[b]	
entry	Ar	yield (%)[c]	ee (%)[d]
1	phenyl (**7a**)	80	96
2	4-Cl-ph (**7b**)	67	94
3	4-CF_3-ph (**7c**)	68	99
4	4-tolyl (**7d**)	78	93
5	2-napth (**7e**)	79	92
6	4-Br-ph (**7f**)	76	99
7	4-F-ph (**7g**)	71	92
8	2-furyl (**7h**)	60	92

[a] Imine (2.5 mmol), aldehyde (2.75 mmol), L-proline (10 mol %), $Ph_3P{=}CHCO_2Et$ (3.75 mmol), 0 °C, 1.5 h then, ethyl bromoacetate (3 mmol), Cs_2CO_3 (6.25 mmol), 50 °C, 6 h. [b] Single diastereoisomer (dr >99:1) was obtained. [c] Isolated yield with respect to imine. [d] Percent enantioselectivity was determined from chiral HPLC analysis.

Next, it was of interest to extend the utility of the *syn*-Mannich adduct for the asymmetric synthesis of densely functionalized pyrrolidine dicarboxylates **9a−h** (Table 2). Thus, Mannich adduct **A** (Ar = Ph) was trapped in situ with $Ph_3P{=}CHCO_2Et$ for 1.5 h, followed by addition of ethyl bromoacetate in the presence of Cs_2CO_3 as base, which facilitated in situ intramolecular Michael addition to produce the expected pyrrolidine dicarboxylate derivative **9a**. Compound **9a** was indeed obtained in 80% yield with 96% ee and >99% diastereoselectivity when carried out at 50 °C for 6 h (Table 2, entry 1). Further, increase of temperature (70 °C), with an overall aim to improve the rate of the reaction and product yield, however, resulted in low yields. With optimized reaction conditions (Table 2, footnote *a*), other substrates bearing a fluoro, chloro, bromo, methyl, and trifluoromethyl substituent on the aromatic nucleus including heteroaryl units underwent this [4 + 1]-annulation cascade smoothly, affording the corresponding pyrrolidine dicarboxylates **9b−h** in high yields with excellent enantio- and diastereoselectivities (Table 2, entries 2−8).

The absolute configuration of the newly generated *syn*-Mannich adduct **A** was assigned on the basis of the previously established configuration of amino aldehydes.[17] The relative stereochemistry of substituted pyrrolidine derivatives **8a−k**[19] and **9a−h** is proven unambiguously from COSY, NOESY studies, and X-ray crystallographic analysis (Figure 2, CCDC 1036949).

The formation of hydroxypyrrolidines **8a−k** can be readily understood on the basis of our previously established study.[14c]

DOI: 10.1021/jo5028886
J. Org. Chem. 2015, 80, 2024−2031

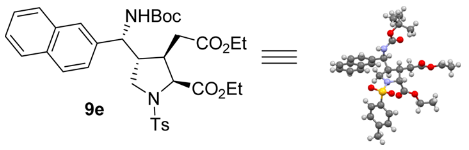


Figure 2. ORTEP diagram of **9e**.

A probable mechanistic pathway for the formation of pyrrolidine dicarboxylates **9a−h** is, however, shown in Scheme 2.[20] Initially, *syn*-Mannich aldehyde **A** in Wittig olefination forms *δ*,*δ*′-diamino *α*,*β*-unsaturated ester **10** (^{1}H and ^{13}C NMR analysis) in situ, which undergoes N-alkylation with ethyl bromoacetate in the presence of Cs_2CO_3 to form the anionic species **B**. This is followed by the intramolecular distereoselective Michael addition to produce pyrrolidine dicarboxylates **9a−h**. The high distereoselectivity can be explained by the formation of favorable (*E*)-enolate (species **C**), in which the cesium ion coordinates to both of the ester carbonyls.

In summary, we have described, for the first time, a novel [4 + 1]-annulation strategy which includes *syn*-Mannich/Corey−Chaykovsky or Wittig olefination/N-alkylation/Michael addition cascade that leads to the asymmetric synthesis of substituted pyrrolidine derivatives **8a−k** and **9a−h**, respectively, with good yields and excellent enantio- and diastereoselectivities. The present approach thus provides for ready access to a large number of kainoid amino acids and their congeners that can be utilized for SAR studies. The salient features of the methodology are as follows: (1) metal-free pyrrolidine synthesis; (2) one-pot 3 or 4 reactions; (3) functional group tolerance and milder reaction conditions; and (4) high yields with excellent enantio- and diastereoselectivity to obtain densely functionalized chiral pyrrolidines.

■ EXPERIMENTAL SECTION

General Information. Solvents were purified and dried by standard procedures before use; petroleum ether in the boiling range of 60−80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a polarimeter. ^{1}H NMR and ^{13}C NMR were recorded on 200, 400, and 500 MHz NMR spectrometers. HRMS data for new compounds were recorded using an Orbitrap mass analyzer associated with an Accela 1250 pump. Elemental analysis was carried on a CHNS-O analyzer. HPLC was performed with a variable wavelength detector. Column chromatography was carried out by using silica gel with the selected particle size of 100−200 mesh or 230−400 mesh. D-Proline and L-proline were purchased from Sigma-Aldrich. Racemic proline was prepared by mixing both enantiomers before use. Imines[16] **7a−k** and *β*-amino aldehyde[15] **4** were freshly prepared prior to use following reported methods.

General Experimental Procedure. *Preparation of Sulfur Ylide.* NaH (90 mg, 3.75 mmol, previously washed with petroleum ether to remove oil) was taken in an oven-dried three-necked flask, followed by the addition of dry DMSO/THF (5 mL each) through a septum to it, and the whole slurry was stirred at 25 °C under N_2 atmosphere. Then trimethyloxosulfonium iodide (835 mg, 3.75 mmol) was added to the slurry over a period of 5 min via a solid addition funnel until it became a homogeneous solution.

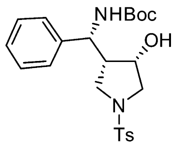
Sequential syn-Mannich/Corey−Chaykovsky Reaction. To a cooled solution of *N*-Boc imines (**7a−k**, 2.5 mmol) and L-proline (10 mol %) in dry CH_3CN (20 mL) at 0 °C was added *β*-amino aldehyde **4** (568 mg, 2.75 mmol), and the mixture was stirred for 8−12 h at 0 °C. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO/THF (3.75 mmol) at −10 °C and allowed to stir for 2 h at the same temperature. The progress of the reaction can be monitored by TLC. It was then quenched by the addition of aq NH_4Cl solution. The mixture was concentrated in vacuum to remove acetonitrile, and concentrate was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by silica gel column chromatography (230−400 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **8a−k**.

Sequential syn-Mannich/Wittig Olefination/N-Alkylation/Michael Addition. To a cooled solution of *N*-Boc imines (**7a−h**, 2.5 mmol) and L-proline (10 mol %) in dry CH_3CN (20 mL) at 0 °C was added *β*-amino aldehyde **4** (568 mg, 2.75 mmol), and the mixture was stirred for 8−12 h at 0 °C. This was followed by the addition of a ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (1.306 g, 3.75 mmol) at 0 °C and allowed to stir for 2 h at the same temperature; ethyl bromoacetate (501 mg, 3.455 mL, 3 mmol) and Cs_2CO_3(2.037 g, 6.25 mmol) were added, and reaction temperature increased to 50 °C and was allowed to stir for 6−8 h at the same temperature. The progress of the reaction can be monitored by TLC. It was then quenched by the addition of an aq NH_4Cl solution. The mixture was then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash silica gel column chromatography (230−400 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **9a−h**.

Corey−Chaykovsky Reaction of β-Amino Aldehyde. To a cooled solution of *β*-amino aldehyde **4** (568 mg, 2.5 mmol) in dry THF (5 mL) at 25 °C was added a solution of dimethyloxosulfonium methylide (2.5 mmol) in DMSO (10 mL), and the reaction mixture was allowed to stir for 2 h at the same temperature. It was then quenched by the addition of aq NH_4Cl solution. The mixture was then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by silica gel column chromatography (100−200 mesh) using petroleum ether and ethyl acetate as eluents (6:4) to afford the pure products **5** (570 mg, 95% yield).

Sequential Wittig Olefination/N-Alkylation/Michael Addition of β-Amino Aldehyde. To a cooled solution of *β*-amino aldehyde **4** (568 mg, 2.5 mmol) in dry CH_3CN (20 mL) at 25 °C was added ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (1.045 g, 3 mmol), and the reaction mixture was allowed to stir for 1.5 h at the same temperature; ethyl bromoacetate (501 mg, 3.455 mL, 3.0 mmol) and Cs_2CO_3(1.956 g, 6.0 mmol) were then added, and reaction temperature increased to 50 °C and was allowed to stir for 6 h at the same temperature. It was then quenched by the addition of an aq NH_4Cl solution. The mixture was then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash silica gel column chromatography (230−400 mesh) using petroleum ether and ethyl acetate as eluents (8:2) to afford the products **6** (860 mg, 90% yield).

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(phenyl)methyl) carbamate (**8a**):*

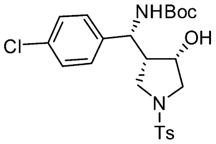


Yield 807 mg, 72%; colorless solid; mp 197−200 °C; $[\alpha]_{25}^{D}$ +10.4 (*c* 0.2, $CHCl_3$); 99% ee (Chiracel OD-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 11.3 min (minor), t_r = 10.1 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 763, 1014, 1296, 1418, 1575, 1652, 1669, 1720, 2917, 3366; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.35−2.40 (m, 1H), 2.44 (s, 3H), 2.84 (t, *J* = 11.5 Hz, 1H), 2.96 (t, *J* = 8.8 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 4.24 (br s, 1H), 4.53 (dd, *J* = 8.1, 10.8 Hz, 1H), 4.73 (br s, 1H), 4.88

DOI: 10.1021/jo5028886
J. Org. Chem. 2015, 80, 2024−2031

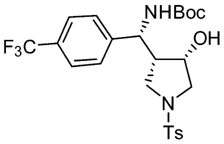
(d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.35−7.40 (m, 3H), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 28.2 (3), 48.3, 52.2, 53.2, 55.9, 69.9, 81.1, 126.7 (2), 127.4 (2), 128.7, 129.4, 129.5, 134.1, 139.1, 143.3, 156.7; HRMS (ESI) calcd for $C_{23}H_{30}N_2O_5S$ [M + Na]$^+$ 469.1772; found 469.1761.

*tert-Butyl ((R)-(4-Chlorophenyl)((3R,4S)-4-hydroxy-1-tosylpyrrolidin-3-yl)methyl)carbamate (**8b**):*



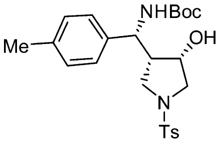
Yield 800 mg, 66%; colorless solid; mp 203−205 °C; $[\alpha]_{25}^{D}$ +15.4 (c 0.2, $CHCl_3$); 96% ee (Chiracel OD-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 15.1 min (minor), t_r = 12.5 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1089, 1158, 1317, 1390, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.98 (s, 1H), 2.38 (br s, 1H), 2.45 (s, 3H), 3.28 (s, 1H), 3.33 (t, J = 10.0 Hz, 1H), 3.40 (s, 1H), 3.65 (t, J = 8.8 Hz, 1H), 3.77 (s, 1H), 4.78 (s, 1H), 5.0 (s, 1H), 7.23 (dd, J = 8.2, 8.0 Hz, 4H), 7.32 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, CD_3OD) δ 21.3, 28.1 (3), 48.8, 49.9, 52.5, 56.9, 69.5, 79.8, 127.3 (2), 128.1 (2), 128.5 (2), 129.6 (2), 133.0, 134.0, 139.9, 143.4, 155.4; HRMS (ESI) calcd for $C_{23}H_{29}ClN_2O_5S$ [M + Na]$^+$ 503.1383; found 503.1391.

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(4-(trifluoromethyl)phenyl)methyl)carbamate (**8c**):*



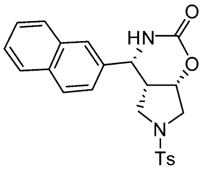
Yield 905 mg, 70%; colorless solid; mp 202−204 °C; $[\alpha]_{25}^{D}$ +27.3 (c 0.3, $CHCl_3$); 95% ee (Chiracel OD-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 93.6 min (minor), t_r = 86.0 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1249, 1418, 1506, 1621, 1653, 1683, 2979, 3366; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.36−2.41 (m, 1H), 2.44 (s, 3H), 2.83 (t, J = 9.7 Hz, 1H), 2.94 (t, J = 7.9 Hz, 1H),3.42 (d, J = 11.6 Hz, 1H), 3.56 (d, J = 10.3 Hz, 1H), 4.23 (s, 1H), 4.43 (br s, 1H), 4.64 (t, J = 8.8 Hz, 1H), 4.93 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.64 (t, J = 7.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 28.2 (3), 48.0, 51.7, 52.8, 55.9, 70.0, 81.3, 122.6 (q, J = 272.8 Hz) 126.4 (2), 127.2 (2), 127.5 (2), 129.6 (2),130.1 (q, J = 32.4 Hz), 134.2, 143.1, 143.3, 156.5; HRMS (ESI) calcd for $C_{24}H_{29}F_3N_2O_5S$ [M + Na]$^+$ 537.1646; found 537.1648.

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(p-tolyl)methyl)carbamate (**8d**):*



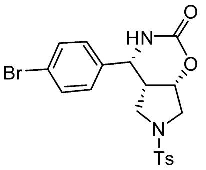
Yield 810 mg, 70%; colorless solid; mp 187−190 °C $[\alpha]_{25}^{D}$ +25.1 (c 0.2, $CHCl_3$); 94% ee (Chiracel OD-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 19.8 min (minor), t_r = 14.3 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 884, 1091, 1248, 1339, 1366, 1472, 1507, 1558, 1653, 1683, 2977, 3366; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.31−2.34 (m, 1H), 2.36 (s, 3H), 2.44 (s, 3H), 2.80 (dd, J = 9.8, 11.5 Hz, 1H), 2.96 (dd, J = 7.6, 9.3 Hz, 1H), 3.43 (d, J = 11.5 Hz, 1H), 3.57 (dd, J = 3.7, 12.9 Hz, 1H), 4.22 (s, 1H), 4.49 (dd, J = 8.1, 11.0 Hz, 1H), 4.75 (br s, 1H), 4.83 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.6, 28.2 (3), 48.3, 52.3, 52.9, 55.9, 69.9, 80.9, 126.6 (2), 127.4 (2), 129.5 (2), 130.0 (2), 134.1, 136.1, 138.5, 143.3, 156.7; HRMS (ESI) calcd for $C_{24}H_{32}N_2O_5S$ [M + Na]$^+$ 483.1930; found 483.1926.

*(4R,4aR,7aS)-4-(Naphthalen-2-yl)-6-tosylhexahydropyrrolo[3,4-e][1,3]oxazin-2(3H)-one (**8e**):*



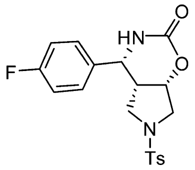
Yield 667 mg, 63%; colorless solid; mp 153−156 °C; $[\alpha]_{25}^{D}$ +14.7 (c 0.3, $CHCl_3$); 99% ee (Chiracel OJ-H (250 × 4.6 mm), n-hexane/i-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 100.7 min (minor), t_r = 80.1 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 740, 1154, 1268, 1718, 2286, 2390, 3010, 3053, 3290; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.57 (d, J = 3.3 Hz, 1H), 3.30 (t, J = 9.1 Hz, 1H), 3.47−3.50 (m, 1H), 3.58 (d, J = 11.9 Hz, 1H), 3.69 (t, J = 9.46 Hz, 1H), 4.56 (s, 1H), 4.67 (d, J = 2.44 Hz, 1H), 6.07 (s, 1H), 7.26 (d, J = 8.54 Hz, 1H), 7.32 (d, J = 8.54 Hz, 2H), 7.49 (d, J = 8.24 Hz,2H), 7.65 (s, 1H), 7.68 (d, J = 6.71 Hz,2H), 7.69−7.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 42.2, 48.4, 53.9, 54.1, 75.8, 123.1, 124.9, 126.7, 127.0, 127.4 (2), 127.7, 127.9, 129.5, 129.9 (2), 133.1, 133.4, 137.4, 144.1, 151.9; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_4S$ [M + H]$^+$ 423.1378; found 423.1379.

*(4R,4aR,7aS)-4-(4-Bromophenyl)-6-tosylhexahydropyrrolo[3,4-e][1,3]oxazin-2(3H)-one (**8f**):*



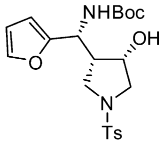
Yield 690 mg, 61%; colorless solid; mp 210−213 °C; $[\alpha]_{25}^{D}$ +12.3 (c 0.3, $CHCl_3$); 98% ee (Chiracel OD-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 34.5 min (minor), t_r = 40.9 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 742, 1160, 1271, 1705, 2286, 2350, 2999, 3290; ^{1}H NMR (500 MHz, $CDCl_3$, CD_3OD) δ 2.45 (s, 3H), 2.48−2.49 (m, 1H), 3.25 (t, J = 9.7 Hz, 1H), 3.50 (dd, J = 4.2, 7.6 Hz,1H), 3.62 (d, J = 11.9 Hz 1H), 3.70 (t, J = 8.1 Hz, 2H) 4.43 (d, J = 2.7 Hz, 1H), 4.67 (t, J = 3.9 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.37 (t, J = 8.2 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, CD_3OD) δ 21.2, 41.8, 48.1, 52.4, 54.1, 75.5, 122.2, 127.1 (2), 127.2 (2), 129.7 (2), 132.0 (2), 133.1, 139.6, 144.0, 152.4; HRMS (ESI) calcd for $C_{19}H_{19}BrN_2O_4S$ [M + Na]$^+$ 473.0141; found 473.0133.

*(4R,4aR,7aS)-4-(4-Fluorophenyl)-6-tosylhexahydropyrrolo[3, 4-e][1,3]oxazin-2(3H)-one (**8g**):*



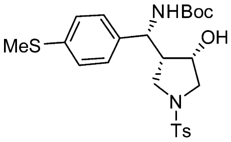
Yield 646 mg, 66%; colorless solid; mp 207−211 °C; $[\alpha]_{25}^{D}$ +12.3 (c 1.0, $CHCl_3$); 94% ee (Chiracel OD-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 29.1 min (minor), t_r = 24.0 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 740, 1158, 1267, 1713, 2293, 2356, 3059, 3282; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.48−2.50 (m, 1H), 3.26 (t, J = 8.54 Hz, 1H), 3.56 (q, J = 8.2 Hz, 2H), 3.64 (dd, J = 7.9, 9.7 Hz, 1H), 4.42 (t, J = 3.0 Hz, 1H), 4.69−4.71 (m, 1H), 5.76 (d, J = 1.5 Hz,1H), 7.08 (t, J = 8.5 Hz, 2H), 7.20 (q, J = 8.5 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 42.6, 48.4, 53.3, 54.0, 75.8, 116.3, 116.5, 127.5,127.6, 127.7, 129.9 (2), 133.5, 136.0, 144.1, 151.7, 161.5 (d, J = 250 Hz); HRMS (ESI) calcd for $C_{19}H_{19}FN_2O_4S$ [M + Na]$^+$ 413.0942; found 413.0929.

*tert-Butyl ((R)-Furan-2-yl((3R,4S)-4-hydroxy-1-tosylpyrrolidin-3-yl)-methyl)carbamate (**8h**):*



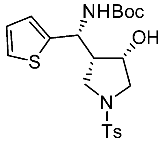
Yield 695 mg, 64%; colorless solid; mp 136−139 °C; $[\alpha]_{25}^{D}$ −16.3 (*c* 0.5, $CHCl_3$); 90% ee (Chiracel OD-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 19.8 min (minor), t_r = 14.3 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 887, 1341, 1366, 1467, 1514, 1558, 1654, 1682, 3365; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.28 (s, 1H), 2.44 (s, 4H), 2.99 (t, *J* = 9.4 Hz, 1H), 3.13 (t, *J* = 10.0 Hz, 2H), 3.33−3.40 (m, 1H), 3.56 (q, *J* = 9.7 Hz, 1H), 3.91−4.04 (m, 1H), 4.94−5.03 (m, 2H), 6.15−6.19 (m,1H), 6.30 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.2 (3), 47.0 (2), 50.5, 52.2, 70.9, 80.8, 106.7, 110.5, 126.5, 127.6 (2), 129.8 (2), 142.3, 143.6, 152.0, 156.3; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_6S$ $[M + Na]^+$ 459.1560; found 459.1551.

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(4-(methylthio)phenyl)methyl)carbamate (**8i**):*



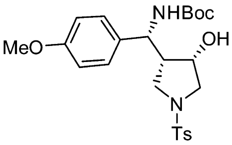
Yield 801 mg, 65%; colorless solid; mp 209−211 °C; $[\alpha]_{25}^{D}$ +1.6 (*c* 0.1, $CHCl_3$); 88% ee (Chiracel OJ-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 34.0 min (minor), t_r = 30.4 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 886, 1096, 1339, 1371, 1467, 1512, 1559, 1658, 1684, 2969, 3366; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.19−2.40 (m, 1H), 2.45 (s, 3H), 2.51 (s, 3H), 2.77 (dd, *J* = 9.6,11.8 Hz, 1H),), 2.96 (dd, *J* = 7. 5, 9.1 Hz, 1H), 3.43 (d, *J* = 11.4 Hz, 1H), 3.55−3.64 (m, 1H), 4.20−4.26 (m, 1H), 4.50 (dd, *J* = 7.9, 10.7 Hz, 1H), 4.61 (br s, 1H), 4.77 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 21.6, 28.3 (3), 48.3, 52.2, 52.8, 56.0, 70.0, 81.1, 127.2 (2), 127.3 (2), 127.6 (2), 129.5 (2), 134.4, 135.8, 139.5, 143.1, 156.6; HRMS (ESI) calcd for $C_{24}H_{32}N_2O_5S_2$ $[M + Na]^+$ 515.1650; found 515.1645.

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(thiophen-2-yl)methyl)carbamate (**8j**):*



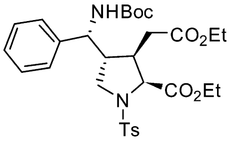
Yield 710 mg, 63%; colorless solid; mp 186−189 °C; $[\alpha]_{25}^{D}$ +37.3 (*c* 0.3, $CHCl_3$); 86% ee (Chiracel OJ-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 18.0 min (minor), t_r = 20.9 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1345, 1370, 1472, 1521, 1565, 1655, 1685, 3369; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s,9H), 1.77 (s, 1H), 2.36 (br s, 1H), 2.44 (s, 3H), 2.96−3.14 (m, 2H), 3.42 (t, *J* = 8.3 Hz,1H), 3.47−3.62 (m,1H), 4.0 (br s, 1H), 5.08 (br s, 2H), 6.87−6.96 (m, 2H), 7.21 (t, *J* = 5.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 28.3 (3),47.2, 49.4, 51.8, 53.0, 71.3, 80.6, 124.5, 124.7, 127.1, 127.6 (2), 129.7 (2), 133.4, 134.1, 143.5, 156.0; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_5S_2$ $[M + Na]^+$ 475.1332; found 475.1320.

*tert-Butyl ((R)-((3R,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)(4-methoxyphenyl)methyl)carbamate (**8k**):*



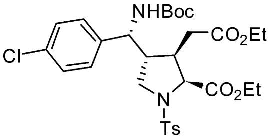
Yield 883 mg, 74%; colorless solid; mp 199−202 °C; $[\alpha]_{25}^{D}$ +33.4 (*c* 0.3, $CHCl_3$); 99% ee (Chiracel OJ-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 70.7 min; IR ($CHCl_3$, cm^{-1}) ν_{max} 887, 1094, 1341, 1369, 1469, 1510, 1561, 1656, 1679, 2974, 3365; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.29−2.40 (m, 1H), 2.45 (s, 3H), 2.78 (dd, *J* = 9.2, 11.6 Hz, 1H), 2.95 (dd, *J* = 7.8, 9.2 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.59 (dd, *J* = 3.7, 12.9 Hz, 1H), 3.83 (s, 3H), 4.18−4.25 (m, 1H), 4.47 (dd, *J* = 7.8,10.7 Hz, 1H), 4.73−4.75 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 28.2 (3), 48.3, 52.4, 52.5, 55.3, 55.9, 70.0, 81.0, 114.8, 127.5 (2), 127.9 (2), 129.5 (2), 131.3 (2), 134.4, 143.1, 156.6, 159.7; HRMS (ESI) calcd for $C_{24}H_{32}N_2O_6S[M + Na]^+$ 499.1873; found 499.1861.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(phenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9a**):*



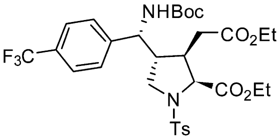
Yield 1.17 g, 80%; colorless solid; mp 150−151 °C; $[\alpha]_{25}^{D}$ +34.3 (*c* 0.5, $CHCl_3$); 96% ee (Chiracel AS-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 10.2 min (minor), t_r = 11.1 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1162, 1214, 1345, 1499, 1736; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22−1.26 (m, 6H), 1.41 (s, 9H), 1.89 (dd, *J* = 5.7 and 11.8 Hz, 1H), 2.44 (s, 3H), 2.51−2.63 (m, 3H), 3.17 (t, *J* = 9.0 Hz, 1H), 3.43 (t, *J* = 8.5 Hz, 1H), 4.0−4.13 (m, 4H), 4.61 (d, *J* = 7.7 Hz, 1H), 4.80 (br s, 1H), 4.99 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 2H), 7.26−7.33 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 21.6, 28.2, 29.7, 33.2, 40.5, 46.9, 48.3, 53.0, 60.6, 61.2, 63.2, 80.0, 125.9,127.4, 128.9, 129.6, 135.6, 140.2, 143.4, 155.3, 170.4, 170.6; HRMS (ESI) $C_{30}H_{40}N_2O_8S$ $[M + Na]^+$ 611.2402; found 611.2395.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(4-chlorophenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9b**):*



Yield 1.04 g, 67%; colorless solid; mp 155−156 °C; $[\alpha]_{25}^{D}$ +23.4 (*c* 0.6, $CHCl_3$); 94% ee (Chiracel AS-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 27.2 min (minor), t_r = 30.6 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1156, 1238, 1512, 1711; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.40 (s, 9H), 1.96 (dd, *J* = 6.1, 10.9 Hz, 1H), 2.42 (s, 3H), 2.54−2.63 (m, 3H), 3.14 (t, *J* = 8.5 Hz, 1H), 3.41 (br s,1H), 3.99−4.03 (m, 1H), 4.06−4.15 (m, 3H), 4.65 (d, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.95 (br s,1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.30 (dd, *J* = 2.4, 7.9 Hz, 4H), 7.69 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 21.5, 28.1, 33.2, 40.4, 46.7, 48.0, 52.5, 60.7, 61.3, 63.1, 80.3, 127.3, 129.0, 129.6, 133.5, 135.3, 138.8, 143.7, 155.3, 170.3, 170.6; HRMS (ESI) calcd for $C_{30}H_{39}ClN_2O_8S$ $[M + Na]^+$ 645.2013; found 645.2001.

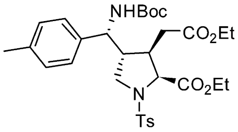
*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(4-(trifluoromethyl)phenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9c**):*



Yield 1.11 g, 68%; colorless solid; mp 169−170 °C; $[\alpha]_{25}^{D}$ +12.1 (*c* 0.4, $CHCl_3$); 99% ee (Chiracel OJ-H (250 × 4.6 mm), *n*-hexane/*i*-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 18.9 min (minor), t_r = 27.9 min (major);IR ($CHCl_3$, cm^{-1}) ν_{max} 1159, 1319, 1513, 1599, 1735; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (dd, *J* = 7.3, 9.1 Hz, 6H), 1.40 (s, 9H), 1.99 (dd, *J* = 5.4, 10.6 Hz, 1H), 2.43 (s, 3H), 2.54−2.60 (m, 2H),

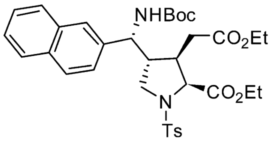
2.67 (s, 1H), 3.20 (t, J = 8.5 Hz, 1H), 3.37 (t, J = 7.6 Hz, 1H), 4.02–4.14 (m, 4H), 4.64 (d, J = 7.3 Hz, 1H), 4.88 (s, 1H), 5.26 (d, J = 8.8 Hz, 1H), 7.31 (t, J = 8.2 Hz, 4H), 7.57(d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 21.6, 28.2, 33.2, 40.5, 46.7, 47.9, 52.7, 60.7, 61.3, 63.0, 80.3, 122.8 (q, J = 271.8 Hz), 125.9, 126.4, 127.1 (q, J = 28.3 Hz), 127.4, 129.6, 130.1 (q, J = 33.3 Hz), 135.5, 143.6 (d, J = 271.8 Hz), 155.3, 170.3, 170.5; HRMS (ESI) calcd for $C_{31}H_{39}F_3N_2O_8S$ $[M + Na]^+$ 679.2271; found 679.2271.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(p-tolyl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9d**):*



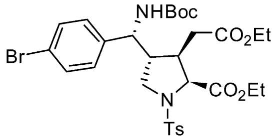
Yield 1.17 g, 78%; colorless solid; mp 177–178 °C; $[\alpha]_{25}^{D}$ +10.9 (c 0.7, $CHCl_3$); 93% ee (Chiracel AS-H (250 × 4.6 mm), n-hexane/i-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 27.2 min (minor), t_r = 39.4 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1162, 1214, 1344, 1499, 1734; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (quint, J = 7.0 Hz, 6H), 1.39 (s, 9H), 1.88 (dd, J = 4.5, 11.6 Hz, 1H), 2.31 (s, 3H), 2.43 (s, 3H), 2.49–2.62 (m, 3H), 3.17 (t, J = 8.8 Hz, 1H), 3.46 (t, J = 7.6 Hz, 1H), 3.98–4.13 (m, 4H), 4.60 (d, J = 7.6 Hz, 1H), 4.74 (s, 1H), 5.02 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 21.0, 21.5, 28.2, 33.2, 40.5, 46.9, 48.4, 52.8, 60.5, 61.1, 63.2, 79.8, 125.8, 127.3, 129.6, 135.5, 137.2, 143.3, 155.3, 170.4, 170.6; HRMS (ESI+, m/z) calcd for $C_{31}H_{42}N_2O_8S$ $[M + Na]^+$ 625.2554; found 625.2558.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(naphthalen-2-yl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9e**):*



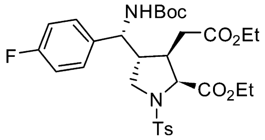
Yield 1.26 g, 79%; colorless solid; mp 160–161 °C; $[\alpha]_{25}^{D}$ +22.7 (c 0.5, $CHCl_3$); 92% ee (Chiracel AS-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 17.8 min (minor), t_r = 26.9 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1163, 1214, 1514, 1738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 6H), 1.41 (s, 9H), 1.95 (dd, J = 4.8, 11.9 Hz, 1H), 2.41 (s, 3H), 2.60 (d, J = 11 Hz, 2H), 2.78 (s, 1H), 3.25 (t, J = 8.8 Hz, 1H), 3.45 (t, J = 7.5 Hz, 1H), 3.99–4.13 (m, 4H), 4.65 (d, J = 7.5 Hz, 1H), 4.98 (s, 1H), 5.19 (s, 1H), 7.26 (d, J = 8.0 Hz, 3H), 7.46 (t, J = 3.9 Hz, 2H), 7.60 (s, 1H), 7.67 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 8.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 21.5, 28.2, 33.3, 40.6, 46.8, 48.3, 53.2, 60.5, 61.2, 63.2, 80.0, 123.9, 124.6, 126.1, 126.4, 127.3, 127.6, 127.9, 128.9, 129.6, 132.7, 133.2, 135.5, 137.5, 143.4, 155.4, 170.4, 170.6; HRMS (ESI) calcd for $C_{34}H_{42}N_2O_8S$ $[M + Na]^+$ 661.2559; found 661.2555.

*Ethyl (2S,3R,4R)-4-((R)-(4-Bromophenyl)((tert-butoxycarbonyl)-amino)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9f**):*



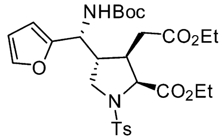
Yield 1.27 g, 76%; colorless solid; mp 161–163 °C; $[\alpha]_{25}^{D}$ +17.4 (c 0.5, $CHCl_3$); 99% ee (Chiracel OJ-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 24.0 min; IR ($CHCl_3$, cm^{-1}) ν_{max} 1155, 1237, 1737, 1511, 1718; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (q, J = 7.2, 7.33 Hz, 6H), 1.40 (s, 9H), 1.96 (dd, J = 6.9, 10.48 Hz, 1H), 2.44 (s, 3H), 2.52–2.60 (m, 3H), 3.15 (t, J = 8.9 Hz, 1H), 3.39 (t, J = 8.4 Hz, 1H), 4.0–4.17 (m, 4H), 4.62 (d, J = 7.0 Hz, 1H), 4.78 (s, 1H), 5.04 (d, J = 9.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.1, 21.5, 28.2, 33.2, 40.4, 46.6, 48.1, 52.6, 60.7, 61.3, 63.1, 80.2, 121.5, 127.2, 127.4, 127.6, 129.6, 131.9, 132.1, 135.3, 139.3, 143.7, 155.3, 170.3, 170.6; HRMS (ESI) calcd for $C_{30}H_{39}BrN_2O_8S$ $[M + Na]^+$ 689.1507; found 689.1517.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(4-fluorophenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9g**):*



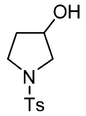
Yield 1.07 g, 71%; colorless solid; mp 148–150 °C; $[\alpha]_{25}^{D}$ +13.2 (c 0.5, $CHCl_3$); 92% ee (Chiracel AS-H (250 × 4.6 mm), n-hexane/i-PrOH, 90:10, 0.5 mL/min, 254 nm), t_r = 17.5 min (minor), t_r = 22.7 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1161, 1214, 1344, 1510, 1736; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J = 7.0 Hz, 3H), 1.24 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H), 1.93 (dd, J = 5.9, 11.0 Hz, 1H), 2.43 (s, 3H), 2.50–2.58 (m, 2H), 2.63 (br s, 1H), 3.15 (t, J = 8.5 Hz, 1H), 3.45 (s,1H), 4.0–4.12 (m, 4H), 4.64 (d, J = 7.6 Hz, 1H), 4.78 (s, 1H), 4.91 (s, 1H), 7.01 (t, J = 8.5 Hz, 2H), 7.13 (dd, J = 2.7, 8.5 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 21.6, 28.2, 28.3, 33.2, 40.6, 46.8, 48.3, 52.6, 60.6, 61.2, 63.2, 80.1, 115.7, 115.9, 127.3, 127.6, 127.7, 129.6, 135.5, 136.2, 143.5, 155.3, 161.0 (d, J = 247 Hz), 170.4, 170.5; HRMS (ESI) calcd for $C_{30}H_{39}FN_2O_8S$ $[M + Na]^+$ 629.2303; found 629.2307.

*Ethyl (2S,3R,4R)-4-((R)-((tert-Butoxycarbonyl)amino)(furan-2-yl)-methyl)-3-(2-ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**9h**):*



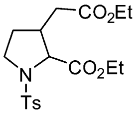
Yield 0.861 g, 60%; gum; $[\alpha]_{25}^{D}$ +34.0 (c 0.9, $CHCl_3$); 92% ee (Chiracel AS-H (250 × 4.6 mm), n-hexane/i-PrOH, 80:20, 0.5 mL/min, 254 nm), t_r = 17.0 min (minor), t_r = 20.7 min (major); IR ($CHCl_3$, cm^{-1}) ν_{max} 1162, 1344, 1513, 1599, 1735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.40 (s, 9H), 1.95 (q, J = 11.1, 5.9 Hz, 1H), 2.44 (s, 4H), 2.58 (s, 1H), 2.68 (m, 1H), 3.20 (t, J = 9.3 Hz, 1H), 3.56 (t, J = 8.4 Hz, 1H), 4.04–4.17 (m, 4H), 4.58 (d, J = 7.9 Hz, 1H), 4.87 (s, 2H), 6.13 (d, J = 3.1 Hz, 1H), 6.28 (br s, 1H), 7.33 (d, J = 7.7 Hz, 3H), 7.69 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 21.6, 28.2, 33.0, 40.2, 45.5, 47.4, 48.4, 60.6, 61.2, 63.0, 80.2, 106.6, 110.5, 127.4, 129.6, 135.8, 142.2, 143.3, 152.6, 155.3, 170.4, 170.7; HRMS (ESI+, m/z) calcd for $C_{28}H_{38}N_2O_9S$) $[M + Na]^+$ 601.2195; found 601.2197.

*1-Tosylpyrrolidin-3-ol (**5**):*



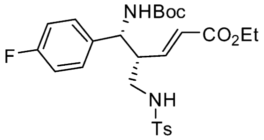
Yield 570 mg, 95%; gum; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.81–1.95 (m, 2H), 2.16 (d, J = 4.0 Hz, 1H), 2.43 (s, 3H), 3.25 (d, J = 11.0 Hz, 1H), 3.30–3.40 (m, 3H), 4.35 (s, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 33.8, 45.9, 55.8, 70.29, 127.4, 129.5, 133.4, 143.3. Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.66; H, 6.19; N, 5.70; S, 13.22.

*Ethyl 3-(2-Ethoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (**6**):*



Yield 860 mg, 90%; gum; IR ($CHCl_3$, cm^{-1}) ν_{max} 1162, 1344, 1513, 1735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22–1.31 (m, 6H), 1.72–2.32 (m, 4H), 2.43 (s, 3H), 2.50–2.74 (m,1H), 3.02–3.30 (m, 1H), 3.62 (t, J = 8.4 Hz, 1H), 3.96–4.22 (m, 4H), 4.35 (d, J = 8.3 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H),7.70 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 14.0, 21.3, 29.6, 34.2, 38.5, 43.0, 60.5, 61.0, 62.3, 65.1, 127.2, 129.5, 135.2, 143.2, 170.1, 170.6. Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.38; H, 6.57; N, 3.65; S, 8.36. Found: C, 56.30; H, 6.50; N, 3.61; S, 8.30.

*Ethyl (4R,5R,E)-5-((tert-Butoxycarbonyl)amino)-5-(4-fluorophenyl)-4-(((4-methylphenyl)sulfonamido)methyl)pent-2-enoate (**10**):*



Yield 75%; gum; IR (CHCl$_3$, cm^{-1}) ν_{max} 1161, 1214, 1344, 1510, 1736; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 2.42 (s, 3H), 2.79–2.82 (m, 1H), 2.85–2.90 (m, 1H), 3.18 (s,1H), 4.08 (q, *J* = 8.5 Hz, 2H), 4.68 (s, 1H), 5.14 (s, 1H), 5.64 (d, *J* = 15.5 Hz, 1H), 5.78 (s, 1H), 6.53 (dd, *J* = 9.1, 14.9 Hz, 1H), 6.96 (d, *J* = 8.24 Hz, 2H), 7.13 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.1, 21.4, 28.2, 43.8, 47.9, 54.9, 60.3, 80.1, 115.5, 115.7, 125.1, 127.0, 128.7, 129.6, 134.9, 136.8, 143.2, 144.4, 155.3, 161.1 (d, *J* = 247 Hz),165.3. Anal. Calcd for $C_{26}H_{33}FN_2O_6S$: C, 59.98; H, 6.39; N, 5.38; S, 6.16. Found: C, 60.0; H, 6.40; N, 5.36; S, 6.18.

■ ASSOCIATED CONTENT

Supporting Information

Full compound characterization and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +91 20 25902547. Fax: +91 20 25902676. E-mail: a.sudalai@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We sincerely thank CSIR, New Delhi, India (Indus MAGIC project CSC-0123) and DST (No. SR/S1/OC-67/2010) for financial support. R.D.A. and B.S.K. thank CSIR, New Delhi, India for research fellowships. We thank Dr. Rajesh G. Gonnade and Mr. Shridhar Thorat (Center for Materials Characterization, CSIR-NCL) for assistance with X-ray crystallography.

■ REFERENCES

(1) (a) Pearson, W. H. In *Studies in Natural Product Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: New York, 1988; Vol. *1*, pp 323–358. (b) Bindra, J. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. *14*, pp 84121. (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (d) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735.

(2) (a) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615. (b) Agbodjan, A. A.; Cooley, B. E.; Copley, R. C. B.; Corfield, J. A.; Flanagan, R. C.; Glover, B. N.; Guidetti, R.; Haigh, D.; Howes, P. D.; Jackson, M. M.; Matsuoka, R. T.; Medhurst, K. J.; Millar, A.; Sharp, M. J.; Slater, M. J.; Toczko, J. F.; Xie, S. *J. Org. Chem.* **2008**, *73*, 3094. (c) Nájera, C.; de Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2007**, 5038. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (e) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenana, R. M.; Dhanaka, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1553. (f) Lynch, J. E.; English, A. R.; Bank, H.; Deligianis, H. *Antibiot. Chemother.* **1954**, *4*, 844. (g) Clayden, J.; Read, B.; Hebditch, K. R. *Tetrahedron* **2005**, *61*, 5713.

(3) (a) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1997**, *38*, 7669. (b) Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett.* **2003**, *5*, 4915. (c) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487. (d) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (e) Pearson, W. H.; Dietz, A.; Stoy, P. *Org. Lett.* **2004**, *6*, 1005. (f) Ayan, S.; Dogan, O.; Ivantcova, P. M.; Datsuk, N. G.; Shulga, D. A.; Chupakhin, V. I.; Zabolotnev, D. V.; Kudryavtsev, K. V. *Tetrahedron: Asymmetry* **2013**, *24*, 838. (g) Randjelovica, J.; Simica, M.; Tasica, G.; Husinecb, S.; Savic, V. *Curr. Org. Chem.* **2014**, *18*, 1073. (h) Li, J.; Wang, J.; Xu, Z.; Zhu, S. *ACS Comb. Sci.* **2014**, *16*, 506. (i) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2576.

(4) (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893 and references cited therein. (b) Zhu, S.; Ye, L.; Wu, W.; Jiang, H. *Tetrahedron* **2013**, *69*, 10375. (c) Barber, D. M.; Duris, A.; Thompson, A. L.; Sanganee, H. J.; Dixon, D. J. *ACS Catal.* **2014**, *4*, 634. (d) Natori, Y.; Kikuchi, S.; Kondo, T.; Saito, Y.; Yoshimura, Y.; Takahata, H. *Org. Biomol. Chem.* **2014**, *12*, 1983.

(5) (a) Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron Lett.* **1998**, *39*, 5755 and references cited therein. (b) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389.

(6) Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385 and references cited therein.

(7) Coldham, I.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennall, G. P. *Synthesis* **2001**, *10*, 1523.

(8) (a) Besev, M.; Engman, L. *Org. Lett.* **2002**, *4*, 3023. (b) Aurrecoechea, J. M.; Fernandez, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345 and references cited therein.

(9) (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471. (b) Dion, I.; Vincent Rocan, J.-F.; Zhang, L.; Cebrowski, P. H.; Lebrun, M.-E.; Pfeiffer, J. Y.; Bedard, A.-C.; Beauchemin, A. M. *J. Org. Chem.* **2013**, *78*, 12735. (c) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K. *J. Am. Chem. Soc.* **2014**, *136*, 13534.

(10) (a) Sletten, E. M.; Liotta, L. J. *J. Org. Chem.* **2006**, *71*, 1335. (b) De Raadt, A.; Ekhart, C. W.; Ebner, M.; Stutz, A. E. *Top. Curr. Chem.* **1997**, *187*, 157. (c) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *ACS Symp. Ser.* **1989**, *386*, 107. (d) Zhao, H.; Cheng, S.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761. (e) Ansaria, A. A.; Vankar, Y. D. *RSC Adv.* **2014**, *4*, 12555.

(11) (a) Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 4541. (b) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053.

(12) (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, *15*, 2670. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Cren, S.; Wilson, C.; Thomas, N. R. *Org. Lett.* **2005**, *7*, 3521.

(13) En, D.; Zou, G.-F.; Guo, Y.; Liao, W.-W. *J. Org. Chem.* **2014**, *79*, 4456.

(14) (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Kumar, B. S.; Venkataramasubramanian, V.; Sudalai, A. *Org. Lett.* **2012**, *14*, 2468.

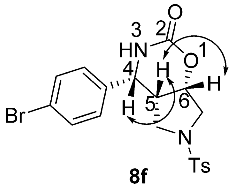
(15) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400.

(16) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(17) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.

(18) See general experimental procedure.

(19) The relative stereochemistry of **8f** was confirmed by COSY and NOESY studies. A significant NOESY correlation was observed between H_6–H_5 and H_5–H_4, confirming a *syn* relationship between H_6, H_5, and H_4.



8f

(20) Kwan, E. E.; Scheerer, J. R.; Evans, D. A. *J. Org. Chem.* **2013**, *78*, 175. (b) Yokoyama, Y.; Tsuchikura, K. *Tetrahedron Lett.* **1992**, *33*, 2823.

DOI: 10.1021/jo5028886
J. Org. Chem. 2015, 80, 2024−2031