Tetrahedron Letters 51 (2010) 3412–3416

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$Sc(OTf)_3$-catalyzed intramolecular aza-Prins cyclization for the synthesis of heterobicycles

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ARTICLE INFO

Article history:
Received 22 February 2010
Revised 21 April 2010
Accepted 23 April 2010
Available online 28 April 2010

Keywords:
Lewis acids
Intramolecular aza-Prins cyclization
Homoallyl amide
Heterobicycles

ABSTRACT

The coupling of (*E*)- and (*Z*)-hex-3-ene-1,6-ditosylamide with various aldehydes in the presence of 10 mol % $Sc(OTf)_3$ gave the corresponding *trans*- and *cis*-fused 1,5-ditosyl-octahydro-1*H*-pyrrolo[3,2-*c*]-pyridines, respectively, in good yields via intramolecular aza-Prins cyclization, whereas the coupling of (*E*)- and (*Z*)-*N*-(6-hydroxyhex-3-enyl)-4-methylbenzenesulfonamide afforded the corresponding *trans*- and *cis*-fused octahydro-1-tosylpyrano[4,3-*b*]pyrroles derivatives, respectively, via intramolecular Prins-cyclization.

The aza-Prins cyclization is one of the most elegant approaches for the synthesis of piperidine derivatives.[1–3] Recently, an intramolecular version of Prins cyclization has also been reported for the synthesis of angularly fused furano[3,2-*c*]pyrans.[4,5] However, there have been no reports on intramolecular aza-Prins cyclization of bis-homoallylic amide with aldehydes. Lewis acid-catalyzed carbon–carbon bond forming reactions are of great importance in organic synthesis because of their high reactivity, selectivity, and mild reaction conditions.[6] Of these, lanthanide triflates are unique Lewis acids that are currently of great research interest. They are highly oxophilic and form strong but labile bonds with oxygen donor ligands. This feature has often allowed sub-stoichiometric amounts of the lanthanide Lewis acid to be used to promote a variety of reactions. Indeed, such Lewis acids are found to be effective in promoting many organic transformations.[7]

In continuation of our interest in the catalytic application of scandium triflate for various transformations,[8] we herein report a new method for the synthesis of diaza-bicycles by means of intramolecular aza-Prins cyclization of hex-3-ene-1,6-ditosylamide with aldehydes. This approach will be highly complementary to our previous results, dealing with the condensation of the same substrates with epoxides and in the presence of *p*-toluenesulfonic acid.[9]

Initially, we attempted the coupling of (*E*)-hex-3-ene-1,6-ditosylamide (**1**) with cinnamaldehyde (**2**) in the presence of 10 mol % of $Sc(OTf)_3$ in 1,2-dichloroethane. The reaction proceeded smoothly at 80 °C and the corresponding *trans*-fused octahydropyrrolo[3,2-*c*]pyridine **3a** was obtained in 78% yield as a major product (Scheme 1).

The *cis*- and *trans*-isomers could easily be separated by silica gel column chromatography. The ratio of *trans*/*cis*-isomers was determined by ^{1}H NMR spectra of the crude product. This result provided incentive for further study of reactions with various aldehydes. Interestingly, the coupling of (*Z*)-hex-3-ene-1,6-ditosylamide with *p*-bromobenzaldehyde in the presence of 10 mol % $Sc(OTf)_3$ in 1,2-dichloroethane at 80 °C gave the *cis*-fused octahydropyrrolo[3,2-*c*]pyridine **3b** exclusively in 65% yield (Scheme 2).

The structure and stereochemistry of product **3b** were established by ^{1}H NMR and NOE experiments. Due to aromatic group, the chemical shift at 5.1 ppm is assigned to proton H_1 and the small coupling (J = 1.6 Hz) between H_1 and H_2 indicates that H_2 is in equatorial orientation. This is further confirmed by the presence of NOE between H_1 and H_2 and the absence of NOE between H_2 and one of the H_4 protons, which is showing large coupling with H_3 (J = 9.4 Hz). H_3 and one of the H_5 also show NOE with *p*-bromophenyl group indicating axial orientation of *p*-bromophenyl group. Based on the coupling constants and NOE correlations, it is confirmed that H_2 is in equatorial orientation and the fusion of the six-membered and five-membered rings is in *cis* fusion. The double-edged arrows show characteristic NOE correlations (Fig. 1).

Further, the structure of **3b** was confirmed by X-ray crystallography and the corresponding ORTEP diagram is given in Figure 2.[10]

The coupling of (*E*)-hex-3-ene-1,6-ditosylamide with *p*-bromobenzaldehyde gave *trans*-isomer **3c** as a major product. The structure of product **3c** was also established by NOE experiments. The

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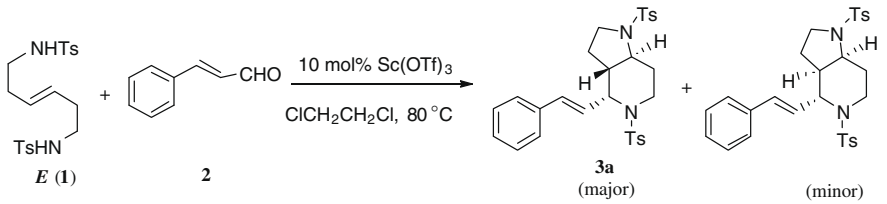
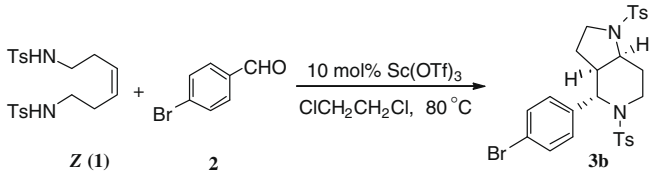
doi:10.1016/j.tetlet.2010.04.093



Scheme 1. Aza-Prins cyclization of *E*-olefin with cinnamaldehyde.



Scheme 2. Aza-Prins cyclization of *Z*-olefin with *p*-bromobenzaldehyde.

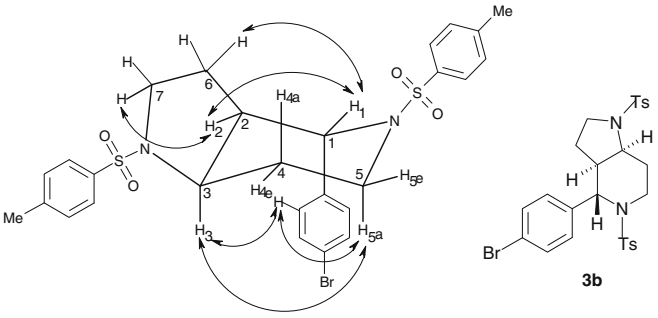


Figure 1. Characteristic NOE's and chemical structure of **3b**.

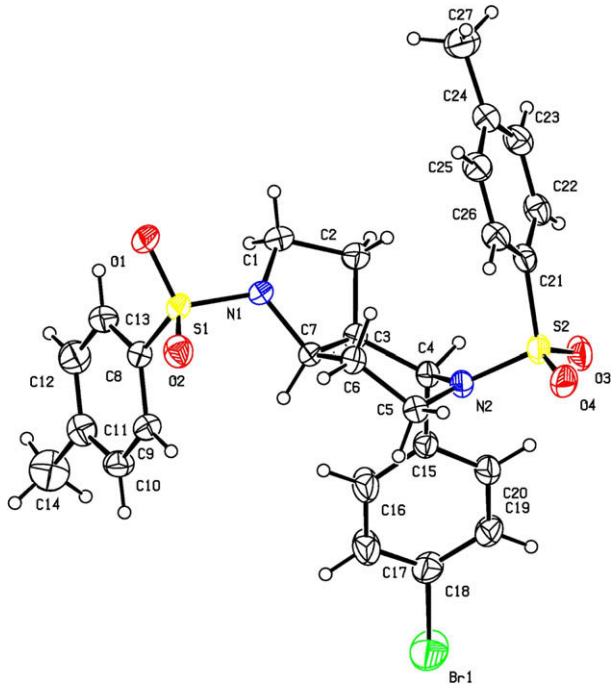


Figure 2. ORTEP diagram of product **3b**.

large coupling between H_1 and H_2 (J = 10.9 Hz) and between H_2 and H_3 (J = 11.2 Hz) indicates that H_2 is in axial orientation. The NOE correlations between H_2 and H_5 and between H_1 and H_3 confirm that the six-membered ring takes a boat conformation. Based on these observations, it is confirmed that H_2 and H_3 are in axial orientation and the fusion between six-membered and five-membered rings is *trans* fusion. The double-edged arrows show characteristic NOE correlations (Fig. 3).

Other aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde, and thiophene-2-carbaldehyde were not so effective for the aza-Prins cyclization. Ketones such as cyclohexanone also failed to give the spiro-diaza-bicyclic product. However, aliphatic aldehydes such as 3-methylbutanal, cyclohexanecarboxaldehyde, and *n*-propionaldehyde participated well in this reaction (Table 1, entries **d**, **e**, and **f**).

Encouraged by the results obtained from hex-3-ene-1,6-ditosylamide, we turned our attention to the Prins cyclization of *N*-(6-hydroxyhex-3-enyl)-4-methylbenzenesulfonamide with aldehydes. Accordingly, treatment of (*E*)-*N*-(6-hydroxyhex-3-enyl)-4-methylbenzenesulfonamide with *o*-nitrobenzaldehyde in the presence of 10 mol % $Sc(OTf)_3$ in 1,2-dichloroethane at 80 °C gave the *trans*-fused octahydropyrano[4,3-*b*]pyrrole **3g** in 80% yield (Scheme 3).

The structure of **3g** was determined by NOE experiments. The chemical shift value of δ 4.84 for proton H_1 prompted us to fix the position of the oxygen as shown in Figure 5. This is because of the electronegative effect of oxygen and aromatic group. It shows a doublet with J = 9.8 Hz coupling, which is an indication that H_1 and H_2 are in axial position. In addition, H_2 also shows large coupling (J = 10.9 Hz) with H_3 indicating an axial position for H_3 proton. From these observations, we can confirm that the fusion of pyran and pyrrolidine rings is in *trans* fusion. H_2 also shows NOE with one of the H_4 protons, which exhibits a large coupling (J = 10.9 Hz) with H_3 and one of the H_5 protons. Based on the coupling constants and NOE correlations, the conformation of **3g** is as shown in Figure 4. The double-edged arrows show NOE correlations.

On the other hand, the Prins cyclization of (*Z*)-*N*-(6-hydroxyhex-3-enyl)-4-methylbenzene-sulfonamide with aldehydes under similar conditions gave *cis*-fused oxa-aza-bicyclic products exclusively (Scheme 4).

The structure of **3h** was also established by extensive NMR experiments. The positions of the oxygen and nitrogen atoms as shown in the figure were fixed based on the NMR spectral parameters like chemical shift and coupling constants. The coupling

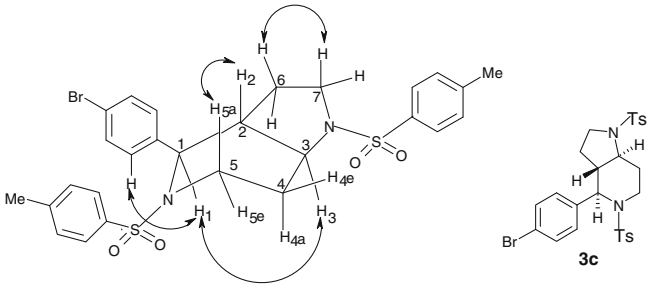


Figure 3. Characteristic NOE's and chemical structure of **3c**.

Table 1
$Sc(OTf)_3$-catalyzed synthesis of diaza- and oxa-aza-bicycles[a]

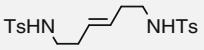
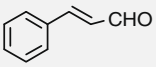
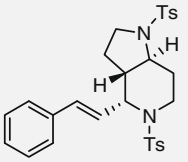
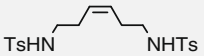
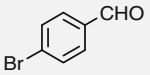
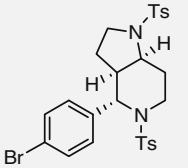
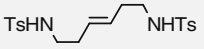
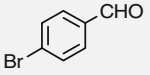
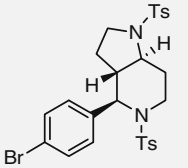
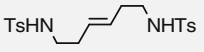
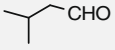
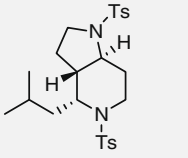
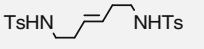
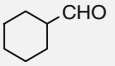
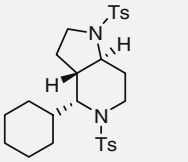
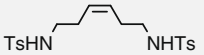
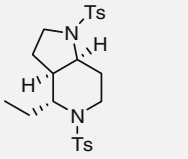
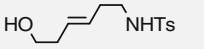
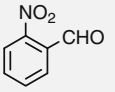
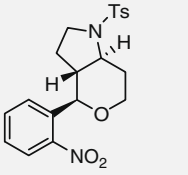
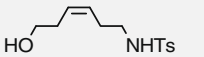
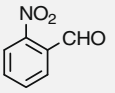
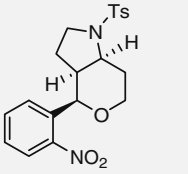
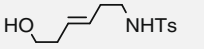
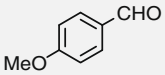
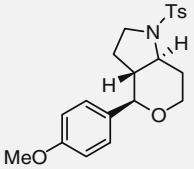
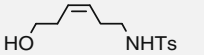
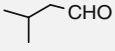
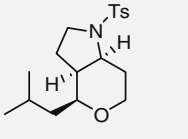
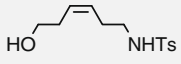
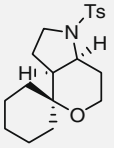
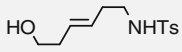
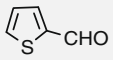
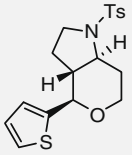
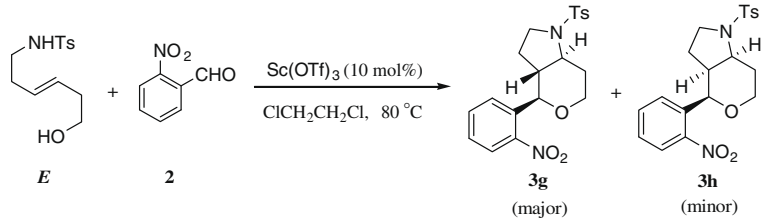
Entry	Olefin (**1**)	Aldehyde (**2**)	Product[b] (**3**)	Time (h)	Yield[c] (%)	*trans:cis* ratio[d]
a				6	78	95:05
b				11	65	—
c				10	67	90:10
d				6	70	95:05
e				7	73	95:05
f				5	66	—
g				5	80	95:05
h				6	77	—
i				6	75	95:05
j				4	70	—

Table 1 (*continued*)

Entry	Olefin (**1**)	Aldehyde (**2**)	Product[b] (**3**)	Time (h)	Yield[c] (%)	*trans:cis* ratio[d]
k				10	68	—
l				6	71	90:10

[a] Reaction was performed with 0.5 mmol olefin, 0.75 mmol aldehyde using 10 mol % $Sc(OTf)_3$ in $ClCH_2CH_2Cl$.
[b] All the products were characterized by ^1H and ^{13}C NMR, IR, and mass spectroscopy.
[c] Yield refers to pure product after column chromatography.
[d] *trans/cis* ratio was determined by ^1H NMR spectra of crude product.



Scheme 3. Prins cyclization of *E*-olefin with *o*-nitrobenzaldehyde.

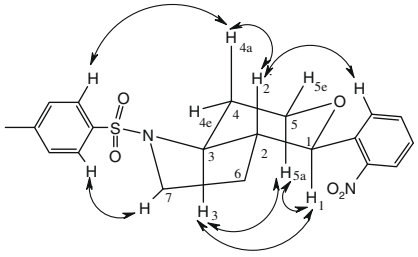


Figure 4. Characteristic NOE's of **3g**.

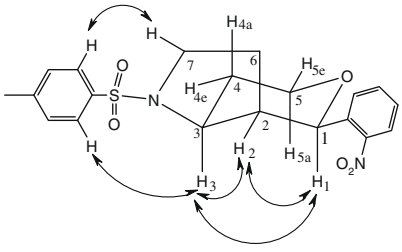
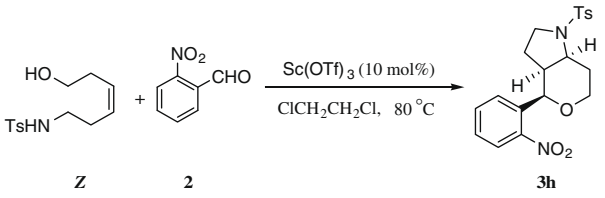


Figure 5. Characteristic NOE's of **3h**.



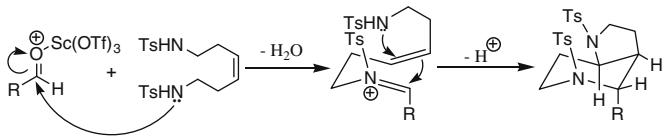
Scheme 4. Prins cyclization of *Z*-olefin with *o*-nitrobenzaldehyde.

between H_1 and H_2 protons is 3.2 Hz indicating that H_2 is in equatorial position. This is further confirmed by the small coupling between H_2 and H_3. Based on the coupling constant and the absence of NOE between H_2 and one of the H_4 protons, which shows large coupling with H_3, it was confirmed that the fusion between the six-membered and five-membered rings is in *cis* fusion. In contrast to *trans* fusion molecule, in this molecule, due to *cis* fusion, the aromatic protons of sulfonic acid deshield H_3 proton and shift to downfield. From these observations, the structure of the compound **3h** is as shown in Figure 5.

The scope of the reaction is illustrated with respect to various aldehydes and the results are summarized in Table 1.[11] Besides *o*-nitrobenzaldehyde, other aromatic aldehydes such as *p*-anisaldehyde, thiophene-2-carbaldehyde, and aliphatic aldehyde such as 3-methylbutanal also participated effectively in this conversion (Table 1, entries **i**, **l**, and **j**). Cyclic ketone such as cyclohexanone also gave the corresponding spiro-oxa-aza-bicycle under the reaction conditions (Table 1, entry **k**).

The effects of various Lewis acids such as $In(OTf)_3$ and $La(OTf)_3$ were studied for this conversion. Of these, $Sc(OTf)_3$ was found to give the best results in terms of yields. For instance, treatment of (*E*)-hex-3-ene-1,6-ditosylamide (**1**) with cinnamaldehyde (**2**) in the presence of 10 mol % of $Sc(OTf)_3$, $La(OTf)_3$, and $In(OTf)_3$ for 6 h gave the product **3a** in 78%, 45%, and 30% yield, respectively. This protocol is simple and convenient and also provides the desired products in good yields with high stereoselectivity. Mechanistically, the reaction proceeds likely via *N*-sulfonyl iminium ion formation from aldehyde and homoallylic tosylamine. The resulting *N*-sulfonyl iminium ion may undergo cyclization with olefin followed by the trapping of the resulting carbocation by terminal *N*-tosylamine group would result in the formation of octahydro-1*H*-pyrrolo[3,2-*c*]pyridine (Scheme 5).

In conclusion, we have developed a new method for the synthesis of octahydro-1*H*-pyrrolo[3,2-*c*]pyridines and octahydropyrano[4,



Scheme 5. A hypothetical reaction mechanism.

3-*b*]pyrroles by means of intramolecular aza-Prins and Prins cyclization, respectively. It is entirely a new approach for the synthesis of heterobicycles from aldehydes and bis-homoallyl derivatives in a one-pot operation. These molecules will be of much interest as part of our programs in medicinal chemistry.

Acknowledgments

This research has been performed as part of the Indo-French 'Joint Laboratory for Sustainable Chemistry at Interfaces'. We thank CSIR and CNRS for support. P.B. and P.P.C. thank CSIR, New Delhi, for the award of fellowships.

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10. *Crystal data*: $C_{27}H_{29}BrN_2O_4S_2$, $M = 589.55$, monoclinic, space group $P2_1/n$, $a = 16.0492(12)$ Å, $b = 10.5839(8)(4)$ Å, $c = 16.0966(12)(6)$ Å, $\beta = 99.636(1)°$, $V = 2695.6(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.453$ mg m^{-3}, $T = 294(2)$ K, $\mu = 1.716$ mm^{-1}, $F(0\,0\,0) = 1216$, $\lambda = 0.71073$ Å. Data collection yielded 25,387 reflection resulting in 4747 unique, averaged reflection, 3613 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final $R = 0.0486$, $wR = 0.1136$, and GOF = 1.032. Intensity data were measured on Bruker Smart Apex with CCD area detector. The crystal structure corresponding to product **3b** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 755175.
11. *Experimental procedure*: To a solution of (*E*)-hex-3-ene-1,6-ditosylamide (211 mg, 0.50 mmol) and cinnamaldehyde (99 mg, 0.75 mmol) in anhydrous 1,2-dichloroethane (5 mL) was added $Sc(OTf)_3$ (10 mol %) and heated at 80 °C for 6 h. After the completion of reaction as indicated by TLC, the organic layer was washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by column chromatography (silica gel, Merck, 100–200 mesh) using ethyl acetate/hexane. Elution starts with 50 mL 8% EtOAc in *n*-hexane, then with 50 mL (two drops of triethylamine) 13% EtOAc in *n*-hexane followed by 100 mL (four drops of triethylamine) 18% EtOAc in *n*-hexane to afford pure product **3a** (210 mg, 78% yield). The spectral data for selected products: Compound **3a**: (3a*R*,4*R*,7a*S*)-octahydro-4-styryl-1,5-ditosyl-1*H*-pyrrolo[3,2-*c*]pyridine: Solid, mp 86–89 °C; IR (KBr): ν_{max} 2926, 1340, 1161, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.54 (m, 4H), 7.30–7.18 (m, 5H), 7.08 (d, $J = 8.1$ Hz, 2H), 7.04–6.96 (m, 2H), 6.34 (d, $J = 15.7$ Hz, 1H), 5.60–5.48 (m, 1H), 4.93–4.84 (m, 1H), 4.00–3.88 (m, 1H), 3.41–3.23 (m, 2H), 2.97–2.75 (m, 2H), 2.58–2.38 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.16–1.99 (m, 1H), 1.79–1.59 (m, 2H), 1.15–0.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 143.2, 136.5, 135.3, 133.7, 130.9, 129.6, 129.4, 128.4, 128.1, 127.5, 126.3, 119.4, 58.7, 58.3, 48.0, 47.8, 40.6, 32.3, 25.3, 21.4, 21.3; ESI-MS: *m/z*: 537 (M^++H); HRMS calculated for $C_{29}H_{32}N_2O_4NaS_2$: 559.1701. Found: 559.1718. Compound **3b**: (3a*S*,4*S*,7a*S*)-4-(4-bromophenyl)-octahydro-1,5-ditosyl-1*H*-pyrrolo[3,2-*c*]pyridine: Solid, mp 161–165 °C; IR (KBr): ν_{max} 2925, 2856, 1337, 1161, 682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.58 (m, 4H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.32–7.22 (m, 4H), 6.96 (d, $J = 8.3$ Hz, 2H), 5.11 (broad s, 1H), 3.83–3.72 (m, 1H), 3.59–3.48 (m, 1H), 3.47–3.38 (m, 1H), 3.06 (q, $J = 9.1$ Hz 1H), 2.97–2.84 (m, 1H), 2.45 (s, 3H), 2.44 (s, 3H), 2.25–2.12 (m, 1H), 1.93–1.80 (m, 3H), 1.78–1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 143.6, 138.6, 137.2, 134.6, 131.6, 129.8, 129.7, 128.6, 127.3, 126.9, 121.5, 56.1, 54.5, 46.3, 40.8, 38.9, 28.2, 27.8, 21.5, 21.5; ESI-MS: *m/z*: 589 (M^++H); HRMS calculated for $C_{27}H_{29}N_2O_4NaS_2Br$: 611.0649. Found: 611.0645. Compound **3d**: (3a*S*,4*R*,7a*S*)-octahydro-4-isobutyl-1,5-ditosyl-1*H*-pyrrolo[3,2-*c*]pyridine: Liquid, IR (Neat): ν_{max} 2926, 1339, 1160, 763, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 8.1$ Hz, 2H), 7.30–7.18 (m, 4H), 4.30–4.20 (m, 1H), 3.83 (dd, $J = 15.1$ and 2.4 Hz, 1H), 3.26–3.08 (m, 2H), 2.95–2.66 (m, 2H), 2.37 (s, 6H), 2.28–2.17 (m, 1H), 1.68–1.44 (m, 3H), 1.34–1.12 (m, 3H), 1.09–0.95 (m, 1H), 0.82–0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 143.3, 138.1, 133.7, 129.8, 129.7, 127.4, 126.8, 58.0, 54.1, 47.7, 46.3, 39.3, 34.5, 32.0, 25.7, 24.5, 23.7, 21.5, 21.4; ESI-MS: *m/z*: 491 (M^++H); HRMS calculated for $C_{25}H_{34}N_2O_4NaS_2$: 513.1857. Found: 513.1850. Compound **3h**: (3a*S*,4*R*,7a*S*)-octahydro-4-(2-nitrophenyl)-1-tosylpyrano[4,3-*b*]pyrrole: Solid, mp 128–131 °C; IR (KBr): ν_{max} 2922, 2866, 1521, 1337, 1169, 710, 661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–7.87 (m, 1H), 7.75–7.67 (m, 3H), 7.61–7.52 (m, 1H), 7.42–7.29 (m, 3H), 5.20–5.16 (m, 1H), 4.15–4.01 (m, 2H), 3.64–3.44 (m, 2H), 3.03–2.91 (m, 1H), 2.46 (s, 3H), 2.12–1.91 (m, 3H), 1.90–1.72 (m, 1H), 1.10–0.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 143.3, 136.2, 135.4, 133.2, 129.8, 128.5, 128.0, 127.2, 124.5, 73.7, 66.5, 57.2, 46.5, 40.6, 29.8, 23.5, 21.6; ESI-MS: *m/z*: 403 (M^++H); HRMS calculated for $C_{20}H_{22}N_2O_5NaS$: 425.1147. Found: 425.1132. Compound **3k**: Solid, mp 102–104 °C; IR (KBr): ν_{max} 2930, 2878, 1335, 1159, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 4.01–3.91 (m, 1H), 3.64–3.42 (m, 3H), 3.15–3.03 (m, 1H), 2.45 (s, 3H), 2.10–1.93 (m, 2H), 1.87–1.68 (m, 2H), 1.67–1.09 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 135.8, 129.6, 127.1, 72.4, 57.9, 55.1, 46.3, 44.8, 36.2, 32.6, 29.3, 25.6, 23.7, 21.5, 21.3, 21.2; ESI-MS: *m/z*: 350 (M^++H); HRMS calculated for $C_{19}H_{27}NO_3NaS$: 372.1609. Found: 372.1624. Compound **3l**: (3a*R*,4*R*,7a*S*)-octahydro-4-(thiophen-2-yl)-1-tosylpyrano[4,3-*b*]pyrrole: Solid, mp 115–118 °C; IR (KBr): ν_{max} 2966, 2854, 1344, 1163, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.23–7.18 (m, 1H), 6.93–6.82 (m, 2H), 4.31 (d, $J = 9.8$ Hz, 1H), 4.26–4.16 (m, 1H), 3.51 (dt, $J = 12.1$ and 2.1 Hz, 1H), 3.43–3.21 (m, 2H), 2.66 (dt, $J = 10.9$ and 3.6 Hz, 1H), 2.52–2.42 (m, 4H), 2.05–1.83 (m, 2H), 1.73–1.58 (m, 1H), 1.25–1.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 142.7, 133.2, 129.7, 127.7, 126.5, 125.2, 124.4, 78.6, 66.4, 63.1, 50.8, 47.7, 33.4, 25.5, 21.5; ESI-MS: *m/z*: 386 (M^++Na); HRMS calculated for $C_{18}H_{21}NO_3NaS_2$: 386.0860. Found: 386.0870.