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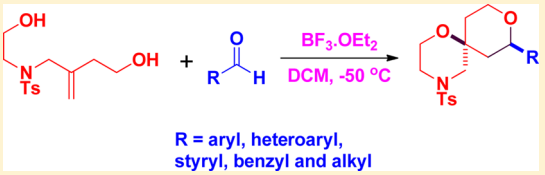
Prins Cascade Cyclization for the Synthesis of 1,9-Dioxa-4-azaspiro[5.5]undecane Derivatives

B. V. Subba Reddy,*[,†] Durgaprasad Medaboina,[†] B. Sridhar,[‡] and Kiran Kumar Singarapu[§]

[†]Natural Product Chemistry, [‡]Laboratory of X-ray Crystallography, and [§]Centre for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Supporting Information

ABSTRACT: A novel Prins cascade process for the synthesis of 1,9-dioxa-4- azaspiro[5.5]undecane derivatives by the coupling of aldehydes with *N*-(4-hydroxy-2-methylenebutyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide has been developed. This is the first report of the synthesis of spiromorpholinotetrahydropyran derivatives through a Prins bicyclization.



Spiroketal derivatives possessing a nitrogen atom have been evaluated as tachykinin antagonists. In particular, spiromorpholine derivatives have been found to exhibit high affinity and excellent central nervous system penetration.[1] They are known to display a broad spectrum of biological activities such as antiproliferative, anti-HIV, and NK_1 receptor antagonist behavior (Figure 1).[2,3] The Prins cyclization is a very useful

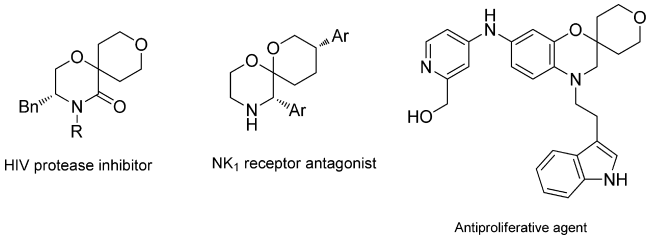


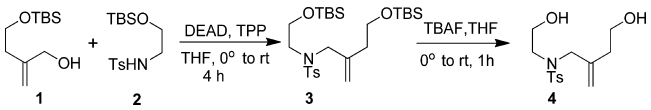
Figure 1. Biologically active spirotetrahydropyrans.

strategy for the construction of the tetrahydropyran ring system, which is a common structural unit in several natural products.[4] In particular, a tandem Prins reaction is a simple and one-pot strategy for the stereoselective synthesis of heterobicycles.[5,6] In spite of its potential applications in the synthesis of biologically active molecules,[7] the scope of a tandem Prins process for the synthesis of dioxaazaspiro[5.5]undecane derivatives from a readily accessible hydroxy-tethered homoallylic alcohol has not yet been explored.

Following our interest in Prins-type cyclizations for the synthesis of heterocycles,[8] we herein report a novel and efficient strategy for the synthesis of 1,9-dioxa-4-azaspiro[5.5]-undecane derivatives through a cascade of Prins reactions.

The requisite homoallyl alcohol, *N*-(4-hydroxy-2-methylenebutyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**4**), was prepared as shown in Scheme 1. Allyl alcohol **1** was prepared according to the literature procedure.[9] Accordingly, the coupling of **1** with aminoethanol derivative **2** under Mitsunobu conditions afforded the di-TBS derivative **3**, which

Scheme 1. Preparation of Starting Material 4



upon desilylation with TBAF gave the desired homoallyl alcohol **4**.

Initially, we attempted the coupling of diol **4** with *p*-chlorobenzaldehyde in the presence of 30 mol % $In(OTf)_3$. However, the corresponding 1,9-dioxa-4-azaspiro[5.5]undecane was obtained as a mixture of **6g** and **7g** in a 66:34 ratio (Table 1, entry a), which were unseparable by column chromatography. Therefore, to improve the selectivity, the above reaction was performed using various acid catalysts at different temperatures, and the results are presented in Table 1. It was observed that the **6g**/**7g** ratio differs with temperature. Interestingly, excellent selectivity for **6g** was obtained at −50 °C in the presence of 1.2 equiv of $BF_3{\cdot}OEt_2$. Under the optimized conditions, the required product **6g** was isolated in excellent yield (95%) and selectivity (92:8) (Table 1, entry e). The ratio of products was determined from the ^1H NMR spectrum of the crude mixture. However, the reaction did not proceed at −60 °C even when the amount of Lewis acid was increased from 1.2 to 2.4 equiv. Next, we examined the effect of the solvent on the conversion. Among the various solvents tested, such as dichloromethane, acetonitrile, tetrahydrofuran, benzene, and dichloroethane, dichloromethane gave the best results in terms of conversion.

The scope of this reaction was further evaluated using various aldehydes containing different electron-withdrawing and -donating substituents on the aromatic ring. As shown in Table 2, the product obtained depends upon the nature of the aldehyde and the electronic character of the substituent. It was observed that activated aromatic aldehydes (Table 2, entries k

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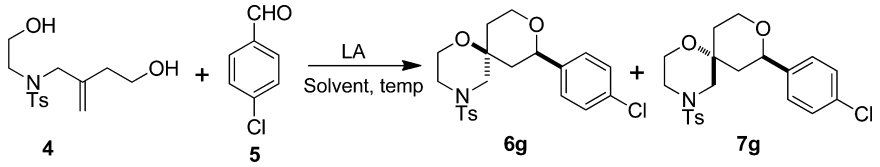
Table 1. Optimization of the Reaction Conditions



4 5 6g 7g

Entry	Lewis acid	Equiv	Solvent	T (°C)	t (h)	Yield (%)[a]	dr (**6g**:**7g**)[b]
a	$In(OTf)_3$	0.3	DCM	rt	3	90	66:34
b	$In(OTf)_3$	0.3	DCM	0	16	–	–
c	$In(OTf)_3$	0.3	DCE	rt	16	70	66:34
d	$Sc(OTf)_3$	0.3	DCM	rt	10	80	66:34
e	$InBr_3$	0.5	DCM	rt	12	–	–
f	$InCl_3$	0.5	DCM	rt	12	–	–
g	$BF_3{\cdot}OEt_2$	1.2	DCM	0	0.5	96	83:17
h	$BF_3{\cdot}OEt_2$	1.2	DCM	−20	0.5	96	89:11
i	**$BF_3{\cdot}OEt_2$**	**1.2**	DCM	**−50**	**0.5**	**95**	**92:8**
j	$BF_3{\cdot}OEt_2$	1.2	DCM	−60	10	–	–
k	$BF_3{\cdot}OEt_2$	2.4	DCM	−60	10	–	–
l	$BF_3{\cdot}OEt_2$	1.2	DCE	−50	1	80	92:8
m	$BF_3{\cdot}OEt_2$	1.2	benzene	−50	1	60	92:8
n	$BF_3{\cdot}OEt_2$	1.2	THF	−50	2	–	–
o	$BF_3{\cdot}OEt_2$	1.2	AcCN	−50	2	–	–
p	TMSOTf	2.4	DCM	−60	10	–	–

[a]Yields refer to the pure products after column chromatography. [b]The product ratios were determined by ^{1}H NMR analysis.

and l) gave the products in slightly lower yields than the halogenated or alkyl-substituted aromatic counterparts. Surprisingly, nitro-substituted benzaldehyde failed to give the desired product at −50 °C. Though the above reaction was successful at room temperature, the **6**:**7** selectivity was very low (approximately a 1:1 ratio).

This method works not only with aromatic aldehydes but also with acid-sensitive cinnamaldehyde and phenylacetaldehyde (Table 2, entries m and n) as well as sterically hindered 2-naphthaldehyde (Table 2, entry e). The efficiency of this method was also exemplified by performing the reaction with aliphatic aldehydes (Table 2, entries q and r) and the heterocyclic aldehyde thiophene-2-carboxaldehyde (Table 2, entry p). Finally, we attempted to remove the tosyl protecting group with lithium naphthalenide. Accordingly, treatment of *N*-tosyl spiropyranomorpholine **6b** with 10 equiv of lithium naphthalenide in THF at −50 °C gave the desired free amine **8** in 80% yield (Scheme 2).

Furthermore, we performed the reaction with homoallylic substrates **9** and **10** bearing *N*-Boc and *N*-Cbz protecting groups, respectively, instead of the *N*-Ts group, but no desired product was obtained with either of these protecting groups. These results clearly reveal that the reaction was successful only with *N*-tosyl protection.

The structure of major isomer **6i** was confirmed by X-ray crystallography.[10] Furthermore, the structure and stereochemistry of **6g** and **7g** were established by detailed 1D and 2D NMR experiments (Figure 2). When the reaction was run at room temperature using 30 mol % $In(OTf)_3$, the diastereomeric ratio of **6g** and **7g** was 10:4, which was measured by integrating the isolated peaks at 4.36 and 4.60 ppm. The ^3J coupling constants $^3J_{H8-H7}$ = 2.3 Hz and $^3J_{H8-H7'}$ = 12.0 Hz for the major isomer and $^3J_{H8-H7}$ = 2.2 Hz and $^3J_{H8-H7'}$ = 11.6 Hz for the minor isomer along with the presence of an NOE cross-peak between H8 and H10′ for both isomers indicate that the stereocenter at carbon C8 is the same in both isomers, having H8 in an axial position and the aryl group in an equatorial position. The large coupling constants $^3J_{H8-H7'}$ = 12.0 Hz and $^3J_{H11'-H10'}$ = 13.2 Hz for the major isomer and $^3J_{H8-H7'}$ = 11.6 Hz for the minor isomer and the presence of NOE cross-peaks between H8 and H10′$_{(ax)}$ and between H7′$_{(ax)}$ and H11′$_{(ax)}$ indicate that the six-membered ring is in the $^9C_6$ chair conformation. The stereochemistry of the major isomer at the spiro center was determined by the appearance of NOE cross-peaks between H8 and H5, H8 and H5′$_{(ax)}$, H5′$_{(ax)}$ and H7, H5 and H7, and H10′$_{(ax)}$ and H5, which indicate that the oxygen is in the equatorial position and the methylene group in the axial position on the six-membered tetrahydropyran ring, as shown in Figure 2. The appearance of NOE cross-peaks between H7′$_{(ax)}$ and H5′$_{(ax)}$, H11′$_{(ax)}$ and H5′$_{(ax)}$, and H11 and H2 in the minor isomer supports the presence of methylene in the equatorial position and oxygen in the axial position on the tetrahydropyran ring.

In order to explain the stereochemical outcome of the Prins cyclization, the reaction is proposed to proceed via the formation of oxocarbenium ion **A** from the aldehyde and the homoallylic alcohol, likely after activation with $BF_3{\cdot}OEt_2$. The oxocarbenium ion is attacked by the internal olefin, resulting in the formation of tertiary carbocation **B**, which is simultaneously trapped by the tethered hydroxyl group, leading to the formation of the spirocycle as depicted in Scheme 3. The exceptional diastereoselectivity in favor of the major isomer **6** is believed to originate from the favorable trapping of the carbocation from the less hindered equatorial side to overcome the unfavorable 1,3-diaxial interactions, as shown in Scheme 3. The interconversion of the chair conformation **B** to the less favored conformation **C** in which the R group is placed in the axial position is more rapid at room temperature than at low temperature, which may be responsible for the formation of the minor isomer **7** at room temperature.

In conclusion, a novel Prins cascade strategy has been developed for the synthesis of 1,9-dioxa-4-azaspiro[5.5]-

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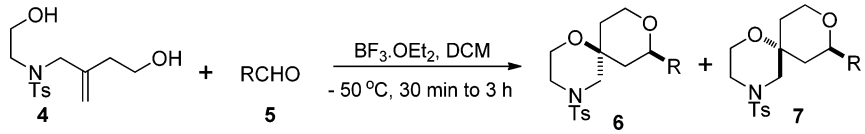
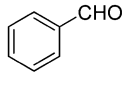
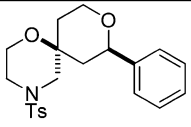
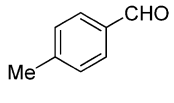
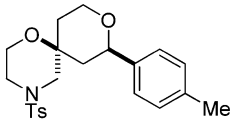
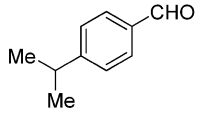
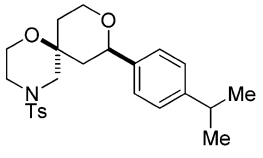
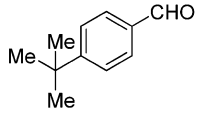
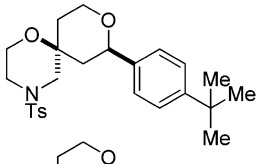
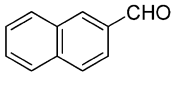
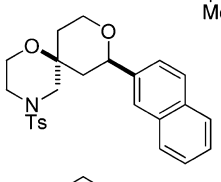
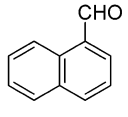
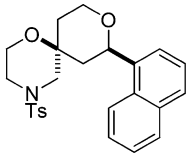
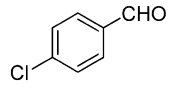
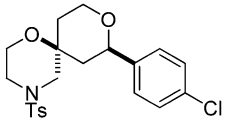
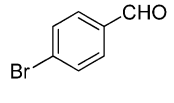
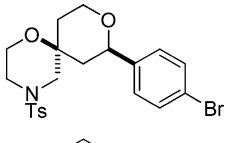
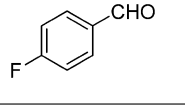
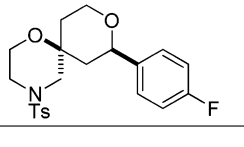
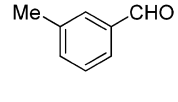
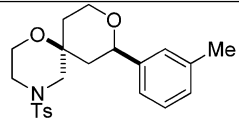
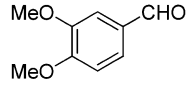
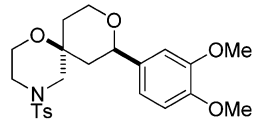
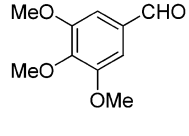
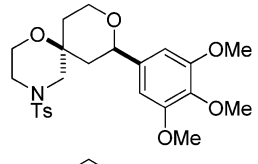
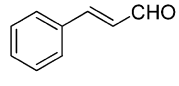
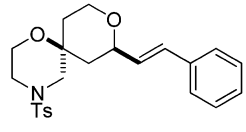
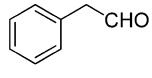
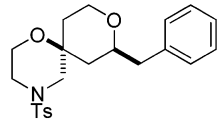
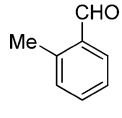
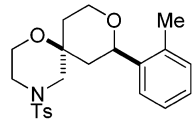
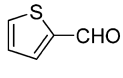
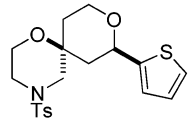
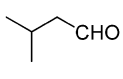
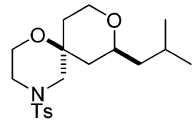
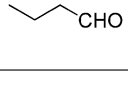
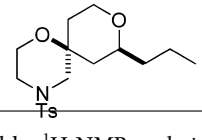
Table 2. Preparation of Azaspiro[5.5]undecane Scaffolds through a Prins Bicyclization



Entry	Aldehyde (**5**)	Product (**6**)	Yield[a] (%)	dr (**6**:**7**)[b]
a			90	96:4
b			95	97:3
c			90	99:1
d			90	98:2
e			85	97:3
f			82	98:2
g			95	92:8
h			90	97:3
i			95	94:6
j			90	93:7
k			83	96:4
l			85	95:5
m			75	95:5
n			70	94:6
o			85	98:2
p			75	92:8
q			85	98:2
r			80	97:3

[a]Yields refer to the pure products after column chromatoraphy. [b]The product ratios were determined by ^{1}H NMR analysis.

undecane derivatives. The reaction is highly diastereoselective and proceeds in good yield in most cases. This method provides direct access to the synthesis of pharmaceutically interesting spirocyclic scaffolds, which are reported to have antiproliferative and anti-HIV activity.

EXPERIMENTAL SECTION

General. All of the solvents were dried according to standard literature procedures. Reactions were performed in oven-dried round-bottom flasks fitted with rubber septa, and the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column

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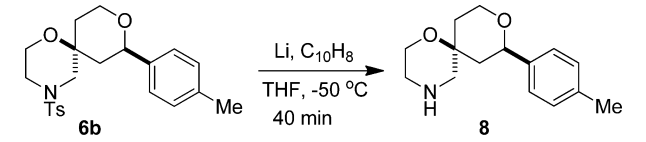
Scheme 2. . Removal of the *p*-Toluenesulfonyl Protecting Group



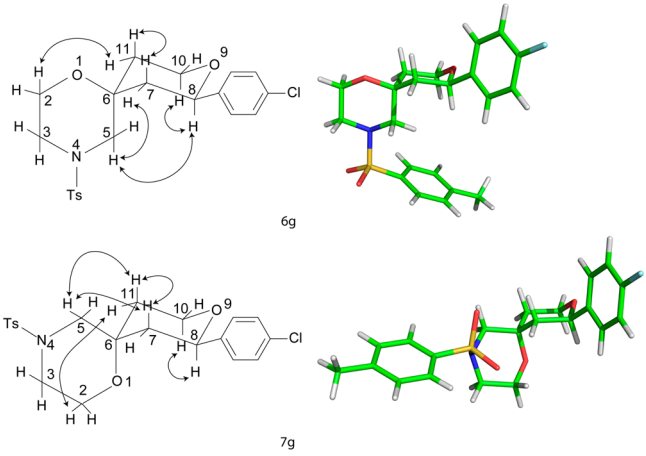
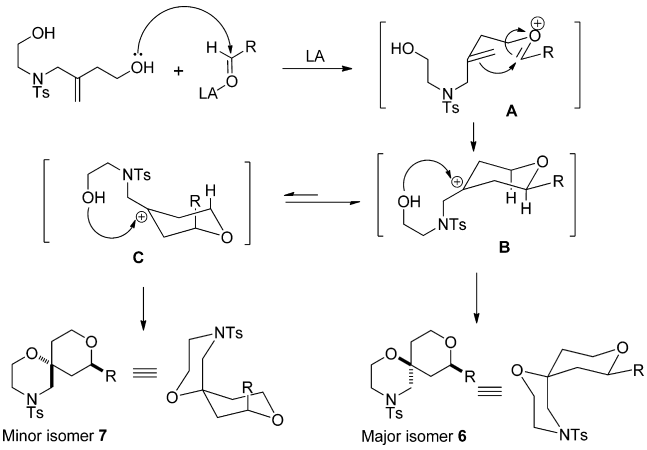


Figure 2. Characteristic NOEs and energy-minimized structures of **6g** and **7g**.

Scheme 3. A Plausible Reaction Mechanism



chromatography on silica gel of 60−120 or 100−200 mesh. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. IR spectra were recorded on an FT-IR spectrometer. ^{1}H and proton-decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz. Mass spectra were recorded on a mass spectrometer using electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI).

Preparation of the Starting Material 4. *N-(4-((tert-Butyldimethylsilyl)oxy)-2-methylenebutyl)-N-(2-((tert-butyldimethylsilyl)oxy) ethyl)-4-methylbenzenesulfonamide (**3**).* To a premixed solution of **1** (1.08 g, 5 mmol), **2** (1.97 g, 6 mmol), and triphenylphosphine (1.57 g, 6 mmol) in THF at 0 °C was added diethyl azodicarboxylate (1.84 g, 6 mmol) dropwise over 5 min. The resulting mixture was stirred at rt for 4 h. After complete consumption of the starting material as indicated by TLC, the solvent was evoporated on rotary evaporator, and the resulting crude product was purified by column chromatography (silica gel, 60−120 mesh) using an ethyl acetate/*n*-hexane gradient mixture to afford the pure product **3** in 70% yield as a colorless liquid. Yield: 1.84 g, 70%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.96 (s, 2H), 3.78 (s, 2H), 3.71 (t, J = 6.7 Hz, 2H), 3.66 (t, J = 6.8 Hz, 2H), 3.17 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.23 (t, J = 6.5 Hz, 2H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.0 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0, 141.6, 136.9, 129.5, 127.1, 115.1, 61.6, 61.4, 54.6, 49.2, 36.2, 25.9, 25.8, 21.4, 18.2, 18.1, −5.3, −5.4. IR (KBr) ν (cm^{-1}): 3448, 2954, 2930, 2888, 2857, 1726, 1650, 1599, 1467, 1345, 1254, 1161, 1096, 1023, 931, 835, 776, 658, 549. MS-ESI: m/z 550 [M + Na]$^+$. HRMS (Orbitrap ESI): calcd for $C_{26}H_{50}O_4NSSi_2$ [M + H]$^+$, 528.2993; found, 528.2980.

*N-(4-Hydroxy-2-methylenebutyl)-N-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**4**).* To a solution of **3** (1.58 g, 3 mmol) in THF at 0 °C was added TBAF (7 mmol) dropwise, and the resulting mixture was allowed to stir at rt for 1 h. After complete consuption of the starting material as indicated by TLC, the reaction was quenched with a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. Removal of the solvent followed by purification by silica gel column chromatography (silica gel, 60−120 mesh) using an ethyl acetate/*n*-hexane gradient mixture afforded the pure product **4** in 95% yield as a colorless liquid. Yield: 0.851 g, 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 5.07 (d, J = 3.7 Hz, 2H), 3.84−3.69 (m, 6H), 3.21 (t, J = 5.2 Hz, 2H), 2.44 (s, 3H), 2.39 (t, J = 6.0 Hz, 2H), 1.66 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 141.6, 135.4, 129.7, 127.2, 115.9, 60.9, 60.4, 55.3, 50.9, 35.9, 21.4. IR (neat) ν (cm^{-1}): 3404 broad, 2928, 1650, 1598,1443, 1331, 1157, 1115, 1085, 1045, 920, 814, 757, 703, 657, 548. MS-ESI: m/z 322.06 [M + Na]$^+$. HRMS (Orbitrap ESI): calcd for $C_{14}H_{22}O_4NS$ [M + H]$^+$, 300.1264; found, 300.1260.

Typical Procedure for Prins Bicyclization. To a mixture of **4** (0.5 mmol) and benzaldehyde (0.6 mmol) in anhydrous DCM (5 mL) was added $BF_3{\cdot}OEt_2$ (1.2 equiv) at −50 °C. The resulting mixture was allowed to stir at the same temperature under a nitrogen atmosphere for the specified time (Table 2). After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution (5 mL) and then extracted with dichloromethane (2 × 5 mL). The organic phases were washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using an ethyl acetate/hexane gradient mixture to afford the pure product **6a** (Table 2, entry a).

*8-Phenyl-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6a**).* White solid; yield 174 mg, 90%; mp 116−118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.39−7.27 (m, 7H), 4.38 (dd, J = 12.0, 2.2 Hz, 1H), 4.13 (ddd, J = 12.3, 5.3, 1.3 Hz, 1H), 3.86−3.80 (m, 2H), 3.64 (td, J = 13.1, 2.2 Hz, 1H), 3.23 (d, J = 11.4 Hz, 1H), 3.1−3.04 (m, 2H), 3.03−2.96 (m, 1H), 2.46 (s, 3H), 2.28 (d, J = 13.1 Hz, 1H), 2.01 (d, J = 13.2 Hz, 1H), 1.78 (td, J = 13.1, 5.4 Hz, 1H), 1.64 (t, J = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 141.6, 132.8, 129.8, 128.3, 127.6, 127.5, 125.8, 76.4, 71.3, 64.5, 59.3, 50.2, 45.7, 41.1, 33.8, 21.4. IR (KBr) ν (cm^{-1}): 3446, 3061, 2927, 2856, 1739, 1598, 1452, 1346, 1283, 1166, 1089, 956, 912, 814, 755, 700, 658, 547. MS-ESI: m/z 410.07 [M + Na]$^+$. HRMS (Orbitrap ESI): calcd for $C_{21}H_{26}O_4NS$ [M + H]$^+$, 388.1577; found, 388.1572.

*8-(p-Tolyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6b**).* White solid; yield 190 mg, 95%; mp 130−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.33 (dd, J = 12.0, 1.8 Hz, 1H), 4.11 (ddd, J = 12.2, 5.1, 1.2 Hz, 1H), 3.82 (t, J = 4.8 Hz, 2H), 3.62 (td, J = 12.9, 2.1 Hz, 1H), 3.19 (d, J = 11.5 Hz, 1H), 3.09 (d, J = 11.5 Hz, 1H), 3.06−2.97 (m, 2H), 2.46 (s, 3H), 2.34 (s, 3H), 2.24 (d, J = 13.1 Hz, 1H), 2.02 (d, J = 13.1 Hz, 1H), 1.76 (td, J = 13.1, 5.4 Hz, 1H), 1.64 (t, J = 12.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 138.6, 137.3, 132.7, 129.8, 129.0, 127.5, 125.7, 76.2, 71.3, 64.5, 59.3, 50.2, 45.7, 41.2, 33.7, 21.4, 21.0. IR (KBr) ν (cm^{-1}): 3449, 2968, 2925, 2855, 1598, 1515, 1452, 1336, 1168, 1099, 1044, 1019, 975, 816,

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764, 662, 550. MS-ESI: m/z 424.22 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{22}H_{28}O_4NS$ $[M + H]^+$, 402.1733; found, 402.1734.

*8-(4-Isopropylphenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6c**).* Off-white solid; yield 193 mg, 90%; mp 142−145 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.31−7.17 (m, 4H), 4.34 (d, J = 10.9 Hz, 1H), 4.11 (dd, J = 11.8, 4.7 Hz, 1H), 3.83 (t, J = 4.9 Hz, 2H), 3.62 (td, J = 12.8, 1.5 Hz, 1H), 3.20 (d, J = 11.5 Hz, 1H), 3.13−2.97 (m, 3H), 2.95−2.84 (m, 1H), 2.46 (s, 3H), 2.26 (d, J = 13.2 Hz, 1H), 2.02 (d, J = 13.1 Hz, 1H), 1.77 (td, J = 13.2, 5.4 Hz, 1H), 1.67 (t, J = 12.6 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 143.9, 138.7, 132.5, 129.7, 127.5, 126.3, 125.9, 76.3, 71.3, 64.5, 64.1, 59.2, 50.2, 45.7, 40.8, 33.7, 25.1, 23.8, 21.4. IR (KBr) ν (cm^{-1}): 3448, 2961, 2927, 2858, 1598, 1512, 1459, 1336, 1214, 1168, 1096, 1047, 1018, 971, 833, 811, 660, 624, 548. MS-ESI: m/z 452.25 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{24}H_{32}O_4NS$ $[M + H]^+$, 430.20466; found, 430.20464.

*8-(4-(tert-Butyl)phenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]-undecane (**6d**).* White solid; yield 199 mg, 90%; mp 186−188 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.1 Hz, 2H), 7.4−7.34 (m, 4H), 7.3−7.24 (m, 2H), 4.34 (d, J = 11.8 Hz, 1H), 4.11 (dd, J = 12.2, 4.1 Hz, 1H), 3.83 (t, J = 4.9 Hz, 2H), 3.62 (td, J = 13.0, 1.8 Hz, 1H), 3.24−2.98 (m, 4H), 2.46 (s, 3H), 2.26 (d, J = 13.2 Hz, 1H), 2.02 (d, J = 13.4 Hz, 1H), 1.77 (td, J = 13.2, 5.2 Hz, 1H), 1.68 (t, J = 12.6 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 143.9, 138.4, 132.7, 129.8, 127.6, 125.7, 125.3, 76.2, 71.3, 64.6, 59.3, 50.2, 45.7, 40.8, 34.4, 33.7, 31.2, 21.5. IR (KBr) ν (cm^{-1}): 3448, 2951, 2869, 1598, 1514, 1459, 1353, 1336, 1277, 1258, 1171, 1126, 1095, 1048, 970, 946, 907, 832, 764, 661, 549. MS-ESI: m/z 466.27 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{25}H_{34}O_4NS$ $[M + H]^+$, 444.2203; found, 444.2204.

*8-(Naphthalen-2-yl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6e**).* White solid; yield 185 mg, 85%; mp 150−152 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.86−7.79 (m, 4H), 7.70 (d, J = 8.1 Hz, 2H), 7.50−7.35 (m, 5H), 4.55 (dd, J = 11.7, 1.3 Hz, 1H), 4.19 (dd, J = 12.2, 4.3 Hz, 1H), 3.83 (t, J = 4.9 Hz, 2H), 3.70 (td, J = 12.8, 1.8, 1H), 3.29 (d, J = 11.7 Hz, 1H), 3.15−2.95 (m, 3H), 2.46 (s, 3H), 2.38 (d, J = 13.2 Hz, 1H), 2.05 (d, J = 13.3 Hz, 1H), 1.83 (td, J = 13.0, 5.2 Hz, 1H), 1.72 (t, J = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 139.0, 133.1, 132.8, 132.6, 129.8, 128.1, 127.9, 127.5, 125.9, 125.7, 124.4, 123.9, 76.4, 71.3, 64.6, 59.3, 50.2, 45.7, 41.1, 33.8, 21.4. IR (KBr) ν (cm^{-1}): 3448, 3051, 2969, 2926, 2854, 1599, 1507, 1335, 1166, 1096, 975, 819, 764, 658, 546. MS-ESI: m/z 459.8 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{25}H_{28}O_4NS$ $[M + H]^+$, 438.1733; found, 438.1734.

*8-(Naphthalen-1-yl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6f**).* White solid; yield 179 mg, 82%; mp 162−164 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.66−7.56 (m, 2H), 7.54−7.43 (m, 2H), 7.37 (d, J = 7.9 Hz, 2H), 5.17 (d, J = 11.3 Hz, 1H), 4.28−4.19 (m, 1H), 3.91−3.72 (m, 3H), 3.68 (d, J = 11.7 Hz, 1H), 3.26−3.16 (m, 1H), 2.94−2.79 (m, 2H), 2.70 (d, J = 13.2 Hz, 1H), 2.45 (s, 3H), 1.99−1.88 (m, 2H), 1.73 (t, J = 12.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 137.3, 133.6, 132.6, 130.0, 129.8, 128.7, 128.0, 127.6, 126.3, 125.5, 125.3, 123.2, 122.7, 73.6, 71.6, 64.8, 59.3, 50.4, 45.9, 39.7, 34.8, 21.5. IR (KBr) ν (cm^{-1}): 3448, 3056, 2945, 2923, 2844, 1594, 1453, 1346, 1283, 1252, 1168, 1092, 956, 911, 802, 758, 657, 603, 543. MS-ESI: m/z 459.8 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{25}H_{28}O_4NS$ $[M + H]^+$, 438.1733; found, 438.1738.

*8-(4-Chlorophenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6g**).* White solid; yield 200 mg, 95%; mp 145−147 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.33−7.26 (m, 4H), 4.36 (dd, J = 11.9, 1.9 Hz, 1H), 4.12 (ddd, J = 12.3, 5.3, 1.2 Hz, 1H), 3.85−3.79 (m, 2H), 3.62 (td, J = 12.9, 2.2 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 3.12−3.07 (m, 1H), 3.05−2.94 (m, 2H), 2.46 (s, 3H), 2.28 (d, J = 13.1 Hz, 1H), 1.99 (d, J = 13.1 Hz, 1H), 1.77 (td, J = 13.2, 5.4 Hz, 1H), 1.56 (t, J = 12.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 140.2, 133.3, 132.7, 129.8, 128.5, 127.5, 127.1, 75.7, 71.2, 64.5, 59.3, 50.2, 45.7, 41.0, 33.8, 21.5. IR (KBr) ν (cm^{-1}): 3447, 2957, 2925, 2852, 1741, 1598, 1492, 1453, 1348, 1283, 1166, 1089, 1042, 957, 818, 756, 659, 549. MS-ESI: m/z 422.06 $[M + H]^+$. HRMS (Orbitrap ESI): calcd for $C_{21}H_{25}O_4NClS$ $[M + H]^+$, 422.1187; found, 422.1183.

*8-(4-Bromophenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6h**).* White solid; yield 209 mg, 90%; mp 135−137 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 4.34 (dd, J = 12.0, 2.1 Hz, 1H), 4.12 (ddd, J = 12.3, 5.3, 1.3 Hz, 1H), 3.86−3.78 (m, 2H), 3.62 (td, J = 12.9, 2.1 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 3.13−2.93 (m, 3H), 2.46 (s, 3H), 2.28 (d, J = 13.2 Hz, 1H), 1.99 (d, J = 13.1 Hz, 1H), 1.76 (td, J = 13.2, 5.4 Hz, 1H), 1.55 (t, J = 13.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 140.7, 132.8, 131.4, 129.8, 127.5, 121.4, 75.7, 71.1, 64.5, 59.4, 50.2, 45.8, 41.0, 33.8, 21.5. IR (KBr) ν (cm^{-1}): 3448, 2925, 2854, 1739, 1632, 1598, 1487, 1453, 1346, 1254, 1166, 1092, 1016, 953, 814, 754, 658, 547. MS-ESI: m/z 490.2 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{21}H_{25}O_4NBrS$ $[M + H]^+$, 466.0682; found, 466.0687.

*8-(4-Fluorophenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6i**).* White solid; yield 192 mg, 95%; mp 140−142 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.35−7.30 (m, 2H), 7.05−7.01 (m, 2H), 4.36 (dd, J = 11.9, 1.9 Hz, 1H), 4.12 (ddd, J = 12.3, 5.4, 1.3 Hz, 1H), 3.86−3.78 (m, 2H), 3.63 (td, J = 12.8, 2.1 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 3.11−2.94 (m, 3H), 2.46 (s, 3H), 2.28 (d, J = 13.1 Hz, 1H), 2.00 (d, J = 13.2 Hz, 1H), 1.71 (td, J = 13.2, 5.4 Hz, 1H), 1.62−1.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.5, 143.9, 137.4, 132.9, 129.8, 127.5, 115.3, 115.0, 75.7, 71.2, 64.6, 59.4, 50.2, 45.8, 41.1, 33.8, 21.5. IR (KBr) ν (cm^{-1}): 3447, 3068, 2955, 2864, 1924, 1735, 1603, 1512, 1454, 1344, 1223, 1165, 1086, 1045, 959, 818, 756, 658, 595, 547. MS-ESI: m/z 428 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{21}H_{25}O_4NFS$ $[M + H]^+$, 406.1482; found, 406.1480.

*8-(m-Tolyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6j**).* White solid; yield 180 mg, 90%; mp 107−109 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.25−7.21 (m, 1H), 7.17 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 4.34 (dd, J = 12.0, 1.9 Hz, 1H), 4.12 (ddd, J = 12.2, 5.3, 1.3 Hz, 1H), 3.86−3.80 (m, 2H), 3.63 (td, J = 12.9, 2.1 Hz, 1H), 3.22 (d, J = 11.4 Hz, 1H), 3.09−2.96 (m, 3H), 2.46 (s, 3H), 2.35 (s, 3H), 2.27 (d, J = 13.1 Hz, 1H), 2.01 (d, J = 13.2 Hz, 1H), 1.78 (td, J = 13.1, 5.4 Hz, 1H), 1.64 (t, J = 12.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 141.5, 138.0, 132.8, 129.8, 128.4, 128.3, 127.6, 126.5, 122.9, 71.3, 64.6, 59.3, 50.3, 45.8, 41.1, 33.8, 21.5, 21.4. IR (KBr) ν (cm^{-1}): 3442, 2951, 2920, 2846, 1597, 1457, 1340, 1283, 1260, 1168, 1094, 962, 820, 757, 658, 546. MS-ESI: m/z 423.8 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{22}H_{28}O_4NS$ $[M + H]^+$, 402.1733; found, 402.1739.

*8-(3,4-Dimethoxyphenyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]-undecane (**6k**).* White solid; yield 185 mg, 83%; mp 140−142 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.95−6.81 (m, 3H), 4.33 (dd, J = 12.0, 1.5 Hz, 1H), 4.12 (dd, J = 12.0, 4.5 Hz, 1H), 3.95−3.81 (m, 8H), 3.63 (td, J = 12.8, 2.2 Hz, 1H), 3.22−3.00 (m, 4H), 2.46 (s, 3H), 2.25 (d, J = 13.5 Hz, 1H), 2.04 (d, J = 12.8 Hz, 1H), 1.78 (td, J = 12.8, 5.2 Hz, 1H), 1.67 (t, J = 12.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 148.5, 143.9, 134.1, 132.6, 129.8, 127.5, 118.2, 110.8, 109.1, 76.2, 71.3, 64.6, 59.3, 55.9, 55.8, 50.2, 45.7, 41.1, 33.6, 21.5. IR (KBr) ν (cm^{-1}): 3449, 3084, 2990, 2928, 2850, 1596, 1518, 1461, 1423, 1349, 1262, 1233, 1164, 1090, 1029, 976, 952, 870, 820, 756, 660, 599, 550. MS-ESI: m/z 470.06 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{23}H_{30}O_6NS$ $[M + H]^+$, 448.1788; found, 448.1790.

*4-Tosyl-8-(3,4,5-trimethoxyphenyl)-1,9-dioxa-4-azaspiro[5.5]-undecane (**6l**).* White solid; yield 202 mg, 85%; mp 152−154 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.59 (s, 2H), 4.33 (dd, J = 12.0, 1.9 Hz, 1H), 4.12 (dd, J = 12.3, 4.7 Hz, 1H), 3.91−3.80 (m, 11H), 3.63 (td, J = 12.8, 1.9 Hz, 1H), 3.23 (d, J = 11.4 Hz, 1H), 3.10−2.96 (m, 3H), 2.47 (s, 3H), 2.29 (d, J = 13.1 Hz, 1H), 2.02 (d, J = 13.1 Hz, 1H), 1.78 (td, J = 13.2, 5.4 Hz, 1H), 1.66 (t, J = 12.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 143.9, 137.3, 137.2, 132.6, 129.8, 127.5, 102.9, 76.5, 71.2, 64.5, 60.7, 59.3, 56.0, 50.2, 45.7, 41.0, 33.7, 21.5. IR (KBr) ν (cm^{-1}): 3447, 2931, 2871, 2845, 1741, 1593, 1508, 1459, 1424, 1347, 1239, 1168,

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1123, 1094, 1016, 950, 826, 762, 657, 547. MS-ESI: m/z 478.21 $[M + H]^+$. HRMS (Orbitrap ESI): calcd for $C_{24}H_{32}O_7NS$ $[M + H]^+$, 478.1894; found, 478.18865.

8-((E)-Styryl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6m**). Pale-yellow solid; yield 154 mg, 75%; mp 86−88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.22 Hz, 2H), 7.4−7.34 (m, 4H), 7.33−7.29 (m, 2H), 7.25−7.22 (m, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 5.7 Hz, 1H), 4.10−4.0 (m, 2H), 3.84 (t, J = 4.7 Hz, 2H), 3.56 (td, J = 12.6, 2.2 Hz, 1H), 3.10−2.99 (m, 4H), 2.46 (s, 3H), 2.15 (d, J = 13.1 Hz, 1H), 2.0 (d, J = 13.1 Hz, 1H), 1.7 (td, J = 12.9, 5.3 Hz, 1H), 1.54 (t, J = 12.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 143.9, 136.7, 132.2, 130.5, 129.7, 129.6, 128.4, 127.7, 127.5, 126.4, 72.4, 70.0, 62.6, 59.5, 55.1, 45.8, 38.4, 32.0, 21.5. IR (KBr) ν (cm^{-1}): 3446, 3026, 2955, 2923, 2852, 1735, 1597, 1494, 1453, 1351, 1284, 1167, 1089, 1028, 969, 934, 815, 755, 657, 547. MS-ESI: m/z 436.15 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{23}H_{27}O_4NNaS$ $[M + Na]^+$, 436.1553; found, 436.1558.

8-Benzyl-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6n**). Sticky solid; yield 140 mg, 70%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.2 Hz, 2H), 7.35−7.19 (m, 7H), 3.96 (ddd, J = 12.2, 5.2, 1.4 Hz, 1H), 3.85−3.73 (m, 2H), 3.60−3.54 (m, 1H), 3.41 (td, J = 12.7, 2.0 Hz, 1H), 3.13 (d, J = 11.6 Hz, 1H), 3.10−3.04 (m, 1H), 2.90−2.80 (m, 3H), 2.71 (dd, J = 13.9, 5.2 Hz, 1H), 2.43 (s, 3H), 2.02 (d, J = 13.0 Hz, 1H), 1.93 (d, J = 13.1 Hz, 1H), 1.61 (td, J = 13.1, 5.4 Hz, 1H), 1.39 (t, J = 12.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 138.0, 132.6, 129.7, 129.3, 128.2, 127.6, 126.2, 74.7, 71.1, 64.1, 59.3, 50.3, 45.7, 42.6, 39.5, 33.2, 21.5. IR (KBr) ν (cm^{-1}): 3448, 3062, 3026, 2926, 2854, 1738, 1598, 1495, 1453, 1345, 1281, 1222, 1164, 1086, 1025, 946, 814, 757, 701, 655, 549. MS-ESI: m/z 423.8 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{22}H_{28}O_4NS$ $[M + H]^+$, 402.17336; found, 402.17332.

8-(o-Tolyl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6o**). White solid; yield 170 mg, 85%; mp 153−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 7.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.24−7.13 (m, 3H), 4.59 (dd, J = 11.9, 1.8 Hz, 1H), 4.13 (ddd, J = 12.2, 5.3, 1.3 Hz, 1H), 3.9−3.83 (m, 1H), 3.80−3.74 (m, 1H), 3.65 (td, J = 12.5, 2.4 Hz, 1H), 3.49 (d, J = 11.4 Hz, 1H), 3.20−3.14 (m, 1H), 2.87−2.79 (m, 2H), 2.46 (s, 3H), 2.43−2.39 (m, 1H), 2.39 (s, 3H), 1.9 (d, J = 13.1 Hz, 1H), 1.83 (td, J = 12.9, 5.3 Hz, 1H), 1.56 (t, J = 12.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 139.7, 134.4, 132.4, 130.3, 129.8, 127.6, 127.3, 126.2, 125.1, 73.4, 71.3, 64.6, 59.2, 50.3, 45.8, 39.3, 34.5, 21.5, 18.9. IR (KBr) ν (cm^{-1}): 3448, 3024, 2956, 2919, 2869, 2845, 1597, 1490, 1349, 1297, 1278, 1169, 1096, 1023, 960, 913, 817, 758, 659, 602, 548. MS-ESI: m/z 423.8 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{22}H_{28}O_4NS$ $[M + H]^+$, 402.1733; found, 402.1728.

8-(Thiophen-2-yl)-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6p**). Yellow solid; yield 147 mg, 75%; mp 85−87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.28−7.24 (m, 1H), 7.01−6.93 (m, 2H), 4.64 (dd, J = 12.0, 2.2 Hz, 1H), 4.10 (dd, J = 12.0, 4.5 Hz, 1H), 3.88−3.80 (m, 2H), 3.65 (td, J = 12.8, 1.5 Hz, 1H), 3.16 (d, J = 12.0 Hz, 1H), 3.10−2.97 (m, 3H), 2.45 (s, 3H), 2.36 (d, J = 12.8 Hz, 1H), 2.07 (d, J = 12.8 Hz, 1H), 1.86−1.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 144.0, 132.5, 129.8, 127.6, 126.4, 124.9, 123.9, 72.1, 71.0, 64.6, 59.4, 50.2, 45.7, 41.0, 33.3, 21.5. IR (KBr) ν (cm^{-1}): 3449, 3067, 2957, 2924, 2851, 2736, 1923, 1735, 1597, 1452, 1349, 1282, 1256, 1166, 1090, 1024, 950, 906, 819, 756, 704, 659, 613, 547. MS-ESI: m/z 416.07 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{19}H_{24}O_4NS_2$ $[M + H]^+$, 394.1141; found, 394.1145.

8-Isobutyl-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6q**). Colorless liquid; yield 156 mg, 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 7.1 Hz, 2H), 7.36 (d, J = 7.4 Hz, 2H), 3.95 (dd, J = 12.2, 5.1 Hz, 1H), 3.81 (t, J = 4.2 Hz, 2H), 3.43 (t, J = 12.6 Hz, 1H), 3.39−3.33 (m, 1H), 3.09−2.93 (m, 4H), 2.45 (s, 3H), 1.99−1.93 (m, 2H), 1.84−1.74 (m, 1H), 1.61 (td, J = 12.9, 5.0 Hz, 1H), 1.52−1.45 (m, 1H), 1.33−1.24 (m, 1H), 1.22−1.14 (m, 1H), 0.9 (d, J = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 132.6, 129.7, 127.6, 72.3, 71.1, 64.1, 59.2, 50.4, 45.8, 45.3, 40.0, 33.7, 24.3, 23.1, 22.3, 21.5. IR (neat) ν (cm^{-1}): 3455, 2955, 2926, 2851, 1733, 1597, 1453, 1351, 1166, 1094, 948, 815, 757, 660, 549. MS-ESI: m/z 390.25 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{19}H_{30}O_4NS$ $[M + H]^+$, 368.1890; found, 368.1895.

8-Propyl-4-tosyl-1,9-dioxa-4-azaspiro[5.5]undecane (**6r**). Colorless liquid; yield 141 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 3.95 (dd, J = 12.0, 5.0 Hz, 1H), 3.81 (t, J = 5.0 Hz, 2H), 3.43 (td, J = 12.9, 1.8 Hz, 1H), 3.33−3.27 (m, 1H), 3.09−2.92 (m, 4H), 2.45 (s, 3H), 1.97 (d, J = 13.1 Hz, 2H), 1.61 (td, J = 13.1, 5.3 Hz, 1H), 1.55−1.43 (m, 2H), 1.41−1.25 (m, 3H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 132.5, 129.7, 127.6, 73.8, 71.1, 64.1, 59.2, 50.4, 45.7, 39.6, 38.3, 33.7, 21.5, 18.6, 14.0. IR (neat) ν (cm^{-1}): 3456, 2957, 2929, 2851, 1726, 1597, 1453, 1351, 1166, 1093, 955, 815, 758, 660, 549. MS-ESI: m/z 376.23 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{18}H_{28}O_4NS$ $[M + H]^+$, 354.1733; found, 354.1735.

Removal of the Tosyl Protecting Group To Give 8. Lithium granules (8.72 mg, 1.24 mmol, 10 equiv) were added to a vigorously stirred solution of naphthalene (159 mg, 1.24 mmol, 10 equiv) in tetrahydrofuran (3 mL) at 30 °C, and the resulting green suspension was allowed to stir for 3 h at 30 °C. A solution of *N*-tosyl pyranomorpholine **6b** (50 mg, 0.124 mmol, 1 equiv) in tetrahydrofuran (2 mL) was then added at −50 °C, and the resulting mixture was stirred at the same temperature for 40 min. Saturated aqueous ammonium chloride solution (4 mL) was then added to this solution at −50 °C. The suspension was stirred at −50 °C for 5 min and then was allowed to warm to rt. The solution was then partitioned between ethyl acetate and brine. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated on a rotary evaporator. The crude product was purified by flash column chromatography using a MeOH/DCM gradient to afford the detosylated product **8** as a yellow oil (24 mg, 80%).

8-(p-Tolyl)-1,9-dioxa-4-azaspiro[5.5]undecane (**8**). Yellow liquid; yield 24 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 4.30 (dd, J = 12.0, 1.9 Hz, 1H), 4.09 (ddd, J = 12.0, 5.3, 1.3 Hz, 1H), 3.74 (t, J = 4.8 Hz, 2H), 3.58 (td, J = 13.4, 2.1 Hz, 1H), 3.08 (d, J = 12.3 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.89−2.84 (m, 2H), 2.65−2.46 (bs, 1H), 2.33 (s, 3H), 2.32−2.29 (m, 1H), 2.09 (dd, J = 13.1, 1.6 Hz, 1H), 1.75 (td, J = 13.2, 5.4 Hz, 1H), 1.64 (t, J = 12.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.0, 137.2, 128.9, 125.8, 76.5, 70.6, 64.8, 60.9, 50.7, 46.1, 41.7, 34.3, 21.0. IR (neat) ν (cm^{-1}): 3424, 2924, 2853, 1642, 1566, 1515, 1451, 1364, 1256, 1088, 1046, 1016, 814, 594. MS-ESI: m/z 248.21 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{15}H_{22}O_2N$ $[M + H]^+$, 248.1645; found, 248.1647.

tert-Butyl (4-Hydroxy-2-methylenebutyl)(2-hydroxyethyl)carbamate (**9**). Colorless liquid; yield 980 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.96 (d, J = 14.3 Hz, 2H), 3.88 (s, 2H), 3.77−3.70 (m, 4H), 3.40−3.35 (m, 2H), 2.26 (t, J = 6.2 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 156.0, 142.0, 112.7, 80.4, 61.9, 60.5, 52.8, 52.4, 49.5, 36.5, 28.2. IR (neat) ν (cm^{-1}): 3401, 2975, 2933, 1672, 1464, 1413, 1367, 1250, 1168, 1132, 1050, 949, 889, 773, 676. MS-ESI: m/z 268.29 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{12}H_{23}O_4NNa$ $[M + Na]^+$, 268.1519; found, 268.1521.

Benzyl (4-Hydroxy-2-methylenebutyl)(2-hydroxyethyl)carbamate (**10**). Colorless liquid; yield 1.185 g, 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.29 (m, 5H), 5.14 (s, 2H), 5.01−4.91 (m, 2H), 4.03−3.91 (m, 2H), 3.81−3.58 (m, 4H), 3.43 (s, 2H), 2.27−2.17 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 156.6, 141.8, 141.6, 136.2, 134.7, 128.4, 127.8, 128.0, 127.5, 112.8, 67.4, 60.7, 60.4, 52.5, 49.7, 48.8, 36.5, 36.3, 26.4. IR (neat) ν (cm^{-1}): 3404, 2939, 1681, 1474, 1422, 1366, 1232, 1126, 1050, 985, 907, 864, 743, 699, 608, 508. MS-ESI: m/z 302.24 $[M + Na]^+$. HRMS (Orbitrap ESI): calcd for $C_{15}H_{21}O_4NNa$ $[M + Na]^+$, 302.1362; found, 302.1360.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray data for compound **6i** as a CIF file and an ORTEP diagram; NOESY and DQFCOSY study of the 10:4 **6g**:**7g** mixture; and copies of ^{1}H and ^{13}C NMR spectra of **6a**−**r**, **3**, **4**,

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8, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: basireddy@iict.res.in. Fax: 0091-40-27160512.

Notes

The authors declare no competing financial interest.

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(10) The supplementary crystallographic data (CIF file) and ORTEP diagram (Figure S1) for compound **6i** are provided in the Supporting Information. CCDC 960107 contains supplementary crystallographic data for the structure **6i**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.