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Thia-Prins Bicyclization Approach for the Stereoselective Synthesis of Dithia- and Azathia-Bicycles

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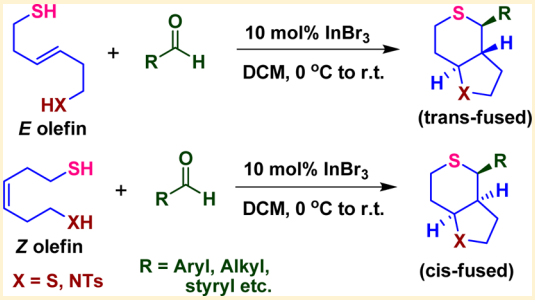
Supporting Information

ABSTRACT: A novel thia-Prins bicyclization approach has been developed for the first time for the synthesis of hexahydro-2*H*-thieno[3,2-*c*]thiopyran derivatives from the coupling of homoallylic mercaptans such as hex-3-ene-1,6-dithiol with various aldehydes using 10 mol % $InBr_3$ in dichloromethane with high selectivity. In addition, the coupling of (*E*)-*N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide with aldedydes affords the corresponding *N*-tosyloctahydrothiopyrano-[4,3-*b*]pyrrole derivatives in good yields. This reaction is a stereoselective affording *trans*-fused product from *E*-homoallyllic mercaptan and *cis*-fused product from *Z*-homoallyllic mercaptan.



The chemistry of sulfur-containing six-membered heterocyclic systems, in particular, thiopyrans, has been less studied than that of oxygen analogues because of its lesser abundance in nature.[1] However, because of their potent pharmacological and medicinal properties, there has been an increasing interest in developing new therapeutic agents with thiopyran ring system.[2] Thiacyclohexane derivatives are found in petroleum ether.[3] They are responsible for interesting biological activities of several pharmaceutical agents such as cephalosporins and dithiathromboxane A_2.[4] The sulfur-containing oligosaccharides have been reported as potential enzyme inhibitors.[5] In addition, octahydrothiopyrano[4,3-*b*]pyrrole skeleton is found in conformationally restricted sulfur-containing analogues of Revastigmine and Nicotine, and they are found to exhibit an acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity (Figure 1).[6]

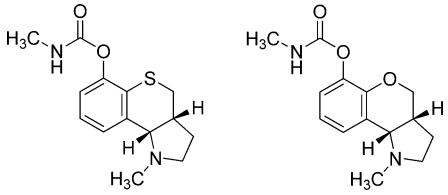


Figure 1. Examples of biologically active octahydrothiopyrano- and pyrano[4,3-*b*]pyrrole motifs.

Furthermore, thiacyclohexane derivatives can be transformed into a variety of structures through simple reactions such as hydrogenolysis, oxidation and olefination.[7] Therefore, still there is a need to develop simple and efficient methods for such sulfur-containing heterocycles.

Of various methods reported for the synthesis of thiacyclohexanes,[8] thia-Prins cyclization of homoallyllic mercaptans with aldehydes in the presence of an acid catalyst is an important synthetic route for the stereoselective construction of thiotetrahydropyran ring with a net addition of an external nucleophile.[9] Recently, a tandem Ene/thia-Prins cyclization has been reported for the stereoslective synthesis of substituted thiotetrahydropyrans.[10] Furthermore, an oxidative thia-Prins cyclization has been developed through C−H bond activation using DDQ.[11] Inspired by an intramolecular version of Prins cyclization with a tethered nucleophiles,[12] we have successfully demonstrated a tandem Prins/Friedel−Crafts cyclization.[13] However, thia-Prins bicyclization of homoallyllic mercaptans with a tethered mercaptan or *N*-tosyl amide has not yet been explored. To the best of our knowledge, there have been no reports on the synthesis of dithia-, azathia-bicycles, i.e., hexahydro-2*H*-thieno[3,2-*c*]thiopyran and *N*-tosyloctahydrothiopyrano[4,3-*b*]pyrrole, from readily accessible hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide, respectively. In continuation of our research program on intramolecular version of Prins cyclization for the stereoselective synthesis of heterobicycles,[13,14] we herein report a novel Prins cascade process for the stereoselective synthesis of hexahydro-2*H*-thieno[3,2-*c*]thiopyran and octahydrothiopyrano[4,3-*b*]pyrrole derivatives.

As a model reaction, we initially attempted the coupling of (*E*)-hex-3-ene-1,6-dithiol (**1**) with *p*-anisaldehyde (**2**) in the presence of 10 mol % $InBr_3$ in dichloromethane. The reaction proceeded smoothly at room temperature affording the corresponding product, i.e., hexahydro-2*H*-thieno[3,2-*c*]-

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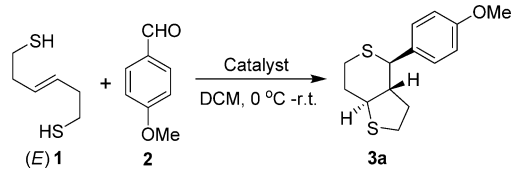
thiopyran **3a**, in 88% yield with complete *trans*-selectivity (Table 1, entry b). Various other Lewis and Brønsted acids were tested for this conversion, and the results are presented in Table 1. Of various acids tested, 10 mol % of $In(OTf)_3$ was also equally effective as compared to $InBr_3$ for this conversion to furnish the product **3a** in 84% yield (entry c). Similarly, 10 mol % of $InCl_3$ afforded the product **3a** in 65% yield (entry a). The efficiency of the In^{3+} may be attributed to the formation of cationic InX_2^+ species, which may activate the carbonyl compounds effectively.[15] Other Lewis acids ($Cu(OTf)_2$, $ZnCl_2$, LiBr) and Brønsted acids (TsOH, CSA, benzoic acid) were found to be ineffective for this reaction.

However, the coupling of (*Z*)-hex-3-ene-1,6-dithiol (**1**) with *p*-anisaldehyde (**2**) in the presence of 10 mol % $InBr_3$ in dichloromethane gave the product **3b** in 85% yield with *cis*-selectivity (Scheme 1, Table 2, entry b).

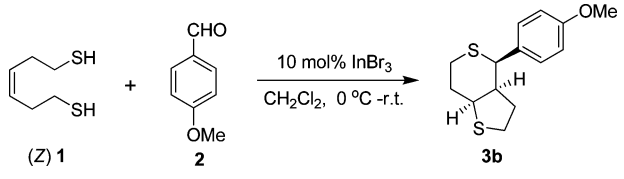
Table 1. Catalyst Optimization for Thia-Prins Bicyclization of (*E*)-Hex-3-ene-1,6-dithiol with *p*-Anisaldehyde[a]



entry	catalyst (10 mol %)	time (h)	yield (%)[b]
a	$InCl_3$	3	65
b	$InBr_3$	2	88
c	$In(OTf)_3$	1	84
d	$Cu(OTf)_2$	4	35
e	LiBr	5	10
f	$ZnCl_2$	6	20
g	TsOH	4	30
h	CSA	4	15
i	benzoic acid	6	trace

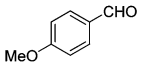
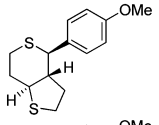
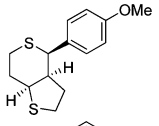
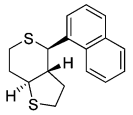
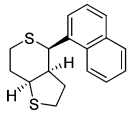
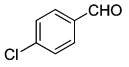
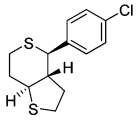
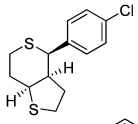
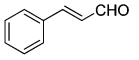
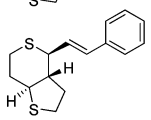
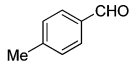
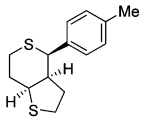
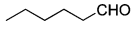
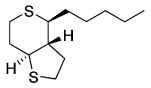
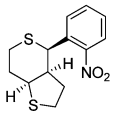
[a]Reaction was performed at 0.5 mmol scale with respect to olefin. [b]Isolated yield.

Scheme 1. Thia-Prins Bicyclization of (*Z*)-Hex-3-ene-1,6-dithiol with *p*-Anisaldehyde



These results provided an incentive to extend this process for various aldehydes, and the results are exemplified in Table 2. Interestingly, several aromatic aldehydes like 1-naphthaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde and 2-nitrobenzaldehyde reacted effectively with (*E*)- or (*Z*)-hex-3-ene-1,6-dithiol to accomplish the respective aryl substituted *trans*- or *cis*-hexahydro-2*H*-thieno[3,2-*c*]thiopyran derivatives (**3**) in good to excellent yields (Table 2, entries c–f, h and j). Remarkably, acid-sensitive α,β-unsaturated aldehyde, for example, cinnamaldehyde, also participated well with faster reaction rate and high yield (entry g). This method works well not only with aromatic aldehydes but also with aliphatic aldehydes. For instance, *n*-hexanal afforded the corresponding *n*-pentyl dithia-bicycle

Table 2. Synthesis of Hexahydro-2*H*-thieno[3,2-*c*]thiopyran Derivatives via Thia-Prins Bicyclization[a]

Entry	Olefin (**1**)	Aldehyde (**2**)	Product (**3**)[b]	Time (h)	Yield (%)[c]
a	*E*			3	88
b	*Z*	,,		3	85
c	*E*			3	90
d	*Z*	,,		3	86
e	*E*			3	85
f	*Z*	,,		3	86
g	*E*			2	90
h	*Z*			3	80
i	*E*			5	74
j	*Z*			3	82

[a]Reaction was performed with 0.5 mmol olefin, 0.525 mmol aldehyde and 10 mol % $InBr_3$ in dichloromethane. [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.

under similar reaction conditions (entry i). The structure and stereochemistry of **3a** and **3f** were characterized by extensive NMR experiments including 2-D nuclear Overhauser effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY).[16] The structure of **3d** was confirmed by X-ray crystallography.[17] From Table 2, it is evident that the geometry of the olefin **1** controls the stereoselectivity of the reaction; i.e., *trans*-olefin provides *trans*-fused product, whereas *cis*-olefin gives *cis*-fused product exclusively.

Inspired by the results obtained with homoallylic bismercaptans **1**, we extended this approach to thia-Prins bicyclization for the stereoselective synthesis of azathia-bicycles, i.e., octahydrothiopyrano[4,3-*b*]pyrroles. Accordingly, (*E*)-*N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide (**4**) was

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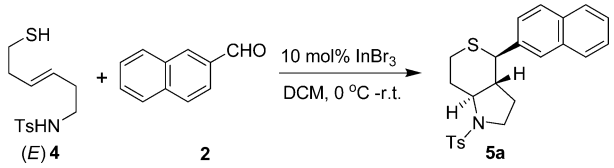
treatedwith 2-naphthaldehyde in the presence of 10 mol % $InBr_3$ in dichloroethane. To our surprize, thia-Prins bicyclization proceeded at room temperature to afford the corresponding *trans*-fused *N*-tosyl-octahydrothiopyrano[4,3-*b*]pyrrole **5a** in 92% yield (Scheme 2, Table 3, entry a).

Scheme 2. Synthesis of *trans*-Fused Azathia-Bicycle via Thia-Prins Bicyclization



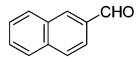
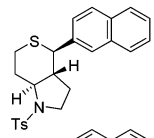
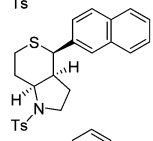
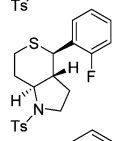
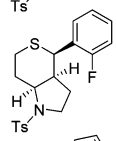
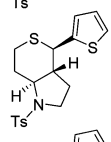
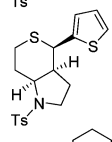
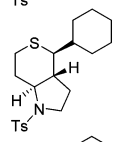
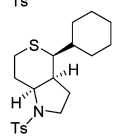
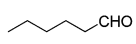
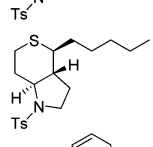
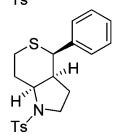
Furthermore, the coupling of (*Z*)-*N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide (**4**) with 2-naphthaldehyde under similar reaction conditions gave the *cis*-fused *N*-tosyl-octahydrothiopyrano[4,3-*b*]pyrrole **5b** in 84% yield (Scheme 3, Table 3, entry b).

The scope of the reaction is illustrated with respect to various aldehydes, and the results are summarized in Table 3. Other aromatic aldehydes like 2-fluorobenzaldenyde, thiophene-2-carboxaldehyde and benzaldehyde participated well in this reaction to furnish the respective *trans*/*cis*-fused thia-aza bicycles (entries b–f and j, Table 3). Alipahatic aldehydes such as cyclohexanecarboxaldehyde and *n*-hexanal also found to be effective for this conversion to afford the respective alkyl substituted octahydrothiopyrano[4,3-*b*]pyrrole derivatives (entries g–i, Table 3). The structure and stereochemistry of **5b** and **5e** were characterized by extensive NMR experiments including NOESY and DQFCOSY.[16] In all the cases, thia-Prins cyclization was observed. No aza-Prins reaction cyclization was observed under the present reaction conditions. This might be attributed to the high reactivity and more nucleophiliciy of the sulfur than nitrogen.[18] Like homoallylic bis-mercaptans, *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide also participated effectively in this cyclization to afford the *trans*-fused product from *trans*-olefin and *cis*-fused product from *cis*-olefin.

All the products were characterized by NMR, mass and IR spectroscopy. Among various acid catalysts studied for this conversion, as depicted in Table 1, $InBr_3$ gave the best results in terms of yield. Next, we examined the effect of various solvents such as dichloromethane, 1,2-dichloroethane, toluene. Among them, dichloromethane gave the best results. This cascade process is simple, convenient and provides diverse range of fused dithia- and azathia-bicycles from easily accessible hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide in a single-step process.

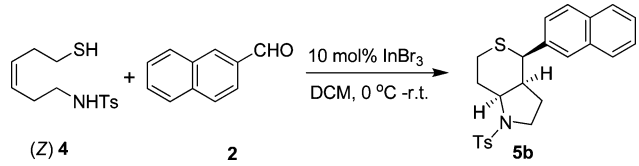
A plausible mechanism for thia-Prins cascade process is proposed in Scheme 4. In case of InX_3 (X = Cl, Br, I) catalysis, as reported by Yu et al,[15] the real catalytic species are the in situ generated cationic species InX_2^+, which may effectively facilitate the formation of thiocarbenium ion from hemithioacetal, which is formed in situ from a homoallylic thiol and an aldehyde, likely after activation through InX_2^+. The intermediate thiocarbenium ion is attacked by an internal olefin resulting in the formation of carbocation, which is simultaneously trapped by a tethered mercaptan or *N*-tosylamide leading to the formation of the desired product. The reaction appears to be stereospecific as the geometry of the olefin controls the selectivity of the reaction.

Table 3. Synthesis of Octahydrothiopyrano[4,3-*b*]pyrrole Scaffolds via Thia-Prins Bicyclization[a]

Entry	Olefin (**4**)	Aldehyde (**2**)	Product (**5**)[b]	Time (h)	Yield (%)[c]
a	*E*			3	85
b	*Z*	,,		3	82
c	*E*			3	90
d	*Z*	,,		3	86
e	*E*			3	90
f	*Z*	,,		3	82
g	*E*			2	80
h	*Z*	,,		3	76
i	*E*			5	76
j	*Z*			3	80

[a]Reaction was performed with 0.5 mmol olefin, 0.525 mmol aldehyde and 10 mol % $InBr_3$ in dichloromethane. [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.

Scheme 3. Synthesis of *cis*-Fused Azathia-Bicycle via Thia-Prins Bicyclization



In conclusion, we have demonstrated a stereoselective synthesis of a novel class of hexahydro-2*H*-thieno[3,2-*c*]-thiopyran and octahydrothiopyrano[4,3-*b*]pyrrole derivatives

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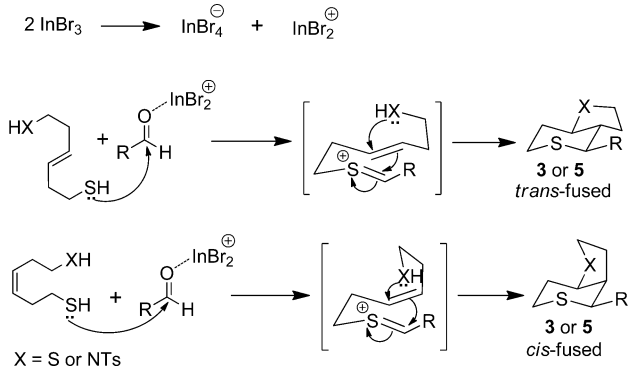
Scheme 4. Plausible Reaction Mechanism for Thia-Prins Bicyclization



via thia-Prins bicyclization. This cascade process provides an easy access to fused dithia- and thia-aza bicycles in good to excellent yields. This approach is a highly stereoselective, affording the corresponding *cis*- and *trans*-fused thia-bicycles from easily accessible hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide in a single step process.

EXPERIMENTAL SECTION

General Methods. Dichloromethane was dried according to a standard literature procedure. Reactions were performed in an oven-dried round-bottom flask, the flasks were fitted with rubber septa, and the reactions were conducted under nitrogen atmosphere. Glass syringes were used to transfer the solvent. Crude products were purified by column chromatography on silica gel of 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 methanolic acidic solution of *p*-anisaldehyde (anis) followed by heating (<1 min) on a hot plate (~250 °C). Organic solvents were concentrated on rotary evaporator at 35−40 °C. IR spectra were recorded on FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ on 300, 500 600, or 700 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on mass spectrometer by gas chromatography−electron impact-mass spectrometry (GC−EI-MS) or electrospray ionization-mass spectrometry (ESI-MS) technique.

Typical Procedure for the Intramolecular Thia-Prins Bicyclization. To a stirred solution of (*E* or *Z*)-hex-3-ene-1,6-dithiol (**1**) or (*E* or *Z*)-*N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide (**4**) (0.50 mmol) and aldehyde (0.525 mmol) in anhydrous dichloromethane (5 mL) at 0 °C was added $InBr_3$ (10 mol %) under nitrogen atmosphere. The resulting mixture was allowed to stir at room temperature for the specified time (Tables 2 and 3). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (0.5 mL), diluted with water (2−3 mL) and extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford the pure product **3** (Table 2) or **5** (Table 3).

(3a*R,4*R**,7a*S**)-4-(4-Methoxyphenyl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3a; Table 2, Entry a).** Yield, 120 mg, 88%. Solid: mp 132−134 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2H), 6.86−6.84 (m, 2H), 3.79 (s, 3H), 3.73 (d, J = 10.5 Hz, 1H), 2.94−2.89 (m, 1H), 2.88−2.84 (m, 1H), 2.77 (td, J = 13.7 and 3.6 Hz, 1H), 2.73−2.67 (m, 2H), 2.42 (qd, J = 12.6 and 3.2 Hz, 1H), 2.17−2.11 (m, 1H), 2.00−1.96 (m, 1H), 1.83 (dq, J = 12.5 and 3.2 Hz, 1H), 1.44−1.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 132.9, 128.6, 114.0, 55.7, 55.2, 51.4, 51.1, 34.5, 33.4, 31.1, 26.7; IR (KBr) ν_{max} 2926, 2859, 1511, 1457, 1256, 1174, 1027, 828, 761 cm^{-1}; GC−EI-MS m/z 266 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{14}H_{18}OS_2$ 266.07991 (M)$^+$, found 266.08092.

(3a*S,4*R**,7a*S**)-4-(4-Methoxyphenyl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3b; Table 2, Entry b).** Yield, 113 mg, 85%. Solid: mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.16 (m, 2H), 6.90−6.81 (m, 2H), 4.41 (d, J = 3.2 Hz, 1H), 3.79 (s, 3H), 3.29−3.18 (m, 1H), 3.05−2.94 (m, 1H), 2.84−2.65 (m, 3H), 2.61−2.49 (m, 1H), 2.46−2.27 (m, 1H), 2.15−2.03 (m, 1H), 1.99−1.81 (m, 1H), 1.77−1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 133.7, 128.4, 113.7, 55.2, 50.9, 49.0, 47.2, 33.2, 30.3, 28.7, 25.2; IR (KBr) ν_{max} 2924, 2852, 1508, 1456, 1249, 1027, 821 cm^{-1}; GC−EI-MS m/z 266 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{14}H_{18}OS_2$ 266.07991 (M)$^+$, found 266.08016.

(3a*R,4*R**,7a*S**)-4-(Naphthalen-1-yl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3c; Table 2, Entry c).** Yield, 128 mg, 90%. Solid: mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22−8.15 (m, 1H), 7.90−7.83 (m, 1H), 7.81−7.74 (m, 1H), 7.72−7.66 (m, 1H), 7.59−7.44 (m, 3H), 4.67 (d, J = 10.2 Hz, 1H), 3.12−2.98 (m, 2H), 2.89−2.79 (m, 1H), 2.76−2.66 (m, 2H), 2.57−2.34 (m, 2H), 2.10−1.85 (m, 2H), 1.50−1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 133.8, 131.1, 129.0, 128.0, 126.3, 125.6, 125.5, 124.8, 122.6, 55.4, 51.8, 45.3, 34.2, 33.6, 31.4, 26.7; IR (KBr) ν_{max} 2919, 2850, 1466, 1218, 1184, 1134, 1083, 916, 722 cm^{-1}; GC−EI-MS m/z 286 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{17}H_{18}S_2$ 286.08499 (M)$^+$, found 286.08506.

(3a*S,4*R**,7a*S**)-4-(Naphthalen-1-yl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3d; Table 2, Entry d).** Crystals for XRD were obtained by dissolving compound in 4−5 mL of methanol, followed by slow evaporation of solvent over 4 days. Yield, 123 mg, 86%. Solid: mp 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11−8.03 (m, 1H), 7.92−7.84 (m, 1H), 7.80−7.73 (m, 1H), 7.61−7.39 (m, 4H), 5.32 (d, J = 3.2 Hz, 1H), 3.43−3.32 (m, 1H), 3.00−2.75 (m, 4H), 2.71−2.58 (m, 1H), 2.52−2.34 (m, 1H), 2.23−2.12 (m, 1H), 2.08−1.90 (m, 1H), 1.55−1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 133.7, 130.2, 129.0, 127.7, 126.3, 125.6, 125.3, 124.9, 122.4, 48.9, 47.1, 45.2, 33.5, 30.7, 28.5, 25.7; IR (KBr) ν_{max} 2925, 2857, 1458, 1265, 1200, 1160, 1108, 777 cm^{-1}; GC−EI-MS m/z 286 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{17}H_{18}S_2$ 286.08499 (M)$^+$, found 286.08484.

(3a*R,4*R**,7a*S**)-4-(4-Chlorophenyl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3e; Table 2, Entry e).** Yield, 114 mg, 85%. Solid: mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 4H), 3.74 (d, J = 10.6 Hz, 1H), 3.00−2.66 (m, 5H), 2.49−2.39 (m, 1H), 2.20−2.02 (m, 1H), 2.00−1.75 (m, 2H), 1.50−1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 133.4, 129.0, 128.9, 55.3, 51.3, 51.1, 34.4, 33.3, 31.0, 26.6; IR (KBr) ν_{max} 2924, 2855, 1521, 1488, 1344, 1088, 829, 756 cm^{-1}; GC−EI-MS m/z 270 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{13}H_{15}ClS_2$ 270.03037 (M)$^+$, found 270.03028.

(3a*S,4*R**,7a*S**)-4-(4-Chlorophenyl)hexahydro-2*H*-thieno-[3,2-*c*]thiopyran (3f; Table 2, Entry f).** Yield, 115 mg, 86%. Solid: mp 86−88 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30−7.27 (m, 2H), 7.22−7.19 (m, 2H), 4.43 (d, J = 3.5 Hz, 1H), 3.24 (td, J = 12.3 and 5.3 Hz, 1H), 3.00−2.97 (m, 1H), 2.79−2.70 (m, 3H), 2.56−2.52 (m, 1H), 2.37−2.30 (m, 1H), 2.11−2.07 (m, 1H), 1.93−1.86 (m, 1H), 1.66−1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 132.9, 128.7, 128.6, 50.4, 49.0, 47.1, 33.0, 30.2, 28.6, 25.0; IR (KBr) ν_{max} 2931, 2860, 1483, 1410, 1275, 1090, 833, 808 cm^{-1}; GC−EI-MS m/z 270 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{13}H_{15}ClS_2$ 270.03037 (M)$^+$, found 270.03041.

(3a*R,4*S**,7a*S**)-4-Styrylhexahydro-2*H*-thieno[3,2-*c*]-thiopyran (3g; Table 2, Entry g).** Yield, 118 mg, 90%. Solid: mp 128−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.34 (m, 2H), 7.34−7.28 (m, 2H), 7.28−7.21 (m, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.12 (dd, J = 16.0 and 9.0 Hz, 1H), 3.50 (t, J = 9.0 Hz, 1H), 2.92−2.84 (m, 1H), 2.82−2.69 (m, 4H), 2.43−2.34 (m, 2H), 1.93−1.83 (m, 1H), 1.74 (dq, J = 12.0 and 4.0 Hz, 1H), 1.58−1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 132.5, 128.5, 128.4, 127.8, 126.4, 54.8, 50.7, 49.7, 34.9, 33.1, 30.1, 26.7; IR (KBr) ν_{max} 2934, 2862, 1445, 1252, 968, 761, 687 cm^{-1}; GC−EI-MS m/z 262 (M)$^+$; HRMS (TOF GC−EI) calcd for $C_{15}H_{18}S_2$ 262.08499 (M)$^+$, found 262.08487.

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(3a*S,4*R**,7a*S**)-4-*p*-Tolylhexahydro-2*H*-thieno[3,2-*c*]-thiopyran (3h; Table 2, Entry h).** Yield, 100 mg, 80%. Solid: mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.08 (m, 4H), 4.42 (d, J = 3.8 Hz, 1H), 3.24 (td, J = 12.1 and 5.3 Hz, 1H), 3.03−2.94 (m, 1H), 2.84−2.67 (m, 3H), 2.62−2.50 (m, 1H), 2.46−2.26 (m, 1H), 2.33 (s, 3H), 2.15−2.02 (m, 1H), 1.99−1.81 (m, 1H), 1.75−1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 136.9, 129.1, 127.3, 50.8, 49.5, 47.4, 33.3, 30.3, 28.8, 25.6, 21.0; IR (KBr) ν_{max} 2922, 2854, 1454, 1271, 1157, 1111, 823 cm^{-1}; GC−EI-MS m/z 250 $(M)^+$; HRMS (TOF GC−EI) calcd for $C_{14}H_{18}S_2$ 250.08499 $(M)^+$, Found 250.08570.

(3a*S,4*S**,7a*S**)-4-Pentylhexahydro-2*H*-thieno[3,2-*c*]-thiopyran (3i; Table 2, Entry i).** Yield, 86 mg, 74%. Viscous liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84−2.66 (m, 5H), 2.52−2.40 (m, 1H), 2.40−2.30 (m, 1H), 1.83−1.60 (m, 2H), 1.56−1.18 (m, 10H), 0.89 (t, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 51.6, 47.6, 34.5, 33.9, 33.5, 31.8, 29.5, 27.1, 26.1, 22.5, 14.0; IR (neat) ν_{max} 2927, 2859, 1457, 771 cm^{-1}; GC−EI-MS m/z 230 $(M)^+$; HRMS (TOF GC−EI) calcd for $C_{12}H_{22}S_2$ 230.11629 $(M)^+$, found 230.11699.

(3a*S,4*R**,7a*S**)-4-(2-Nitrophenyl)hexahydro-2*H*-thieno[3,2-*c*]thiopyran (3j; Table 2, Entry j).** Yield, 115 mg, 82%. Solid: mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.85 (m, 1H), 7.65−7.54 (m, 2H), 7.46−7.37 (m, 1H), 5.01 (d, J = 3.2 Hz, 1H), 3.30 (td, J = 12.1 and 5.3 Hz, 1H), 3.08−2.98 (m, 1H), 2.92−2.65 (m, 4H), 2.55−2.38 (m, 1H), 2.18−2.07 (m, 1H), 2.02−1.85 (m, 1H), 1.76−1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 135.9, 132.9, 130.4, 128.1, 124.7, 47.9, 46.9, 44.5, 33.2, 30.6, 28.7, 25.4; IR (KBr) ν_{max} 2924, 2854, 1523, 1460, 1344, 1273, 750 cm^{-1}; GC−EI-MS m/z 281 $(M)^+$; HRMS (TOF GC−EI) calcd for $C_{13}H_{15}NO_2S_2$ 281.05442 $(M)^+$, found 281.05451.

(3a*R,4*R**,7a*S**)-4-(Naphthalen-2-yl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5a; Table 3, Entry a).** Yield, 180 mg, 85%. Solid: mp 225−227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.67 (m, 6H), 7.52−7.32 (m, 5H), 3.80 (d, J = 10.6 Hz, 1H), 3.40−3.24 (m, 2H), 3.13−2.80 (m, 3H), 2.70−2.58 (m, 1H), 2.47 (s, 3H), 2.50−2.33 (m, 1H), 2.04−1.86 (m, 1H), 1.62−1.48 (m, 1H), 1.06−0.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 136.6, 133.8, 133.2, 133.0, 129.7, 128.5, 127.7, 127.6, 126.7, 126.3, 126.1, 125.3, 65.3, 51.6, 51.1, 47.4, 33.8, 29.7, 28.2, 21.5; IR (KBr) ν_{max} 2922, 2854, 1339, 1155, 1094, 1047, 806, 664 cm^{-1}; ESI-MS m/z 424 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{24}H_{26}NO_2S_2$ 424.13995 $(M + H)^+$, found 424.13986.

(3a*S,4*R**,7a*S**)-4-(Naphthalen-2-yl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5b; Table 3, Entry b).** Yield, 173 mg, 82%. Solid: mp 158−160 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79−7.74 (m, 3H), 7.72−7.70 (m, 2H), 7.64 (s, 1H), 7.47−7.42 (m, 2H), 7.31−7.26 (m, 3H), 4.45 (d, J = 3.5 Hz, 1H), 3.90 (td, J = 11.0 and 6.4 Hz, 1H), 3.56−3.53 (m, 1H), 3.08−3.01 (m, 1H), 2.78−2.72 (m, 2H), 2.50−2.42 (m, 1H), 2.42 (s, 3H), 2.36−2.32 (m, 1H), 2.09−2.50 (m, 1H), 1.88−1.82 (m, 1H), 1.43−1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 137.6, 135.4, 133.1, 132.6, 129.7, 128.1, 127.7, 127.5, 127.1, 126.3, 126.2, 126.0, 125.5, 59.9, 48.2, 46.4, 44.6, 30.3, 27.9, 23.2, 21.5; IR (KBr) ν_{max} 2921, 2879, 1330, 1154, 1134, 1092, 813, 669 cm^{-1}; ESI-MS m/z 424 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{24}H_{26}NO_2S_2$ 424.13995 $(M + H)^+$, found 424.14002.

(3a*R,4*R**,7a*S**)-4-(2-Fluorophenyl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5c; Table 3, Entry c).** Yield, 176 mg, 90%. Solid: mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.66 (m, 2H), 7.51−7.33 (m, 3H), 7.25−7.17 (m, 1H), 7.16−7.08 (m, 1H), 7.04−6.94 (m, 1H), 4.07 (d, J = 10.6 Hz, 1H), 3.39−3.26 (m, 2H), 3.12−2.78 (m, 3H), 2.64−2.52 (m, 1H), 2.47 (s, 3H), 2.39−2.22 (m, 1H), 1.90 (dq, J = 12.1 and 3.8 Hz, 1H), 1.63−1.51 (m, 1H), 1.07−0.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (d, J = 246.1 Hz), 143.6, 133.4, 129.7, 129.1 (d, J = 8.2 Hz), 128.7, 127.5 126.0 (d, J = 14.5 Hz), 124.6 (d, J = 2.7 Hz), 115.4 (d, J = 22.7 Hz), 65.1, 51.1, 47.2, 42.0, 33.7, 29.4, 27.7, 21.5; IR (KBr) ν_{max} 2924, 1487, 1339, 1156, 1097, 755, 666 cm^{-1}; ESI-MS m/z 392 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{20}H_{23}FNO_2S_2$ 392.11542 $(M + H)^+$, found 392.11533.

(3a*S,4*R**,7a*S**)-4-(2-Fluorophenyl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5d; Table 3, Entry d).** Yield, 168 mg, 86%. Solid: mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.75 (m, 2H), 7.47−7.41 (m, 1H), 7.37−7.21 (m, 4H), 7.09−7.02 (m, 1H), 4.50 (broad s, 1H), 4.33 (td, J = 13.0 and 4.0 Hz, 1H), 3.55−3.45 (m, 1H), 2.92−2.84 (m, 1H), 2.75−2.63 (m, 2H), 2.47−2.28 (m, 3H), 2.44 (s, 3H), 2.08−1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (d, J = 246.4 Hz), 144.6, 136.9, 129.4, 129.2 (d, J = 2.2 Hz), 128.9 (d, J = 8.8 Hz), 128.2, 126.6 (d, J = 13.2 Hz), 124.9 (d, J = 2.2 Hz), 115.0 (d, J = 22.0 Hz), 55.7, 49.4, 46.0, 45.1, 32.1, 30.2, 26.1, 21.6; IR (KBr) ν_{max} 2924, 1370, 1166, 1088, 856, 754, 661 cm^{-1}; ESI-MS m/z 392 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{20}H_{23}FNO_2S_2$ 392.11542 $(M + H)^+$, found 392.11549.

(3a*R,4*R**,7a*S**)-4-(Thiophen-2-yl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5e; Table 3, Entry e).** Yield, 170 mg, 90%. Solid: mp 182−184 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.70−7.89 (m, 2H), 7.35−7.34 (m, 2H), 7.20−7.19 (m, 1H), 6.92−6.89 (m, 2H), 3.99 (d, J = 10.5 Hz, 1H), 3.38−3.35 (m, 1H), 3.31 (dt, J = 10.5 and 6.7 Hz, 1H), 3.01 (qd, J = 13.2, 3.2, 3.6, and 3.2 Hz, 1H), 2.94−2.90 (m, 1H), 2.81 (td, J = 14.2 and 3.6 Hz, 1H), 2.56 (dt, J = 10.5 and 3.0 Hz, 1H), 2.46 (s, 3H), 2.27−2.21 (m, 1H), 1.81 (dq, J = 12.6 and 3.6 Hz, 1H), 1.72−1.69 (m, 1H), 1.02−0.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.3, 133.7, 129.7, 127.5, 126.5, 125.2, 124.8, 65.0, 53.4, 47.2, 45.9, 33.5, 29.8, 28.2, 21.5; IR (KBr) ν_{max} 2924, 2855, 1521, 1450, 1330, 1289, 1155, 1096, 811, 662 cm^{-1}; GC−EI-MS m/z 379 $(M)^+$; HRMS (TOF GC−EI) calcd for $C_{18}H_{21}NO_2S_3$ 379.07344 $(M)^+$, found 379.07362.

(3a*S,4*R**,7a*S**)-4-(Thiophen-2-yl)-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5f; Table 3, Entry f).** Yield, 155 mg, 82%. Solid: mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.67 (m, 2H), 7.35−7.26 (m, 2H), 7.18−7.12 (m, 1H), 6.93−6.84 (m, 2H), 4.59 (d, J = 3.8 Hz, 1H), 3.89−3.79 (m, 1H), 3.61−3.52 (m, 1H), 3.20−3.08 (m, 1H), 2.73−2.64 (m, 2H), 2.43 (s, 3H), 2.35−2.22 (m, 1H), 2.15−1.93 (m, 2H), 1.91−1.73 (m, 1H), 1.72−1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 142.8, 135.4, 129.8, 127.2, 126.6, 124.8, 124.3, 59.5, 46.3, 44.7, 42.8, 30.1, 28.2, 23.5, 21.5; IR (KBr) ν_{max} 2924, 2854, 1338, 1161, 1091, 754, 664 cm^{-1}; GC−EI-MS m/z 379 $(M)^+$; HRMS (TOF GC−EI) calcd for $C_{18}H_{21}NO_2S_3$ 379.07344 $(M)^+$, found 379.07356.

(3a*R,4*S**,7a*S**)-4-Cyclohexyl-1-tosyloctahydrothiopyrano-[4,3-*b*]pyrrole (5g; Table 3, Entry g).** Yield, 152 mg, 80%. Solid: mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.65 (m, 2H), 7.37−7.30 (m, 2H), 3.47−3.23 (m, 2H), 2.96−2.85 (m, 1H), 2.81−2.63 (m, 2H), 2.62−2.54 (m, 1H), 2.51−2.39 (m, 1H), 2.44 (s, 3H), 2.09−1.97 (m, 1H), 1.96−1.85 (m, 1H), 1.80−1.44 (m, 8H), 1.43−0.92 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 133.8, 129.7, 127.5, 65.7, 52.9, 48.9, 47.7, 40.5, 34.1, 31.5, 27.7, 26.9, 26.6, 26.4, 26.3, 21.5; IR (KBr) ν_{max} 2926, 2851, 1447, 1340, 1298, 1159, 1099, 1040, 811, 661 cm^{-1}; ESI-MS m/z 380 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{20}H_{30}NO_2S_2$ 380.17180 $(M + H)^+$, found 380.17198.

(3a*S,4*S**,7a*S**)-4-Cyclohexyl-1-tosyloctahydrothiopyrano-[4,3-*b*]pyrrole (5h; Table 3, Entry h).** Yield, 145 mg, 76%. Solid: mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.66 (m, 2H), 7.35−7.26 (m, 2H), 3.75−3.64 (m, 1H), 3.57−3.47 (m, 1H), 3.32−3.18 (m, 1H), 2.86−2.78 (m, 1H), 2.62−2.51 (m, 1H), 2.50−2.37 (m, 2H), 2.43 (s, 3H), 2.28−2.10 (m, 1H), 2.00−1.85 (m, 2H), 1.83−1.50 (m, 7H), 1.34−1.02 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 135.9, 129.6, 127.1, 59.9, 49.3, 46.2, 40.2, 40.1, 31.6, 30.4, 30.1, 26.7, 26.2, 26.0, 25.9, 22.2, 21.4; IR (KBr) ν_{max} 2926, 2853, 1508, 1343, 1160, 1092, 814, 665 cm^{-1}; ESI-MS m/z 380 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{20}H_{30}NO_2S_2$ 380.17180 $(M + H)^+$, found 380.17174.

(3a*R,4*S**,7a*S**)-4-Pentyl-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5i; Table 3, Entry i).** Yield, 140 mg, 76%. Solid: mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.68 (m, 2H), 7.32−7.25 (m, 2H), 4.36−4.27 (m, 1H), 3.96−3.85 (m, 1H), 3.09 (dt, J = 11.3 and 3.8 Hz, 1H), 2.99−2.87 (m, 1H), 2.86−2.69 (m, 2H), 2.48−2.39 (m, 1H), 2.42 (s, 3H), 2.13−2.03 (m, 1H), 1.93−1.83 (m, 1H), 1.68−1.40 (m, 3H), 1.39−1.14 (m, 6H), 0.92−0.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 138.5, 129.6, 126.9, 56.8, 51.1, 44.0,

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40.4, 31.9, 31.6, 31.6, 28.7, 26.2, 25.4, 22.5, 21.5, 14.0; IR (KBr) ν_{max} 2938, 2860, 1491, 1344, 1228, 1156, 1087, 1024, 818, 763, 664 cm^{-1}; ESI-MS *m/z* 368 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{19}H_{30}NO_2S_2$ 368.17180 $(M + H)^+$, found 368.17188.

(3a*S*,4*R***,7a*S***)-4-Phenyl-1-tosyloctahydrothiopyrano[4,3-*b*]pyrrole (5j; Table 3, Entry j).** Yield, 150 mg, 80%. Solid: mp 186−188 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83−7.72 (m, 2H), 7.46−7.24 (m, 7H), 4.33 (td, *J* = 12.7 and 4.0 Hz, 1H), 4.24 (brs, 1H), 3.51−3.34 (m, 1H), 2.92−2.78 (m, 1H), 2.77−2.56 (m, 2H), 2.53−2.26 (m, 3H), 2.43 (s, 3H), 2.12−1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 139.4, 137.0, 129.4, 128.8, 128.3, 127.4, 127.3, 56.4, 52.8, 49.4, 47.8, 32.1, 30.1, 26.0, 21.6; IR (KBr) ν_{max} 2924, 2854, 1373, 1165, 1085, 811, 662 cm^{-1}; ESI-MS *m/z* 374 $(M + H)^+$; HRMS (Orbitrap ESI) calcd for $C_{20}H_{24}NO_2S_2$ 374.12430 $(M + H)^+$, found 374.12479.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of products (**3a−3j**, **5a−5j**), NOESY and DQFCOSY study of selected compounds, ORTEP diagram of **3d**, and X-ray data (CIF) of compounds (**3d**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The discussion on 1NMR and NOE studies of these compounds has been provided in Supporting Information.

(17) The supplementary crystallographic data (CIF File) and respective ORTEP diagram for this compound have been provided in Supporting Information.

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■ NOTE ADDED AFTER ASAP PUBLICATION

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