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Synthesis of a C_{11} Spiropiperidino derivative of 8-Chloro-6,11-dihydro 5*H*-Benzo[5,6]cyclohepta[1,2-b]pyridine

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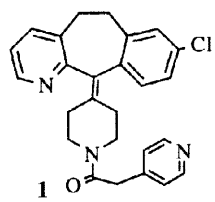
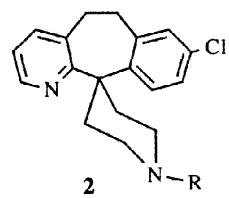
Abstract: A method using N-tosyl aziridine for the synthesis of a spiropiperidine **2** (R=H) is described. Cleavage of the N-tosyl group of the intermediate **8** to form the spiropiperidinone **9** was found to proceed in high yield with conc. sulfuric acid. Acylated derivatives of **2** were required for a structure-activity study aimed at defining the spatial requirements of the N-acyl residue in the lead Farnesyl-Protein-Transferase inhibitor **1**.

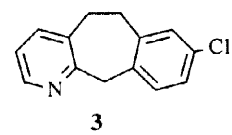
Selective inhibition of Farnesyl-Protein-Transferase (FPT) in the post translational prenylation of Ras protein is a therapeutic target of current interest for the development of antitumor agents. The tricyclic heterocycle **1** has been reported by our laboratories as a novel nonpeptidic, nonthiol-containing and selective FPT inhibitor.[1] The N-acyl functionality was found to be necessary for the biological activity of **1** and its analogs. As part of a structure–activity program based on this lead compound, we were interested in synthesising chemical structures which alter the spatial location of the N-acyl residue of **1** relative to the top benzocycloheptapyridine tricycle.[2] In this paper we report the synthesis of the spiropiperidino compound **2** (R=H) which was one of the chemical modifications of **1** that we required for the structure-FPT activity study.



1



2



3

Alkylation of activated methylene groups with N-(protected)bis(2-chloroethyl)amine is a commonly used method for preparing spiropiperidines.[3] Attempts to apply this prior methodology to the readily obtainable 8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine[4] (**3**) to prepare the target structure **2**, were unsuccessful. The approach that we developed for the synthesis of **2** involves a two step alkylation of the C_{11} methylene of **3** with functionalities that can undergo an intramolecular cyclization to form a spiropiperidinone (Scheme 1). Thus, reaction of the carbanion of **3** with N-tosyl aziridine[5] afforded **4**. The tosylamino group of **4** is protected as the TBDMS derivative **5** followed by deprotonation with *n*-butyl lithium and reaction with methyl

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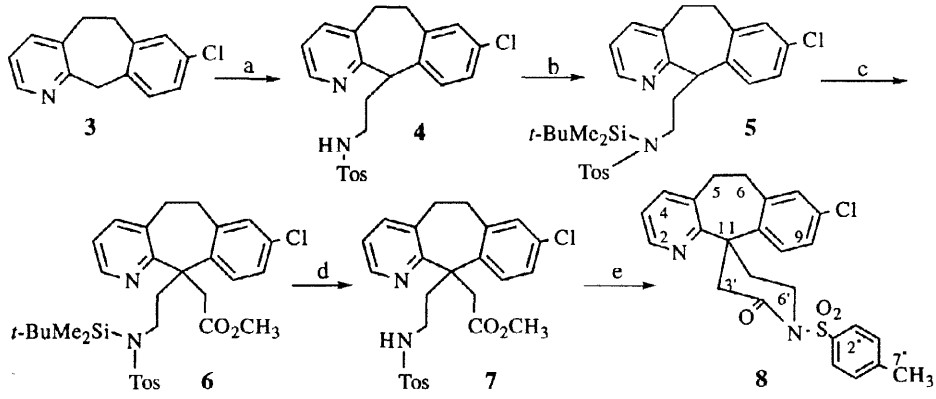
bromoacetate to provide the C_{11} dialkylated intermediate **6**. Fluoride mediated desilylation of **6** provided the tosylamino ester **7** which upon heating in toluene undergoes an intramolecular cyclization to form the spiropiperidinone **8**.

Scheme 1[a]



[a]Reagents: (a) i. *n*-BuLi, THF/-78 °C; ii. N-tosylaziridine (b) i. NaH, THF/0 °C; ii. *t*-$BuMe_2SiCl$ (c) i. *n*-BuLi, THF/-78 °C; ii. $BrCH_2CO_2CH_3$ (d) $Bu_4N^+F^-$, THF/20 °C (e) $PhCH_3$/110 °C

Proton NMR data for the product are consistent with the assigned structure **8**. Table 1 summarizes the proton assigments which are based on the (^{1}H-^{1}H)2D COSY spectra. Included in Table 1 are δ values for the C_2-H of **8** at three temperatures. The observed temperature dependent values for the chemical shift is indicative of an inherent conformational mobility in this molecule.

Table 1. ^{1}H NMR Assignments for **8**

Atom #	^{1}H δ (mult. *J* Hz)[a]	Atom #	^{1}H δ (mult. *J* Hz)
2	7.60 (dd, 1H, *J* = 5.0, 2.0 Hz)	3'	3.00 (d, 1H, *J* = 15.5 Hz)
	δ [b]: 7.42 (25 °C); 7.51 (50 °C); 7.62 (75 °C)		3.58 (dd, 1H, *J* = 15.5, 2.5Hz)
3	6.96 (dd, 1H, *J* = 8.0, 5.0 Hz)	5'	2.85 (m, *J* = 14.5, 5.0, 4.0, 2.5 Hz)
			2.56 (ddd, *J* = 14.5, 10.5, 5.0 Hz)
4	7.34 (dd, 1H, *J* = 8.0, 2.0 Hz)	6'	3.82 (dt, *J* = 12.0, 5.0, 5.0 Hz)
			3.17 (ddd, *J* = 12.0, 10.5, 4.0 Hz)
5, 6	3.66, 3.24, 2.90 (m)	2"	7.79 (d, 1H, *J* = 8.0 Hz)
7	7.20 (d, 1H, *J* = 2.0 Hz)	3"	7.31 (d, 1H, *J* = 8.0 Hz)
9	7.00 (dd, 1H, *J* = 8.5, 2.0 Hz)	7'	2.50 (s, 3H)
10	7.12 (d, 1H, *J* = 8.5 Hz)		

[a] Chemical shift data in $CDCl_3$. [b] Variable temperature chemical shift data in DMSO-d_6.

The structure of **8** was unambiguously established by single crystal X-ray analysis (Figure 1).[6] Subsequent steps of the synthesis are shown in Scheme 2. Initial attempts at N-detosylation or reduction of the carbonyl of **8** were not successful.[7] However, we found that N-detosylation of **8** was achieved in high yield to afford the spiropiperidinone **9** by heating a solution of the N-tosyl

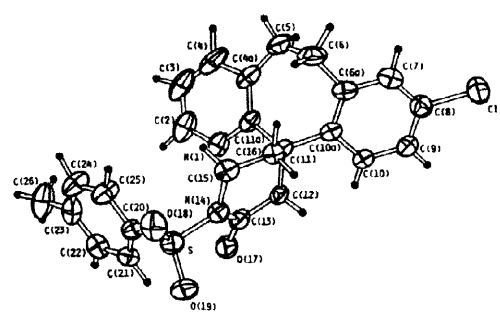
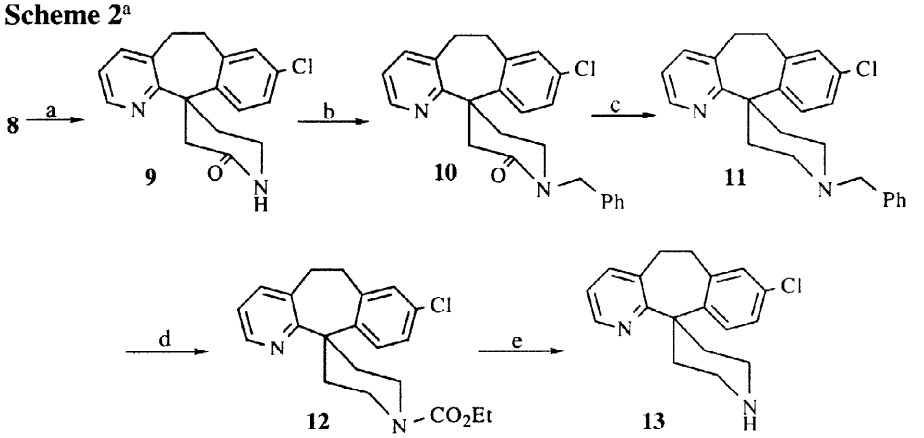


Figure 1. ORTEP diagram of **8**

compound in conc. sulfuric acid. Reduction of the piperidinone **9** required an N-benzylation step to afford **10**; thus, while **8** and **9** were resistant to LAH reduction, the same reduction conditions converted the N-benzyl derivative **10** to the desired spiropiperidine **11**. Debenzylation of **11** was conducted by conversion with ethyl chloroformate to the carbamate **12** followed by acid hydrolysis to afford the target C_{11} spiropiperidine compound **13**.[8]

Scheme 2[a]



[a]Reagents: (a) conc.H_2SO_4/75 °C (b) i. NaH, DMF/0 °C; ii. $PhCH_2Cl$ (c) LAH, THF/75 °C (d) ClCOOEt, $PhCH_3$/110 °C (e) 6N HCl/110 °C.

In summary, we describe here a method for the synthesis of the C_{11} spiropiperidine benzocycloheptapyridine tricycle **13** which uses the alkylation of N-tosylaziridine as the key step. Compound **13** was used to prepare various acylated derivatives needed for a structure-FPT activity study[9] based on our lead FPT inhibitor **1**.

Acknowledgements: We thank our Analytical Services for the physical data of the compounds reported here.

References and Notes:

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6. Crystal structure data may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK).
7. Compound **8** was resistant to conventional N-detosylation conditions e.g. HBr, electrochemical reduction; use of sodium amalgam/ethanol did provide a detosylated product with concomitant 1,2-reduction of the pyridine ring. Compound **8** was also resistant to LAH reduction.
8. Physical data for **4**: white crystals from EtOAc: (quant.); mp 189–190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02, 2.30 (m, 2H), 2.40 (s, 3H), 2,70, 3.00,3.15 (m, 6H), 4.30 (dd, 1H), 6.89 (d, 1H), 7.04 (m, 2H), 7.10 (s,1H), 7.26 (d, 2H), 7.35 (dd, 1H), 7.70 (d, 2H), 8.28 (dd,1H). Anal. Calcd for $C_{23}H_{22}N_2O_2ClS$: C, 64.86; H, 5.21; N, 6.58. Found: C, 64.35; H, 5.43; N, 6.51.

5: white crystals from EtOAc-hexane: (87%); mp 142-143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.28 (s,3H), 0.30 (s,3H), 1.0 (s, 9H); HRMS(FAB) calcd for $C_{29}H_{38}N_2O_2SiClS$ 541.2112, found 541.2093.

6: white crystals from EtOAc-hexane: (44%); mp 86-100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.03 (d,1H), 3.41 (s, 3H), 4.18 (d, 1H); HRMS(FAB) calcd for $C_{32}H_{41}N_2O_4SiClS$ 613.2323, found 613.2318.

8: white crystals from EtOAc-hexane: (61%); mp 217-218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ ; MS(FAB) *m/z* 467 (MH^+). Anal. Calcd for $C_{25}H_{23}N_2O_3ClS$: C, 64.30; H, 4.96; N, 6.00; S, 6.87. Found: C, 64.50; H, 5.01; N, 6.03, S, 6.81.

9: white crystals from CH_2Cl_2: (75%); mp 263-264 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00(d, 2H, *J*=17Hz), 3.00 (d,1H)5.76(s,1H); MS(CI) *m/z* 313 (MH^+). Anal. Calcd for $C_{18}H_{17}N_2OCl$: C, 69.12; H,5.48; N, 8.96. Found: C, 68.98; H, 5.58; N, 9.09.

10: white crystals from hexane: (90%); mp 133-134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15 (d, 1H, *J*=15 Hz), 4.10 (d,1H, *J*=15 Hz), 4.40 (d, 1H *J*=14.6 Hz), 4.65 (d, 1H, *J*=14.6 Hz); MS(CI) *m/z* 403 (MH^+). Anal. Calcd for $C_{25}H_{23}N_2OCl$: C, 74.52; H,5.75; N, 6.95. Found: C, 74.09; H, 5.77; N, 7.00.

11: pale yellow resin: (46%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40 (m, 4H), 2.68 (m, 2H), 3.00(m, 2H), 3.30 (m,4H), 3.45 (s, 2H); HRMS(FAB) calcd for $C_{25}H_{26}N_2Cl$: 389.1785, found 389.1788.

12: pale yellow resin: (85%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H), 2.22 (m, 2H), 3.06 (m, 2H), 3.36 (b, 6H), 3.86 (m, 2H), 4.10 (q, 2H); MS(CI) *m/z* 371 (MH^+). Anal. Calcd for $C_{21}H_{23}N_2O_2Cl$: C, 68.01; H, 6.25; N, 7.55. Found: C, 68.16; H, 6.42; N, 7.49.

13: pale yellow resin:(quant.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (m, 2H), 2.76 (m, 1H), 3.10 (m, 5H), 3.32 (m, 4H); MS(FAB) *m/z* 299 (MH^+). Anal. Calcd for $C_{18}H_{19}N_2Cl(0.25xCH_2Cl_2)$: C, 68.47; H, 6.14; N, 8.76. Found: C, 68.27; H, 6.37; N, 8.56.
9. The biological activity of these derivatives will be reported in a forthcoming manuscript.