

Tetrahedron Letters 39 (1998) 7661-7664

TETRAHEDRON LETTERS

## Synthesis of a C<sub>11</sub> Spiropiperidino derivative of 8-Chloro-6,11-dihydro 5*H*-Benzo[5,6]cyclohepta[1,2-b]pyridine

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Received 17 June 1998; accepted 7 August 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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.<sup>1</sup> 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.<sup>2</sup> 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.



Alkylation of activated methylene groups with N-(protected)bis(2-chloroethyl)amine is a commonly used method for preparing spiropiperidines.<sup>3</sup> Attempts to apply this prior methodology to the readily obtainable 8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine<sup>4</sup> (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<sup>5</sup> 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

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.



\*Reagents: (a) i. *n*-BuLi, THF/-78 °C; ii. N-tosylaziridine (b) i. NaH, THF/O °C; ii. *t*-BuMe<sub>2</sub>SiCl (c) i. *n*-BuLi, THF/-78 °C; ii. BrCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> (d) Bu<sub>4</sub>N\*F; THF/20 °C (e) PhCH<sub>3</sub>/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  $\delta$  values for the C<sub>2</sub>-

Atom #	<sup>1</sup> H $\delta$ (mult. J Hz) <sup>a</sup>	Atom #	'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 <sup>b</sup> : 7.42 (25 °C); 7.51 (50 °C); 7.62 (75 °C)		$3.58 (\mathrm{dd}, 1\mathrm{H}, J = 15.5, 2.5\mathrm{Hz})$
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)		

 Table 1. <sup>1</sup>H NMR Assignments for 8

<sup>a</sup> Chemical shift data in CDCl<sub>3</sub>.<sup>b</sup> Variable temperature chemical shift data in DMSO-d<sub>6</sub>.

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.

The structure of 8 was unambiguously established by single crystal X-ray analysis (Figure 1).<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup>



"Reagents: (a) conc.H<sub>2</sub>SO<sub>4</sub>/75 °C (b) i. NaH, DMF/0 °C; ii. PhCH<sub>2</sub>Cl (c) LAH, THF/75 °C (d) ClCOOEt, PhCH<sub>3</sub>/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<sup>9</sup> 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:**

- Bishop, R. W.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, G.; Cattino, J.; Schwartz, J.; Windsor, W.; Syto, R.; Carr, D.; James, L.; Kirshmeier, P. J. Biological Chem. 1995, 270, 30611.
- Kelly, J.; Wolin, R.; Connolly, M.; Afonso, A.; James, L.; Kirshmeier, P.; Bishop, W.R.; McPhail, A. T. Biorg. Med. Chem. 1998, 6, 673.
- Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. J. Med. Chem. 1992, 35, 2033.
- Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A.J. Med. Chem. 1972,15, 750.

- 5. Martin, A. E.; Ford, T. M.; Bulkowski, J. E. J. Org. Chem. 1982, 47, 412.
- 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.
- Physical data for 4: white crystals from EtOAc: (quant.); mp 189–190 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>ClS: 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ ; MS(FAB) *m/z* 467 (MH<sup>+</sup>). Anal. Calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>ClS: 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<sub>2</sub>Cl<sub>2</sub>: (75%); mp 263-264 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 4.00(d, 2H, *J*=17Hz), 3.00 (d,1H)5.76(s,1H); MS(CI) *m*/z 313 (MH<sup>+</sup>). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>OCl: 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  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<sup>+</sup>). Anal. Calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>OCl: C, 74.52; H,5.75; N, 6.95. Found: C, 74.09; H, 5.77; N, 7.00. **11**: pale yellow resin: (46%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  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<sub>25</sub>H<sub>26</sub>N<sub>2</sub>Cl: 389.1785, found 389.1788.

12: pale yellow resin: (85%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  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<sup>+</sup>). Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>Cl: C, 68.01; H, 6.25; N, 7.55. Found: C, 68.16; H, 6.42; N, 7.49.

13: pale yellow resin:(quant.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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<sup>+</sup>). Anal. Calcd for C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>Cl(0.25xCH<sub>2</sub>Cl<sub>2</sub>): 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.