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

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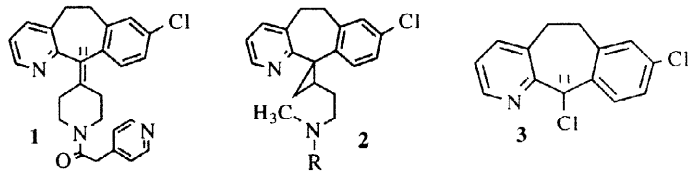
Abstract: The carbanion derived from 8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridine (**3**) reacts with methyl acrylate to form the C_{11} spirocyclopropane carboxylic acid methyl ester **6**. Compound **6** was converted in five steps to the N-methyl 2'-ethylamino spirocyclopropane **2** (R=H) which was required for a structure-activity study based on the lead Farnesyl Protein Transferase inhibitor **1**.

Our laboratories have reported the discovery of the tricyclic heterocycle **1** as a novel nonpeptidic, nonthiol-containing selective inhibitor of Ras farnesylation by Farnesyl Protein Transferase (FPT); such inhibitors are of current interest for the development of antitumor agents to control cell proliferation in *ras* associated tumors.[1] The N-acyl functionality was found to be crucial to the FPT inhibition activity of **1**. As part of a structure–activity study based on this lead compound, we were interested in chemical modifications of the pendant piperidine ring of **1** aimed at altering the spatial location of the N-acyl residue relative to the top benzocycloheptapyridine tricycle.[2] In this paper we report the synthesis of the spirocyclopropyl amine **2** (R=H) which contains an acyclic version of the piperidine ring in **1** and is designed to allow greater conformational mobility for its N-acylated derivatives.



The synthesis of 2 utilizes the readily obtainable 11-chloro benzocycloheptapyridine **3**.[3] Compound **3** is a reactive electrophile, however we have found that it can be used as an α-halo carbonyl equivalent in the McCoy cylopropanation method[4] provided the deprotonation at C_{11} is carried out under controlled conditions. Thus, **3** is deprotonated with *n*-butyl lithium under high dilution conditions (0.08M solution of **3** in THF) to form the stabilized carbanion/carbenoid **4** (Scheme 1).[5] Reaction of the resulting carbanion/carbenoid **4** with an excess of methyl acrylate afforded the spirocyclopropane methyl ester **6** as a single diastereoisomer, in modest yield (30%).[6] Only trace amounts of **6** were detectable when the reaction was performed under conventional reactant

0040-4039/98/$ - see front matter
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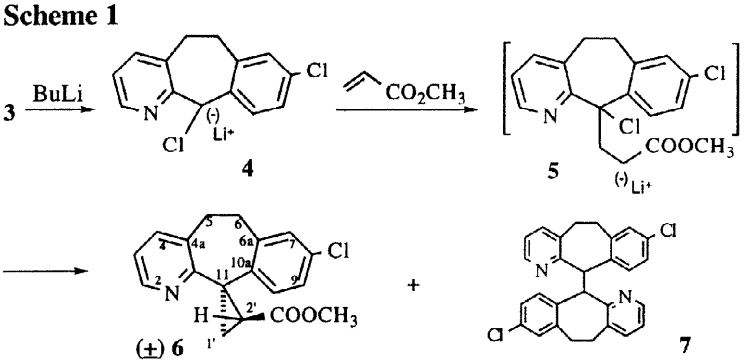
concentrations (e.g. 0.2M solution of **3** in THF). The exclusive diastereoselectivity in the formation of the cyclopropane carboxylic ester **6** is not obvious but may result from a preferential π-overlap of the carbomethoxy group with the chlorophenyl ring in the intermediate anion adduct **5** prior to cyclization to the cyclopropane. An attempted preparation of a spirocyclopropane from a dibenzosuberane species corresponding to **4** (N = CH) has been reported previously.[7]

Scheme 1



NMR data for the product are in agreement with the assigned structure **6**. The chemical shift assignments shown in Table 1 are based on ^{1}H, ^{13}C(+APT), HMBC and HMQC analysis.

Table 1. NMR data of **6**

Atom #	^{13}C δ	^{1}H δ (mult.*J* Hz)	Atom #	^{13}C δ	^{1}H δ (mult.*J* Hz)
2	146.3	8.29 (dd, 5.0, 2.0)	9	126.4	7.13 (dd, 8.0, 1.0)
3	122.7	7.08 (dd, 8.0, 5.0)	10	131	7.32 (d, 8.0)
4	138.8	7.38 (dd, 8.0, 2.0)	10a	135.9	
4a	134.5		11	38.8	
5	32.5	2.97, 3.45 (m)	11a	155.9	
6	30.7	2.80, 3.53 (m)	1'	16.6	2.11 (dd, 6.0, 5.0)
6a	142.7		2'	31.3	2.24 (bt)
7	128.4	7.12 (d, 1.0)	C=O	170.7	
8	133.4		OCH_3	51.8	3.48 (s)

The structure of **6** was unambiguously established by single crystal X-ray analysis (Figure 1).[8]

A competing side product formed in this reaction was assigned the dimeric structure **7**. This product can arise from *n*-butyl lithium attack on the C_{11}-Cl of **3** to generate a carbanion which then alkylates a second molecule of **3**. The balance of the reaction products are polar / polymeric and their identity was not investigated.

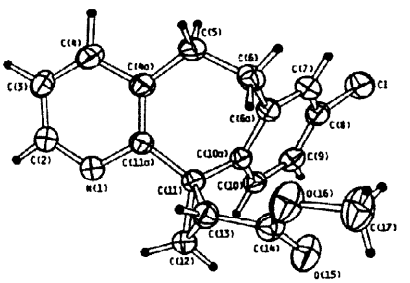
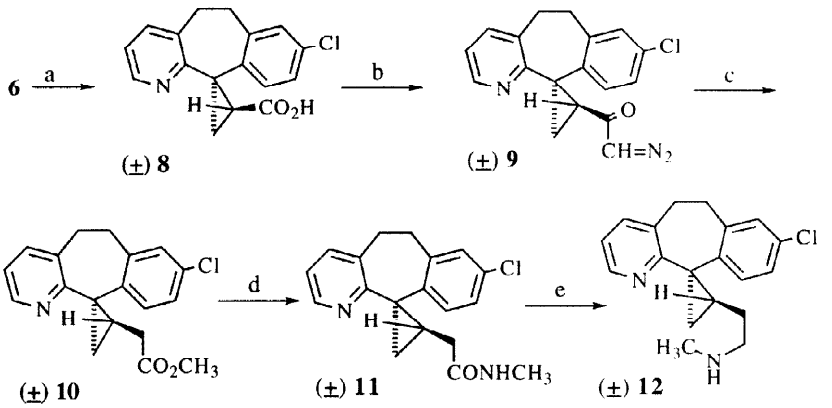


Figure 1. ORTEP diagram of **6**

The subsequent steps for the synthesis of **2** (R=H) are shown in Scheme 2. Homologation of the cyclopropane carboxylic acid methyl ester **6** was accomplished by applying the Arndt-Eistert methodology. Thus, base hydrolysis of **6** followed by conversion of the resulting carboxylic acid **8** into the acid chloride and reaction with diazomethane afforded the diazoketone **9**. Rearrangement of **9** in the presence of methanolic silver

Scheme 2[a]



[a]Reagents: (a) NaOH, acetone-water; (b) i. oxalyl chloride, CH_2Cl_2; ii. diazomethane, ether (c) silver oxide, methanol; (d) methylamine, methanol (e) lithium aluminum hydride, THF.

oxide gave the homologated methyl ester **10** which was then converted to the methyl amide **11** by aminolysis with methanolic methylamine. Lithium aluminum hydride reduction of **11** provided the desired N-methyl 2'-ethylamino spirocyclopropane **12**.[9]

In conclusion, we report here the application of the McCoy cyclopropanation methodology to the 11-chloro benzocycloheptapyridine **3** under controlled deprotonation conditions, to obtain the spirocyclopropane **6**. This compound was converted in five steps to the secondary amine **12** which was used to prepare various acylated derivatives needed for a structure-FPT activity study[10] based on our lead FPT inhibitor **1**.

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References and Notes

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2. Kelly, J.; Wolin, R.; Connolly, M.; Afonso, A.; James, L.; Kirshmeier, P.; Bishop, W.R.; McPhail, A. T. *Bioorg. Med. Chem.*, **1998**, *6*, 673.

3. Piwinski, J. J.; Green, M. J.; Wong, J. *U.S.Patent* 5,151,423 *(1992).*
4. McCoy, L. L. *J. Am. Chem. Soc.*, **1958**, *80*, 6568.
5. Milder bases such as LDA and LHMDS are less efficient for the deprototnation of **3** under these reaction conditions.
6. In a representative experiment, *n*-BuLi (1 eq) is added to a 0.08M solution of **3** in THF at -78 °C and after 5 min the resulting burgundy color solution is reacted with methyl acrylate (4 eq) for 10 min at the same temp. followed by warming to rt for 16 h and work-up. Most of **7** is filtered out from a toluene solution of the crude product prior to flash chromatography on silica gel (15% EtOAc-hexane).
7. Moritani, I.; Murashi, S.-I.; Yoshinaga, K.; Ashitaka, H. *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 1506.
8. Details of crystal structure data may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK).
9. Yields and physical data for **6:** white crystals from hexane (30%); mp 112-113 °C; NMR data is given in Table 1 ; MS (CI) *m / z* 314 (MH^+). Anal. Calcd for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.98; H, 5.34; N, 4.48.

   7: white crystals from ethylacetate; mp 260-262 °C (dec.); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90 (m, 4H), 3.75 (m, 4H), 5.08 (s, 2H), 6.39 (d, 2H, *J* = 8 Hz), 6.82 (m, 4H), 7.18 (s, 2H), 7.26 (d, 2H, *J* = 8 Hz), 7.99 (d, 2H, *J* = 4 Hz); HRMS (FAB) calcd for $C_{28}H_{23}N_2Cl$ 457.1238, found 457.1248.

   8: white crystals (97%); mp 244-245 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (dd, 1H, *J* = 5.0, 6.0 Hz), 2.22 (bt, 1H), 2.80 (m, 2H), 2.97 (m, 1H), 3.49, 3,53 (m, 2H), 7.10 (m, 1H), 7.11(s, 1H), 7.12 (m, 1H), 7.30 (d, 1H, *J* = 8 Hz), 7.39 (d, 1H, *J* = 7 Hz), 8.26 (d, 1H, *J* = 5 Hz); MS (FAB) *m / z* 300 (MH^+). Anal. Calcd for $C_{17}H_{14}NO_2Cl$: C, 68.12; H, 4.71; N, 4.67. Found: C, 67.95; H, 4.89; N, 4.71.

   10: pale yellow oil (49%); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (bt, 1H), 1.65 (bm, 2H), 2.45, 2.90 (bm, 2H), 2.65, 2.90 (m, 2H), 3,50 (m, 2H), 3.64 (s, 3H), 7.10, 7.12 (m, 3H), 7.25 (d, 1H), 7.40 (m, 1H), 8.31 (d, 1H, *J* = 5 Hz); MS (CI) *m / z* 328 (MH^+).

   11: white crystals from ether (68%); mp 164-165 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 1H, *J* = 6.0 Hz), 1.25 (bm, 1H), 2.35 (bm, 1H), 2.80 (d, 3H, *J* = 6.0 Hz), 2.70-2.95 (bm, 4H), 3.50 (m, 2H), 7.10, 7.12 (m, 3H), 7.25 (d, 1H), 7.40 (m, 1H), 8.31 (d, 1H, *J* = 5 Hz); MS (CI) *m / z* 327 (MH^+). Anal. Calcd for $C_{19}H_{19}N_2OCl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.49; H, 6.06; N, 8.44.

   12: tan oil (58%); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s,9H), 2.90 (t, 2H), 3.50 (t, 2H), 3.75 (s, 6H), 6.30 (s, 1H), 6.35 (s, 2H), 7.55 (s, 1H), 7.75 (bs, 1H), 8.40 (s, 1H); HRMS (FAB) calcd for $C_{19}H_{22}N_2Cl$ 313.1472, found 313.1466.
10. The biological activity of these derivatives will be reported in a forthcoming manuscript.