# A Stereoselective Synthesis of (±)-3-Aryl-6-phenyl-1-oxa-7-azaspiro[4.5]-decanes

Piotr Raubo,* Janusz J. Kulagowski, Christopher J. Swain

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, UK
Fax +44(1279)440187; E-mail: piotr_raubo@merck.com
*Received 24 July 2003*

**Abstract:** A novel stereoselective synthesis of the 3-aryl-6-phenyl-1-oxa-7-azaspiro[4.5]decane ring is reported. Palladium(0)-mediated cyclocarbonylation of γ-iodoallylic alcohol is a key step in the formation of the spirocyclic ring.

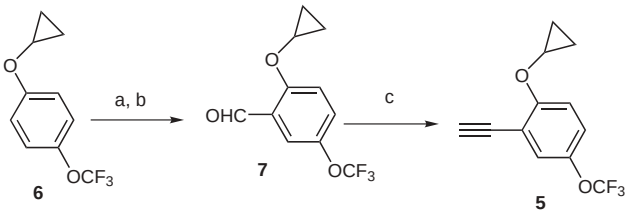
**Key words:** spirocyclic compounds, lactones, stereoselective synthesis, regioselective lithiation, substance P ($NK_1$ receptor) antagonist

The demonstration of antidepressant activity by substance P ($NK_1$ receptor) antagonists[1] has significantly accelerated efforts in identification of new selective $NK_1$ receptor ligands. Since 1991, when the first non-peptidic antagonist was reported,[2] numerous selective and structurally diverse $NK_1$ modulators have been identified and subsequently developed.[3,4]

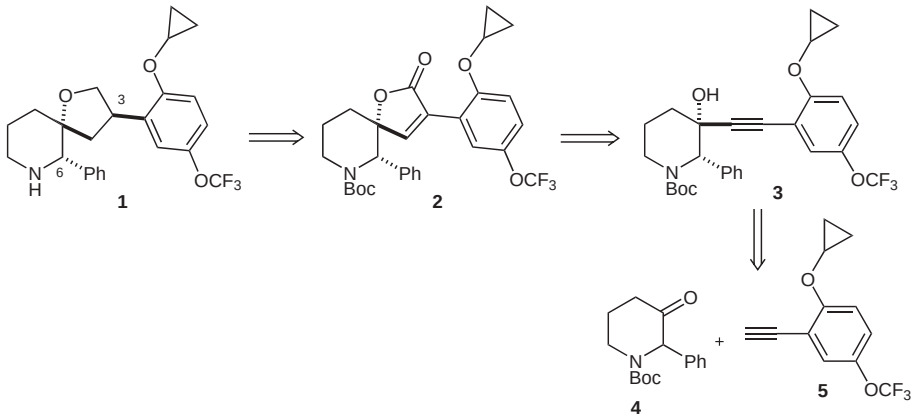
As a part of our existing programme, we were interested in examining conformationally restricted piperidine derivatives. The 6-phenyl-1-oxa-7-azaspiro[4.5]decane ring system can operate as a structural scaffold to dispose both aromatic rings required for binding to the $NK_1$ receptor.[4e] Recently, the synthesis of spirocyclic $NK_1$ receptor antagonist (+)-**1** has been disclosed.[5] In addition, two different routes to the 6-phenyl-1-oxa-7-azaspiro[4.5]decane scaffold have been published.[6] We herein report an alternative approach to racemic **1** that was developed in our laboratory.

We envisaged that **1** could be accessible from the spirocyclic lactone **2** through stereoselective manipulation of the double bond (Scheme 1). Palladium(0)-mediated cyclocarbonylation of the propargyl alcohol **3** would be then required to form the spirocycle in **2**. A further disconnection at $C_4$–$C_5$ in **3** leads to the known ketone **4**[7] and alkyne **5**.

The synthesis began with the regioselective *ortho*-lithiation of the hydroquinone derivative **6**[8] (Scheme 2) followed by treatment with *N*,*N*-dimethylformamide to give the aldehyde **7** in 76% yield. The terminal acetylene at C2 was subsequently created by reaction of the aldehyde **7** with the Ohira reagent.[9]




**Scheme 2** a) *t*-BuLi, THF, –78 °C; b) DMF, 76%; c) $CH_3COC(N_2)PO(OMe)_2$, $K_2CO_3$, MeOH, r.t., 94%.




**Scheme 1**

*SYNLETT* 2003, No. 13, pp 2021–2024
Advanced online publication: 08.10.2003
DOI: 10.1055/s-2003-42040; Art ID: D18803ST

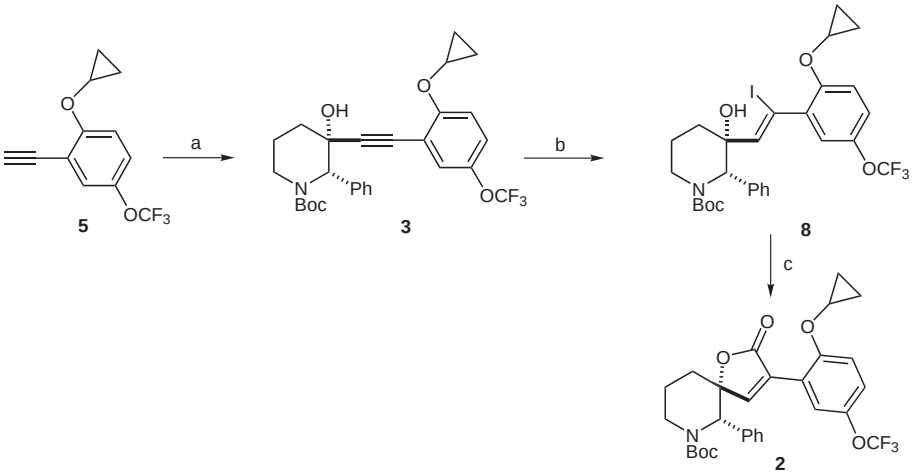
Addition of the Grignard reagent, derived from alkyne **5**, to racemic ketone **4** was diastereoselective, affording the adduct **3** as a single stereoisomer in 62% yield.[10] Formation of the desired spirocyclic lactone **2** was accomplished by a three-step sequence beginning with regioselective and stereoselective hydroalumination of the propargyl alcohol **3** with Red-Al® followed by metal-halogen exchange using iodine. The vinyl iodide **8** was obtained as a single isomer in 78% yield.[11] Subsequently, palladium(0)-mediated cyclocarbonylation[12,13] of **8** provided the spirocyclic lactone **2** in 68% yield (Scheme 3).[14]

Reduction of the double bond in the model lactone **9**[15] using $NaBH_4$ in the presence of a cat. amount of nickel(II) chloride favoured the unwanted α isomer **10a** (**10a**:**10b** = 2.5:1, Scheme 4). Several attempts were made to invert the configuration at the C3 centre in **10a**, but all were largely unsuccessful. For example, treatment of the 2.5:1 mixture of **10a** and **10b** with cat. 1,8-diazabicyclo[5.4.0]undec-1-ene (DBU) provided a 1:1.2 mixture of **10a** and **10b**.

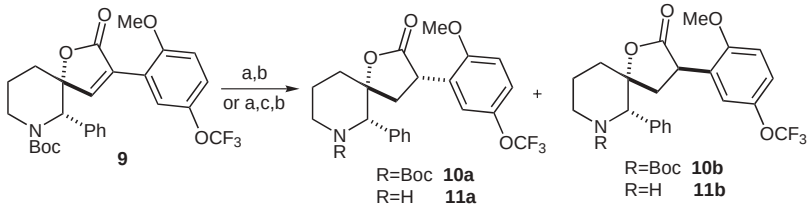
Conformational analysis showed that in the preferred conformation of carbamate **10a** the phenyl substituent occupies a *pseudo*-axial position on the piperidine.[5] Given the relatively unhindered environment of the C3 phenyl ring in this conformation, there is presumably little energetic preference for either epimer, resulting in an equilibrium ratio approaching unity. However, inversion of conformation of the piperidine ring would bring the two aryl rings into much closer proximity, resulting in greater steric repulsion in the case of the α-epimer. This would be expected to favour the desired β-epimer under conditions of thermodynamic equilibration. To test this hypothesis, the Boc protecting group in **10a,b** (**10a**:**10b** = 1.3:1) was removed and the resulting amino lactone subjected to 1,8-diazabicyclo[5.4.0]undec-1-ene (DBU) promoted equilibration. This afforded a 10:1 mixture of diastereoisomeric lactones **11b** and **11a**, respectively from which the required isomer **11b** could be obtained in pure form simply by crystallisation (Scheme 5).

By analogy, the Boc group in **2** was removed by treatment with TFA and the double bond reduced with $NaBH_4$ in the presence of cat. nickel(II) chloride to give a 3:1 mixture of diastereoisomers in favour of the α isomer **12a** (Scheme 6). DBU promoted epimerisation at C3 resulted in a 1:10 mixture of **12a** and **12b** in favour of the desired β isomer **12b**, which crystallised from the reaction mixture. To complete the synthesis, reduction of **12b** with $LiAlH_4$ and subsequent cycloetherification of the resulting intermediate diol under Mitsunobu conditions afforded the spirocyclic ether **1** in 55% yield.[16]

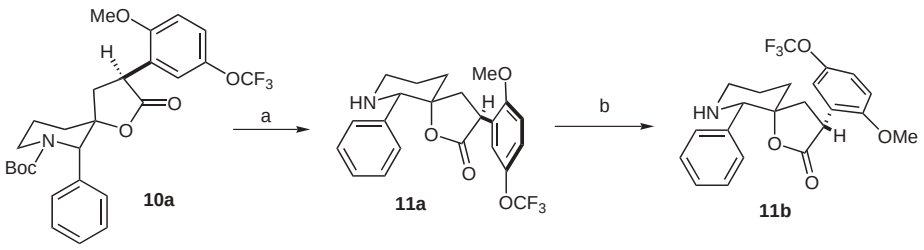
In conclusion, a new convergent synthesis of the 6-phenyl-1-oxa-7-azaspiro[4.5]decane **1** has been developed allowing its preparation with high diastereocontrol.



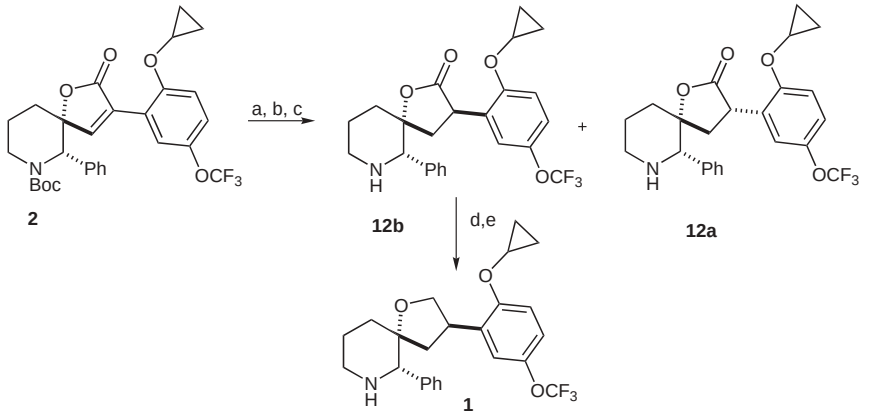

**Scheme 3** EtMgBr, THF, then **4**, 0 °C–r.t., 62%; b) Red-Al, $Et_2O$, r.t., then $I_2$, –78 °C–r.t., 78%; c) CO, $[Ph_3P]_2PdCl_2$, $N_2H_4$, $K_2CO_3$, THF, 50 °C, 68%.




**Scheme 4** a) $NaBH_4$, $NiCl_2$·hexahydrate (cat.), MeOH; b) DBU (cat.), $CH_2Cl_2$, r.t.; c) TFA, $CH_2Cl_2$, r.t., 88%.




**Scheme 5** a) TFA, $CH_2Cl_2$, r.t.; b) DBU (cat.), $CH_2Cl_2$, r.t.




**Scheme 6** a) TFA, $CH_2Cl_2$, r.t.; b) $NaBH_4$, $NiCl_2$·hexahydrate (cat.), MeOH, **12a**:**12b** = 3:1; c) DBU(cat.), $CH_2Cl_2$, **12a**:**12b** = 1:10, 82%; d) $LiAlH_4$, THF; e) DEAD, $Ph_3P$, THF, 55%.

## References


(1) Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science* **1998**, *281*, 1640.

(2) Snider, R. M.; Constantine, J. W.; Lowe, J. A. III; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J. *Science* **1991**, *251*, 435.

(3) Seward, E. M.; Swain, C. J. *Expert Opin. Ther. Pat.* **1999**, *9*, 571.

(4) For recent advances, see: (a) Shaw, D.; Chicchi, G. G.; Elliott, J. M.; Kurtz, M.; Morrison, D.; Ridgill, M. P.; Szeto, N.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3031. (b) Elliott, J. M.; Castro, J. L.; Chicchi, G. G.; Cooper, L. C.; Dinnell, K.; Hollingworth, G. J.; Ridgill, M. P.; Rycroft, W.; Kurtz, M. M.; Shaw, D. E.; Swain, C. J.; Tsao, K.-L.; Yang, L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1755. (c) Cooper, L. C.; Carlson, E. J.; Castro, J. L.; Chicchi, G. G.; Dinnell, K.; Di Salvo, J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K.-L.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1759. (d) Seward, E. M.; Carlson, E.; Harrison, T.; Haworth, K. E.; Herbert, R.; Kelleher, F. J.; Kurtz, M. M.; Moseley, J.; Owen, S. N.; Owens, A. P.; Sadowski, S. J.; Swain, C. J.; Williams, B. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2515. (e) Williams, B. J.; Cascieri, M. A.; Chicchi, G. G.; Harrison, T.; Owens, A. P.; Owen, S. N.; Rupniak, N. M. J.; Tattersall, D. F.; Williams, A.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2719. (f) Gale, J. D.; O'Neill, B. T.; Humphrey, J. M. *Expert Opin. Ther. Pat.* **2001**, *11*, 1837.

(5) Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D.; Ashwood, M. S.; Cameron, M. *J. Org. Chem.* **2002**, *67*, 1093.

(6) (a) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett.* **2001**, *3*, 667. (b) Wallace, D. J.; Bulger, P. G.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Synlett* **2001**, *3*, 357.

(7) Kersey, I. D.; Fishwick, C. W. G.; Findlay, J. B. C.; Ward, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1271.

(8) Hollingworth, G. J.; Dinnell, K.; Dickinson, L. C.; Elliott, J. M.; Kulagowski, J. J.; Swain, C. J.; Thomson, C. G. *Tetrahedron Lett.* **1999**, *40*, 2633.

(9) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(10) Experimental Procedure for the Preparation of **3**: A solution of EtMgBr in THF (1 M, 4.1 mL, 4.1 mmol) was added dropwise to a stirred solution of **5** (1.0 g, 4.1 mmol) in THF (10 mL) at r.t. After 30 min, the mixture was cooled to 0 °C and a solution of **4** (1.07 g, 3.9 mmol) in THF (10 ml) was added dropwise over 5 min. The mixture was stirred at 0 °C for 2 h and at r.t. overnight. After quenching with sat. aq $NH_4Cl$, the mixture was extracted into 2-methylpentane. The combined organic extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel (2-methylpentane–$Et_2O$) to give the alcohol **3** (1.17 g, 62%). $^1H$ NMR (360 MHz, $CDCl_3$): δ = 0.78–0.90 (m, 4 H), 1.32 (s, 9 H), 1.80 (m, 1 H), 2.00–2.15 (m, 2 H), 2.14 (s, 1 H), 2.22 (m, 1 H), 3.11 (m, 1 H), 3.78 (m, 1 H), 4.15 (dd, *J* = 5.6, 13.4 Hz, 1 H), 5.48 (s, 1 H), 7.15 (dd, *J* = 2.0, 9.2 Hz, 1 H), 7.17–7.40 (m, 6 H), 7.55 (d, *J* = 7.2 Hz, 2 H). Relative stereochemistry was assigned by $^1H$ NMR experiments.[6a]

(11) Experimental Procedure for the Preparation of **8**: A solution of Red-Al® in toluene (0.9 mL, 3.1 mmol) was added dropwise to a stirred solution of **3** (1.17 g, 2.25 mmol) in anhyd $Et_2O$ (15 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred at r.t. for 2.5 h. The mixture was cooled to –78 °C and a solution of $I_2$ (1 g, 4 mmol) in anhyd $Et_2O$ (10 mL) was added over 5 min. The reaction mixture was allowed to warm to r.t. over 2 h and quenched with sat. aq $Na_2SO_3$. The mixture was extracted into $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel (2-methylpentane–$Et_2O$) to give the iodide **8** (1.14 g, 78%). $^1$H NMR (360 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 4 H), 1.34 (s, 9 H), 1.74–1.90 (m, 2 H), 2.05 (m, 1 H), 2.31 (dt, *J* = 5.2, 13.2 Hz, 1 H), 2.63 (s, 1 H), 3.18 (ddd, *J* = 5.8, 11.3, 13.6 Hz, 1 H), 3.78 (m, 1 H), 4.10 (m, 1 H), 5.39 (s, 1 H), 6.35 (s, 1 H), 7.06 (d, *J* = 2.8 Hz, 1 H), 7.20 (dd, *J* = 2.3, 8.5 Hz, 1 H), 7.22 (d, *J* = 8.9 Hz, 1 H), 7.25–7.40 (m, 4 H), 7.52 (d, *J* = 7.2 Hz, 2 H).

(12) El, A. B.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357.

(13) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

(14) Experimental Procedure for the Preparation of **2**: A solution of hydrazine in THF (0.07 mL, 0.07 mmol) was added, under an atmosphere of CO, to a stirred mixture of **8** (320 mg, 0.5 mmol), $(Ph_3P)_2PdCl_2$ (50 mg, 0.07 mmol), $K_2CO_3$ (138 mg, 1 mmol) and THF (5 mL). The mixture was stirred at 50 °C for 5 d. After cooling to r.t., the mixture was diluted with $Et_2O$ and filtered through a pad of Celite. The filtrate was concentrated and the residue purified on silica gel (2-methylpentane–EtOAc) to give the lactone **2** (184 mg, 68%). $^1$H NMR (360 MHz, $CDCl_3$): δ = 0.76–0.94 (m, 4 H), 1.39 (s, 9 H), 1.82–2.04 (m, 3 H), 2.30 (m, 1 H), 3.20 (dt, *J* = 4.8, 13.7 Hz, 1 H), 3.82 (m, 1 H), 4.22 (dd, *J* = 5.6, 13.4 Hz, 1 H), 5.25 (s, 1 H), 7.19 (dd, *J* = 1.4, 9.2 Hz, 1 H), 7.22–7.33 (m, 4 H), 7.39 (d, *J* = 7.3 Hz, 1 H), 7.98 (d, *J* = 2.9 Hz, 1 H), 8.08 (s, 1 H).

(15) Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrison, T.; Hollingworth, G. J.; Jackson, P. S.; Kulagowski, J. J.; Seward, E. M.; Swain, C. J.; Williams, B. J. WO Patent 97/49710, **1997**; *Chem. Abstr.* **1998**, *128*, 88921.

(16) The spectral data exhibited by **1** was identical to reported.[15]