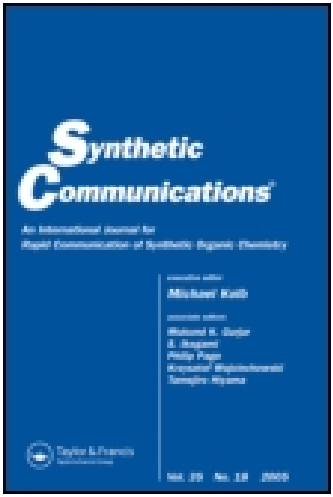



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Synthesis of Substituted Indole-2-carboxylates: Versatile Introduction of a Carbamoyl Moiety at the C-3 Position

Simone A. Giacobbe [a b], Romano Di Fabio [a], Davide Baraldi [a], Alfredo Cugola [a] & Daniele Donati [a]

[a] Glaxo Wellcome S.p.A., Medicines Research Centre, Via A. Fleming 4, I-37135, Verona, Italy

[b] European Patent Office, Ehrardtstrasse 27, Munich, Germany

Published online: 17 Sep 2007.

To cite this article: Simone A. Giacobbe, Romano Di Fabio, Davide Baraldi, Alfredo Cugola & Daniele Donati (1999) Synthesis of Substituted Indole-2-carboxylates: Versatile Introduction of a Carbamoyl Moiety at the C-3 Position, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:18, 3125-3135, DOI: 10.1080/00397919908085936

To link to this article: http://dx.doi.org/10.1080/00397919908085936

SYNTHETIC COMMUNICATIONS, 29(18), 3125-3135 (1999)



# SYNTHESIS OF SUBSTITUTED INDOLE-2-CARBOXYLATES: VERSATILE INTRODUCTION OF A CARBAMOYL MOIETY AT THE C-3 POSITION

Simone A. Giacobbe,* # Romano Di Fabio,*
Davide Baraldi, Alfredo Cugola, Daniele Donati

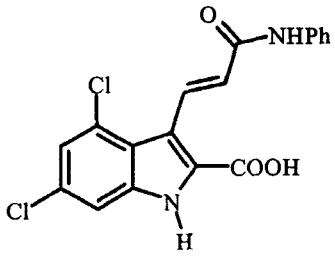
GlaxoWellcome S.p.A., Medicines Research Centre,
Via A. Fleming 4, I-37135 Verona, Italy

**Abstract:** This paper deals with a novel and versatile synthetic approach for the introduction of a functionalized ethynyl side chain at the C-3 position of the 2-carboxyindole nucleus. The key step of this process is represented by the coupling reaction between the dianion deriving from the 2-carboxylate-3-acetylide with different isocyanates.

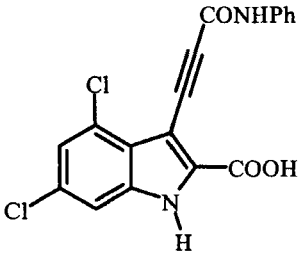
The prolonged activation of several specific neuronal receptors that respond to the natural agonist L-glutamate seems to be instrumental in the insurgence and the progression of a number of pathological conditions of the Central Nervous System (CNS) such as stroke[1], Huntingdon's disease[2], Alzheimer disease[3] and neurotrauma.[4] Among them, the receptor responding to the exogenous agonist N-Methyl-D-Aspartic acid (NMDA)[5] is now widely recognized as being a potentially attractive target for neuroprotective therapy after the stroke onset.

* To whom the correspondence should be addressed.
# Present address: European Patent Office, Ehrardtstrasse 27, Munich, Germany.

**Figure 1**




**1 (GV150526)**



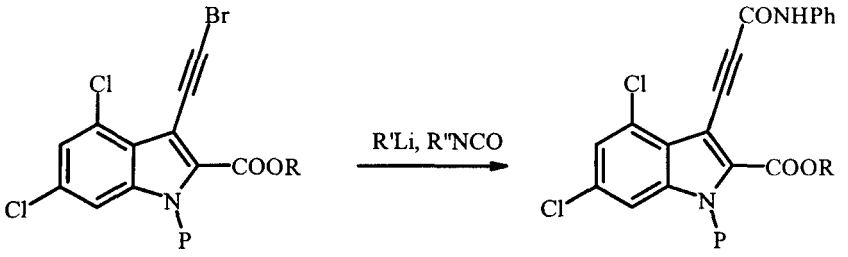

**2**

Studies carried out in our laboratories[6] over the last few years have resulted in the identification of 2-carboxyindole derivative **1**[7], shown in Figure 1, as potent and selective antagonists acting at the glycine binding site associated with the NMDA receptor.[8] As part of a broader SAR investigation, it was decided to introduce at the C-3 position of the indole nucleus a series of ethynylcarboxyamides, since compound **2**, was seen by receptor mapping techniques to fit the pharmacophore model of the glycine site of the NMDA receptor quite well.[9]

It was highly desirable to adopt a synthetic approach that would allow the maximum flexibility in the introduction of the various groups at the terminal postion of the C-3 side chain, identified as candidates for the exploration of the North-Eastern region of the glycine binding site. With this in mind, the coupling of acetylene **6 a** with the appropriate set of commercially available isocyanates, as shown in Scheme 1, was perceived as the key step.

Compound **2** was chosen as the first target: in Scheme 2 its stepwise assembly starting from the known aldehyde derivative **4 a** is reported.[9]

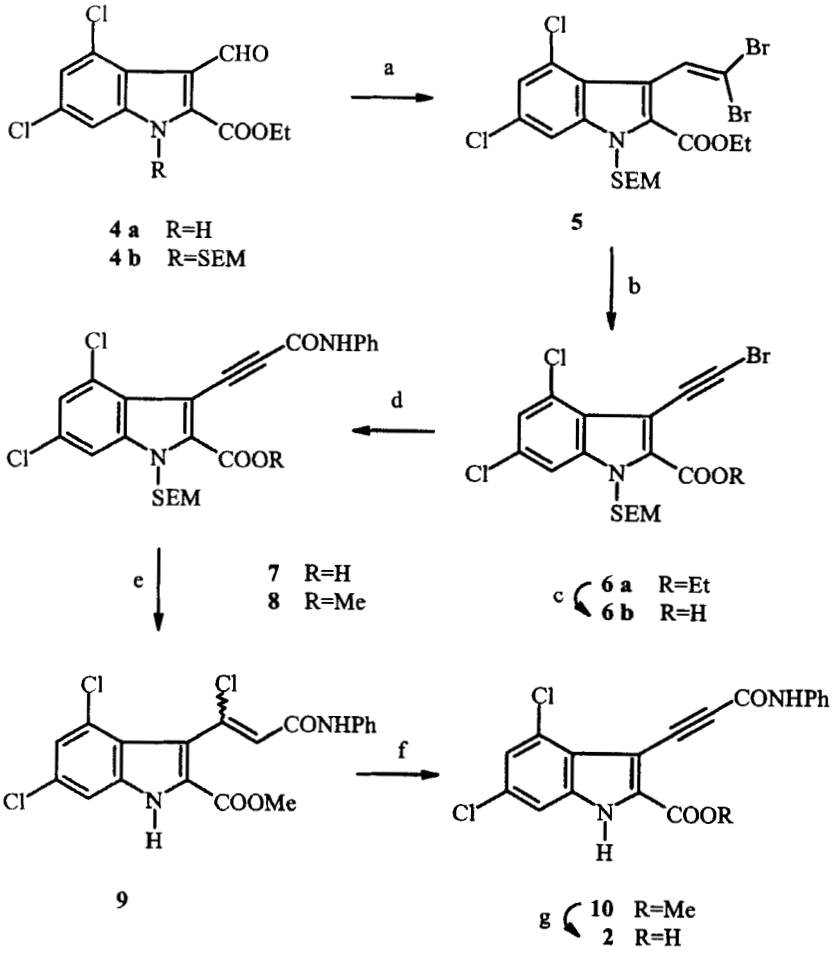
**Scheme 1**




**6 a** **2**

After protection of the acidic indole nitrogen with the acid-stable SEM group,[10] aldehyde **4 b** was converted in high yields into dibromoolefin **5** following the known Corey-Fuchs procedure ($CBr_4$, $PPh_3$, $CH_2Cl_2$).[11] Subsequent treatment of the dibromo derivative **5** with LHMDS in THF at 0°C gave the key acetylenic intermediate **6 a**. The optimal conditions for the following key coupling step were next carefully investigated. In particular, the acetylenic anion of **6 a**, formed by metal-halogen exchange with t-BuLi in THF at -78°C, did not react with a variety of π–carbon electrophiles such as phenyl isocyanate, $CO_2$ or ethyl chloroformate, and only the corresponding debrominated terminal acetylene derivative could be isolated in good yield after aqueous workup. The problem was successfully overcome by generating the dianion from the free acid derivative **6 b**. In the event, **6 b** was treated with 2.2 eq of t-BuLi at -78°C and then reacted with phenyl isocyanate while allowing the temperature to rise slowly to -5°C. After re-esterification with $TMSCHN_2$[12] and purification by flash chromatography, the desired product **8** was isolated in 45% overall yield. This coupling reaction,

**Scheme 2**




a) i. NaH, SEMCl, DMF, 0°C; ii. $PPh_3$, $CBr_4$, $CH_2Cl_2$, -10°C; b) LHMDS, THF, 0°C; c) LiOH, EtOH, r.t.; d) i. t-BuLi 2.25 eq, THF, -78°C, then PhNCO 1.1eq, -78°C then to -5°C; ii. $TMSCHN_2$, $CH_2Cl_2$/MeOH 4:1, 0°C; e) HCl 5N, EtOH, reflux; f) LiOH, THF-$H_2O$ 2:1, 10°C; g) LiOH, THF-$H_2O$ 2:1, 45°C.

performed with different aryl and alkyl isocyanates consistently gave yields between 35%-50%, further confirming the efficacy of this synthetic method. The removal of the SEM protecting group (5N HCl, EtOH, reflux) caused the unexpected addition of HCl across the triple bond, giving product **9** in 51% yield after purification by column chromatography. This complication was overcome in the next and final step, the basic hydrolysis of the methyl ester with excess NaOH (6 eq) in aqueous ethanol at 45°C, which also caused the acetylenic functionality to be smoothly restored,[13] thereby giving the final compound **2** in 65% yield. It was later observed that yields tended to be higher if the two steps were performed separately; the triple bond could be easily restored by treatment of **9** with LiOH at 10°C to give the acetylenic derivative in 78% yield, and the ester function removed at higher temperature (45°C) with the same amount of base, to give final product **2** in 67% yield.

In conclusion, a versatile procedure for the introduction of an ethynylcarbamoyl side chain at the C-3 position of 2-carboxyindole template has been identified. The pharmacological characterisation of the novel indole derivative **2** and some related aryl and cycloalkyl analogues will be reported in due course.

## EXPERIMENTAL

All reagents were purchased from commercial sources and used as received. Solvents were distilled under a nitrogen atmosphere from sodium benzophenone ketyl (THF), $CaH_2$ (triethylamine), or $P_2O_5$ ($CH_2Cl_2$). TLC were performed on Merck silica gel 60, $F_{254}$ plates (layer thickness 0.25 mm). The $^1H$ NMR spectra

were recorded on a Varian VXR5000S (300 MHz) and are given in ppm relative to $Me_4Si$ line as external standard, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants (J, Hz).[14] Infrared spectra were recorded on a Bruker IFS48 spectrometer as nujol emulsion. The FAB-mass spectra were measured on a Fisons VG-4 instrument. Elemental analysis (C, H, N) were performed on a CHNS-O EA-1108 Elemental Analyzer.

**4,6-Dichloro-3-formyl-1-(2-trimethylsilanylethoxymethyl)-indole-2-carboxylic acid ethyl ester (4 b).**

Aldehyde **4 a**, (prepared as shown in Ref. 7a), (4g, 14mmol) was dissolved in dry DMF (40ml) at 0°C under nitrogen atmosphere and NaH (0.42g, 16.8mmol) was added followed by SEMCl (2.96ml, (3g, 7.2mmol). The reaction mixture was stirred for 1h, then quenched with a saturated solution of $NH_4Cl$. The layers were separated and the organic phase washed with $H_2O$ and brine and then dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue purified by flash cromatography (cyclohexane/AcOEt 7:3) to give 4.65g (80%) of title compound **4 b** as a viscous oil.

$^1H$ NMR δ (300 MHz,$CDCl_3$) 10.71 (s, 1H), 7.54 (d, 1H), 7.37 (d, 1H), 5.61 (s, 2H), 4.50 (q, 2H), 3.49 (t, 2H), 1.43 (t, 3H), 0.87 (t, 2H), -0.037 (s, 9H). IR (Nujol): $\nu_{max}$ $cm^{-1}$ 1728, 1680, 1610, 1590. M/z [M+H]+ 416, 358, 270. *Anal* Calcd. for $C_{18}H_{23}Cl_2NO_4Si$: C, 51.92; H, 5.57; N, 3.36. Found: C, 52.23; H, 5.29; N, 3.10.

**4,6-Dichloro-3-(2,2-dibromovinyl)-1-(2-trimethylsilanylethoxymethyl)-indole-2-carboxylic acid ethyl ester (5).**

Compound **4 b** (3g, 7.2mmol), $PPh_3$ (11.4g, 43.2mmol) and $CBr_4$ (7.19g,

21.6mmol) were dissolved in $CH_2Cl_2$ (70ml) at -20°C and the solution was stirred for 1.5 h, whilst allowing the temperature to increase slowly to -10°C. The organic phase was washed with brine and dried over $Na_2SO_4$. After evaporation *in vacuo*, the crude residue was purified by flash chromatography (cyclohexane/AcOEt 7:3) to afford 3.9g (95%) of pure compound **5**, as a viscous yellow oil.

$^1H$ NMR δ (300 MHz,$CDCl_3$) 7.68 (s, 1H), 7.49 (d, 1H), 7.21 (d, 1H), 5.49 (s, 2H), 4.39 (q, 2H), 3.50 (t, 2H), 1.44 (q, 3H), 0.85 (t, 2H), 0.0 (s, 9H). IR (nujol): $\nu_{max}$ $cm^{-1}$ 1715, 1603. M/z 569 [M]+, 490. *Anal* Calcd. for $C_{19}H_{23}Cl_2Br_2NO_3Si$: C, 39.88; H, 4.05; N, 2.45. Found: C, 40.06; H, 4.38; N, 2.75.

**3-Bromoethynyl-4,6-dichloro-1-(2-trimethylsilanyl-ethoxymethyl)-indole-2-carboxylic acid ethyl ester (6 a)**

Compound **5** (2.7g, 4.8mmol) was dissolved in THF (30ml) and treated at 0°C with LHMDS (5.8mmol) for 0.5h. The reaction was then quenched with a saturated solution of $NH_4Cl$, the layers were separated and the organic phase washed with $H_2O$ and brine and then dried over $Na_2SO_4$. Final purification by flash chromatography (cyclohexane/EtOAc 9.5:0.5) gave **6** (2.0g, 87%) as an orange oil. $^1H$ NMR δ ($CDCl_3$) 7.48 (d, 1H), 7.21 (d, 1H), 5.90 (s, 2H), 4.42 (q, 2H), 3.50 (t, 2H), 1.46 (t, 3H), 0.86 (t, 2H), -0.07 (s, 9H); IR ($CDCl_3$) $\nu_{max}$ ($cm^{-1}$) 1705, 1605; *m/z* (relative intensity) 489 $[M]^+$, 416, 372, 226 (100). *Anal* Calcd. for $C_{19}H_{22}Cl_2BrNO_3Si$: C, 46.45; H, 4.81; N, 2.85. Found: C, 46.12; H, 5.01; N, 2.99.

**4,6-Dichloro-3-bromoethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-indole-2-carboxylic acid (6 b).**

Intermediate **6 a** (2g, 4mmol) was dissolved in ethanol (30ml) and treated

overnight at room temperature with $LiOH \cdot H_2O$ (0.34g, 8mmol). When the reaction was complete, the solvent was evaporated *in vacuo* and the crude residue was triturated with 1N HCl, then filtered and dried, to give title compound **6 b** (1.79g, 80%). $^1H$ NMR δ (DMSO) 14.00 (bs, 1H), 7.90 (d, 1H), 738 (d, 1H), 5.92 (s, 2H), 3.41 (t, 2H), 0.76 (t, 2H), -0.13 (s, 9H); IR (Nujol) $\nu_{max}$ ($cm^{-1}$) 1676, 1690; *m/z* 463 $[M + H]^+$. *Anal* Calcd. for $C_{17}H_{18}Cl_2BrNO_3Si$: C, 44.08; H, 3.02; N, 3.92. Found: C, 43.78; H, 3.18; N, 3.78.

**4,6-Dichloro-3-[(2-phenylcarbamoyl)-ethynyl]-1-(2-trimethylsilyl-ethoxy methy )-indole-2-carboxylic acid methyl ester (8)**

Bromoacetylene **6 b** (1.6g, 3.46mmol) was dissolved in dry THF (53ml) and treated with t-BuLi (4.6ml, 7.8mmol) at -78°C. After 3h PhCNO (0.42ml, 3.8mmol) was added and the mixture kept at -60°C for 0.5h then warmed to -5°C over 3h. The reaction was quenched with 0.01N HCl, extracted with EtOAc and washed with brine, dried over $Na_2SO_4$ and evaporated. It was then taken up in $CH_2Cl_2$ (60ml) and the resulting solution was cooled to 0°C and treated with an excess of $TMSCHN_2$. After 1h the solvent was evaporated and the crude solid purified by flash chromatography (cyclohexane/EtOAc 78/22) to give compound **8** (0.8g, 45%). $^1H$ NMR δ (DMSO) 10.72 (bs, 1H), 8.02 (d, 1H), 7.67 (d, 2H), 7.50 (d, 1H), 7.35 (m, 2H), 7.12 (m, 1H), 5.95 (s, 2H), 3.96 (s, 3H), 3.47 (t, 2H), 0.79 (t, 2H), -0.12 (s, 9H); IR (Nujol) $\nu_{max}$ ($cm^{-1}$) 2220, 1717, 1653; *m/z* (relative intensity) 517 $[M + H]^+$ (100), 399, 366. *Anal* Calcd. for $C_{25}H_{26}Cl_2N_2O_4Si$: C, 58.02; H, 5.06; N, 5.41. Found: C, 58.34; H, 5.25; N, 5.63.

**4,6 - Dichloro-3-[1-chloro-2-(phenylcarbamoyl)-vinyl]-indole-2-carboxylic acid methyl ester (9).**

Product **8** (0.8g, 1.6mmol) was dissolved in EtOH (30ml) and treated with 5N HCl (30ml) for 3.5h at reflux. The reaction was diluted with water and extracted with EtOAc, washed with brine, and the organic phase dried and evaporated. Final purification by flash chromatography (cyclohexane/EtOAc 7/3) gave title product **9** (0.34g, 51%). $^1$H NMR δ (DMSO) 12.67 (bs, 1H), 10.16 (bs, 1H), 7.48 (d, 1H), 7.45 (d, 2H), 7.27 (d, 1H), 7.23 (t, 2H), 7.01 (t, 1H), 6.85 (s, 1H), 3.87 (s, 3H); IR (Nujol) $\nu_{max}$ (cm$^{-1}$) 3437-3279, 1711, 1666, 1616; *m/z* 423 $[M + H]^+$, 330. *Anal* Calcd. for $C_{19}H_{13}Cl_3N_2O_3$: C, 53.86; H, 3.09; N, 6.61. Found: C, 53.89; H, 2.79; N, 6.95.

**4,6-Dichloro-3-phenylcarbamoylethynyl-indole-2-carboxylic acid methyl ester (10).**

Compound **9** (0.34g, 0.8mmol) was dissolved in a 2/1 mixture of THF and $H_2O$ (15ml), treated at 10°C with LiOH·$H_2O$ (101mg, 2.4mmol) for 1h then 0.01N HCl was added and extracted with EtOAc. The combined organic phase was washed with brine, dried and evaporated. The crude solid was purified by trituration with diethyl ether giving product **10** (0.24g, 78%) as a white solid. $^1$H NMR δ (DMSO) (shows the presence of a possible rotational isomer* in 10%mol) 13.05 (bs, 1H), 12.69* (bs), 10.71 (bs, 1H), 7.68 (d, 2H), 7.52 (d, 1H), 7.40 (d, 1H), 7.35 (t, 2H), 7.11 (t, 1H), 3.96 (s, 3H); IR (Nujol) $\nu_{max}$ (cm$^{-1}$) 3273, 2220, 1686, 1636; *m/z* (relative intensity) 387 $[M + H]^+$ (100), 351, 294. *Anal* Calcd. for $C_{19}H_{12}Cl_2N_2O_3$: C, 58.93; H, 3.12; N, 7.23. Found: C, 58.96; H, 3.41; N, 7.21.

**4,6-Dichloro-3-phenylcarbamoylethynyl-indole-2-carboxylic acid (2).**

Product **10** (0.2g, 0.56mmol) was dissolved in a 2/1 mixture of THF and $H_2O$ (15ml) and treated at 45°C with $LiOH{\cdot}H_2O$ (78mg, 1.84mmol) for 11h. The solvent was evaporated in vacuo and 0.5N HCl was added with stirring to the resulting aqueous solution to give a precipitate which was filtered, washed with water and dried to give **2** (0.14g, 67%) as a yellow solid. $^1H$ NMR δ (DMSO) (shows the presence of a possible rotational isomer* in 4%mol) 14.00 (bs, 1H), 12.88 (bs, 1H), 12.48* (s), 10.71 (bs, 1H), 7.67 (d, 2H), 7.51 (d, 1H), 7.435* (d), 7.35 (d, 1H), 7.33 (m, 2H), 7.10 (t, 1H); IR (Nujol) $\nu_{max}$ ($cm^{-1}$) 3169, 2240, 1745, 1661; *m/z* 373 $[M + H]^+$, 337. *Anal* Calcd. for $C_{18}H_{10}Cl_2N_2O_3$: C, 57.93; H, 2.70; N, 7.51. Found: C, 58.06; H, 2.65; N, 7.23

## REFERENCES AND NOTES


1. Meldrum, B. *Clin. Sci.*, **1985**, *68*, 113. Lehman, J. *Drugs of the Future* **1989**, *14*, 1059. DeFreudis, F.V. *Drugs of Today*, **1989**, *25*, 677. Choi, D.W. *J. Neurosci.* **1990**, *10*, 2493.
2. Choi, D.W.; Koh, J.Y. and Peters, S. *J. Neurosci.* **1988**, *8*, 185.
3. Maragos, W.; Greenamyre, J.; Penney, J.; Jr and Young, A. *Trends Neurosci.* **1987**, *10*, 65
4. Faden, A.; Demediuk, P.; Panter, S. and Vink, R. *Science* **1989**, *244*, 798.
5. Meldrum, B. S. In *Excitatory Amino Acid Antagonists*; Blackwell Scientific Publications: **1991**. Kyle, D. J.; Patch, R. J. and Karbon, E. W. In *Excitatory Amino Acid Receptors*; Krogsgaard-Larsen, P. and Hansen, J. J. Eds; Ellis Horwood: New York, **1992**. *The NMDA Receptor*, Collingridge, G. L. and Watkins, J. C. Eds; Oxford University Press: Oxford, **1994.**
6. Gaviraghi, G.; Cugola, A. and Giacobbe, S. *Eur Patent 0568136 A1,* **1993**.
7. a) Di Fabio, R.; Capelli, A.M.; Conti, N.; Cugola, A.; Donati, D.; Feriani, A.; Gastaldi, P.; Gaviraghi, G.; Hewkin, C.T.; Micheli, F.; Missio, A.; Mugnaini, M.; Pecunioso, A.; Quaglia, A.M.; Ratti, E.; Rossi, L.; Tedesco,

G.; Reggiani, A. *J. Med Chem.* **1997**, *40*, 841. b) Bordi, F.; Pietra, C.; Ziviani, L. and Reggiani, A. *Experimental Neurology* **1997**, *145*, 425-433. c) Di Fabio, R.; Cugola, A.; Donati, D.; Feriani, A.; Gaviraghi, G.; Ratti, E.; Trist, D. G. and Reggiani, A. *Drugs of the Future*, **1998**, *23*, 61.

8. Johnson, J. W. and Asher, P. *Nature* **1987**, *325*, 529. Kleckner, N. W. and Digledine, R. *Science* **1988**, *241*, 835. McBain, C. J.; Kleckner, N. W.; Wyrick, S. and Digledine, R. *Mol. Pharmacol.* **1989**, *33*, 2944. Carter, A. J. *Drugs of the Future* **1992**, *17* , 595. Kemp, J. A. and Leeson, P. D. *TiPS* **1993**, *14*, 20. Leeson, P. D. and Iversen, L. L. *J. Med. Chem.* **1994**, *37*, 4053. Di Fabio, R.; Gaviraghi, G. and Reggiani, A. *La Chimica e l'Industria* **1996**, *78*, 283.

9. Aldehyde **4** was prepared as shown in Ref. 7a.

10. a) Muchowski, J. M. and Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203. b) Edwards, M. P.; Doherty, A. M.; Ley, S. W. and Organ, H. N. *Tetrahedron* **1986**, *42*, 3723. c) Matthews, D.P.; Whitten, J. P. and McCarthy, J. R. *J. Heterocyclic Chem.* **1987**, *24*, 689.

11. Corey, E. J. and Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

12. Hashimoto, N.; Aoyama, T. and Shioiri, T. *Chem. Pharm. Bull.*, **1981**, *29*, 1475.

13. The fact that LiOH is able to eliminate HCl across the double bond came as a surprise. Studies are under way to clarify the mechanism of this unusual reaction, but we believe that the indole nitrogen should play a pivotal role. The results of these studies will be published in due course.

14. The only assessable coupling constant for all the compounds synthesised was $J_{6,8} = 2$ Hz.

Received in the UK 12 October 1998