A Synthetic Approach to Benzo[1,2-*b*: 4,3-*b*']dipyrroles from Isoquinolines

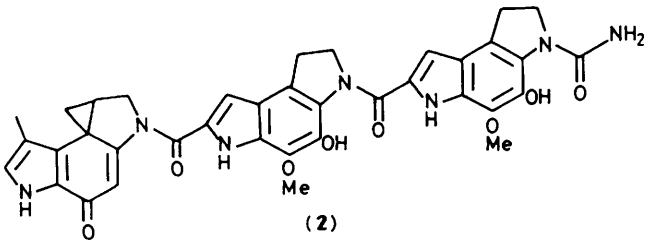
Premji Meghani, Jonathan D. Street, and John A. Joule*

Chemistry Department, Manchester University, Manchester M13 9PL, U.K.

6,7-Dimethoxy-1-methylisoquinoline has been converted into 3-acetyl-3,6-dihydro-4,5-dimethoxybenzo[1,2-*b*: 4,3-*b*']dipyrrole (**6b**) and thence into 3,6-diacetyl-1,2,3,6-tetrahydro-4,5-dimethoxybenzo[1,2-*b*: 4,3-*b*']dipyrrole (**7**).

The 1,2,3,6-tetrahydrobenzo[1,2-*b*: 4,3-*b*']dipyrrole nucleus is present in the phosphodiesterase inhibitors PDE-I and -II[1] (**1a**, **b**) and in CC-1065[2] (**2**), a highly potent antitumour antibiotic isolated from *Streptomyces zelensis*. Considerable synthetic efforts have been devoted to this tricyclic system and a fascinating variety of approaches described.[3] This Communication details an additional example which we believe represents a synthetically useful alternative, starting as it does from an isoquinoline, synthetic routes to which have been thoroughly examined.[4]

Our approach was suggested by the report[5] of the conversion of 5-nitroisoquinoline methiodide into 4-methylamino-



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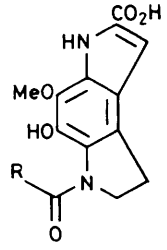
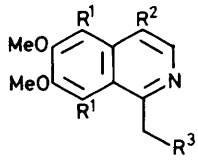
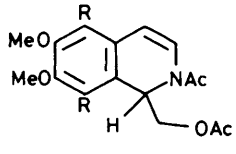


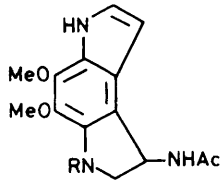
(1)	R
a	NH_2
b	Me



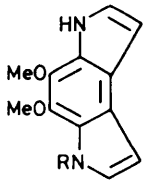
(3)	R^1	R^2	R^3
a	H	H	H
b	NO_2	H	H
c	NO_2	AcO	H
d	NO_2	H	AcO



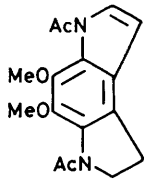
(4)	R
a	NO_2
b	NH_2



(5)	R
a	H
b	Ac



(6)	R
a	H
b	Ac



(7)

methylindole on treatment with titanium trichloride, a process involving, as well as nitro-group reduction, partial reduction of the pyridine ring, ring opening by cyclic enamine hydrolysis, and reclosure in the alternative sense. As a model for the oxygenation pattern observed in the natural compounds, 6,7-dimethoxy-1-methylisoquinoline (**3a**) was utilised for the sequence described hereinafter.

Nitration of (**3a**)[6] with conc. HNO_3–conc. H_2SO_4 at 0 °C gave 6,7-dimethoxy-1-methyl-5,8-dinitroisoquinoline (**3b**)† (65%, m.p. 142—144 °C), already having all the atoms required for construction of the target compound. Treatment with AcOH–H_2O_2 (30%) (2 : 1) at 100 °C smoothly produced the *N*-oxide (91%, m.p. 173—175 °C), reaction of which with acetic anhydride at room temperature gave a mixture of the 4-acetoxy-isoquinoline (**3c**) (33%, m.p. 113—115 °C) and the required 1-acetoxymethyl-derivative (**3d**) (66%, m.p. 115—116 °C).

Careful reduction of (3d) with lithium aluminium hydride in tetrahydrofuran (THF) at −70 to 0 °C followed immediately, and without purification, by trapping with acetyl chloride at room temperature, produced the enamide-acetate (**4a**) (52%, m.p. 142—143 °C). Selective reduction of the nitro groups in (**4a**) using aqueous titanium trichloride at 10—15 °C gave (**4b**) (96%, amorphous), in which the stage was set for opening of the six-membered nitrogen ring and formation of the two five-membered rings.

Treatment of (**4b**) with conc. HCl–EtOH (1 : 15) at reflux produced the tetrahydrobenzodipyrrole (**5a**) (48%, amorphous). Following acetylation of the basic nitrogen [→ (**5b**) (98%, m.p. 250—253 °C)] attempts were made to remove the substituent 1-acetamido-group by catalytic hydrogenolysis, but to no avail. Complications also attended efforts to hydrolyse the side-chain amide in (**5a**). The solution to removal of the side-chain nitrogen function was suggested by the mass spectrum of (**5a**) which showed a base peak corresponding to the benzodipyrrole (**6a**), formed, we hypothesised, by thermally induced elimination in the spectrometer. Thus pyrolysis of (**5b**) at 205—210 °C and 100—110 mmHg smoothly and cleanly produced (**6b**) (62%, amorphous).

Brief treatment of (**6b**) with NaOH—MeOH at room temperature gave the known benzodipyrrole (**6a**), m.p. 200—201 °C (lit.,[7] 201 °C). Reduction of (**6b**) with Na(CN)BH_3–AcOH at 10—15 °C and then reaction with acetic anhydride gave 3,6-diacetyl-1,2,3,6-tetrahydro-4,5-dimethoxybenzo[1,2-*b*: 4,3-*b'*]dipyrrole (**7**) (>95%, amorphous) [δ 7.56 (1H, d, *J* 4 Hz), 6.48 (1H, d, *J* 4 Hz), 4.36 (2H, t, *J* 6 Hz), 3.08 (2H, t, *J* 6 Hz), 4.01, 3.81, 2.67, and 2.29 (4 × 3H, 4 × s)].

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References

1 Y. Enomoto, Y. Furutan, H. Naganawa, M. Hamada, T. Takeguchi, and H. Umezawa, *Agric. Biol. Chem.*, 1978, **42**, 1331, 1337.
2 For reviews see V. I. Reynolds, J. P. McGovren, and L. H. Hurley, *J. Antibiotics*, 1986, **39**, 319; L. H. Hurley and D. R. Needham-VanDevanter, *Acc. Chem. Res.*, 1986, **19**, 230.
3 For a review see V. H. Rawal, R. J. Jones, and M. P. Cava, *Heterocycles*, 1987, **25**, 701.
4 'The Chemistry of Heterocyclic Compounds,' series eds. A. Weissberger and E. C. Taylor, vol. 38, Part 1, ed. G. Grethe, Interscience, New York, 1981.
5 M. Somei and F. Yamada, *Chem. Lett.*, 1979, 943.
6 E. Spath and N. Polgar, *Monatsh. Chem.*, 1929, **51**, 190.
7 V. H. Rawal and M. P. Cava, *J. Am. Chem. Soc.*, 1986, **108**, 2110.

† Satisfactory combustion (crystalline compounds) and spectroscopic analyses were obtained for all new compounds.