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A NOVEL SYNTHESIS OF THE 5HT$_3$-RECEPTOR ANTAGONIST BRL 49231

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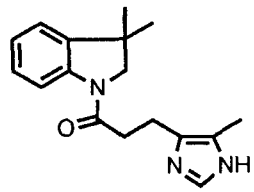
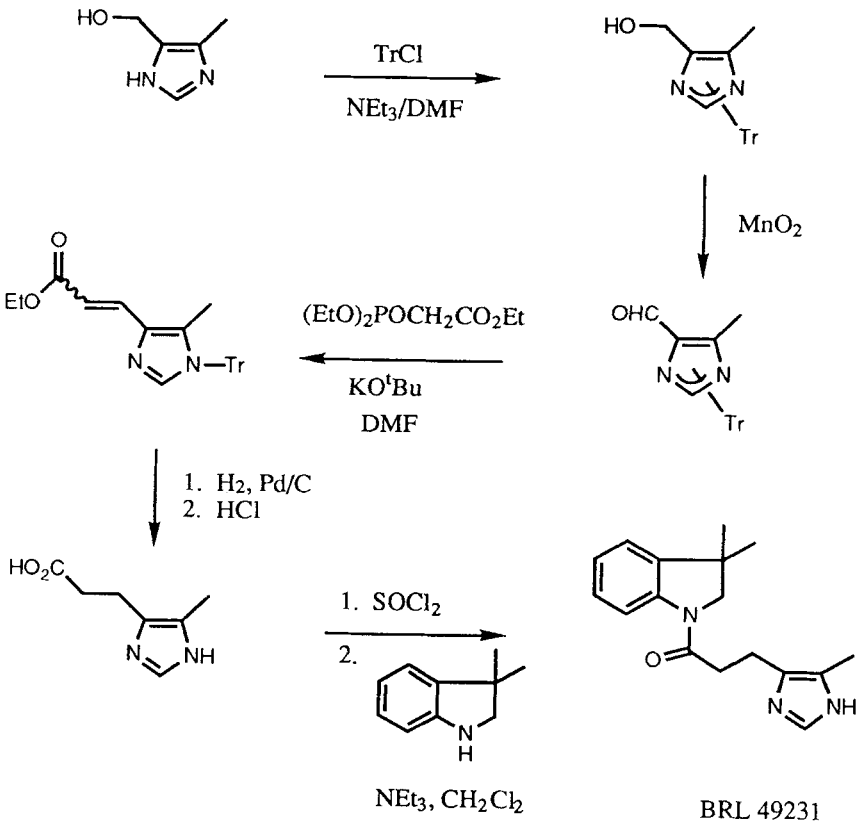
Abstract: A short route to the 5HT$_3$ receptor antagonist BRL 49231 involving alkylation of the amide enolate of 1-acetyl-3,3-dimethylindoline is described.

BRL 49231, a 5HT$_3$-receptor antagonist,[1] has been under consideration for development within SmithKline Beecham as an anti-emetic agent. Small quantities of the compound were prepared using the published procedure[1] which is outlined in Scheme 1, however, the route is lengthy and suffers from the use of a high molecular weight protecting group at the start of the synthesis. Our interest has been in the discovery of alternative routes which could eventually be used for the manufacture of the compound. In this paper we present our results from one attractive strategy, illustrated in Scheme 2,

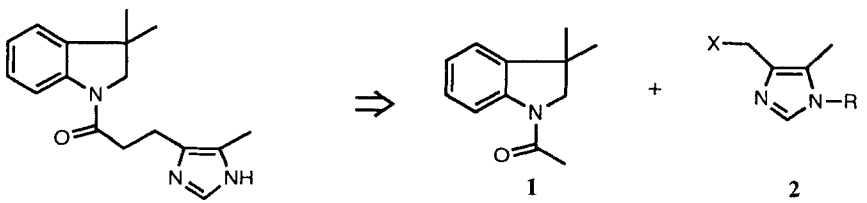
BRL 49231



Scheme 1



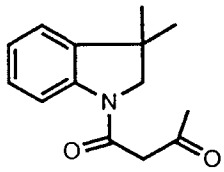
Scheme 2



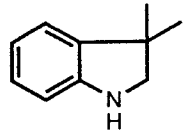
which involves alkylation of the amide enolate of the readily available 1-acetyl-3,3-dimethylindoline (**1**).[2,3,4]

Displacement of the leaving group, X, from protected imidazoles e.g. **2**, X=Cl, R=SO_2NMe_2, Bn, or CPh_3 by various nucleophiles is reported in the literature, [5,6,7] and, in the latter case, chloride is displaced by the carbon nucleophile Ph_2CLi under CuCN catalysis. The use of unprotected imidazoles in displacement reactions as reported by Webb et al[8] was of particular interest because one of the long term goals of this project was to obviate the need for a protecting group.

The first experiment was designed to check that the amide enolate of **1** could be formed satisfactorily. Thus, **1** was added to a solution of 1 equivalent of LDA in THF at -78°C and the resulting anion was quenched after 1 hour at -78°C with d_4-acetic acid. After an aqueous work-up, a weight recovery of **1** of 94% was obtained with a deuterium incorporation of 75% as measured by ^{1}H NMR. This clearly indicated that the enolate could be formed cleanly. However, when the amide enolate was allowed to warm to -40°C for 30 minutes prior to the quench, the acetoacetate **3**[9] and 3,3-dimethylindoline **4** were observed as major products alongside **1**. These products are presumably generated because insufficient base is present to effect complete deprotonation of **1** and an acetyl transfer reaction is then able to take place. It is interesting to note, that this may be a catalytic process in that the products **3** or **4** can protonate the amide enolate to regenerate the starting material **1**. The presence of **3** was not of concern to us since we reasoned that in the longer term its formation could be prevented by the use of a slight excess of the base.



3



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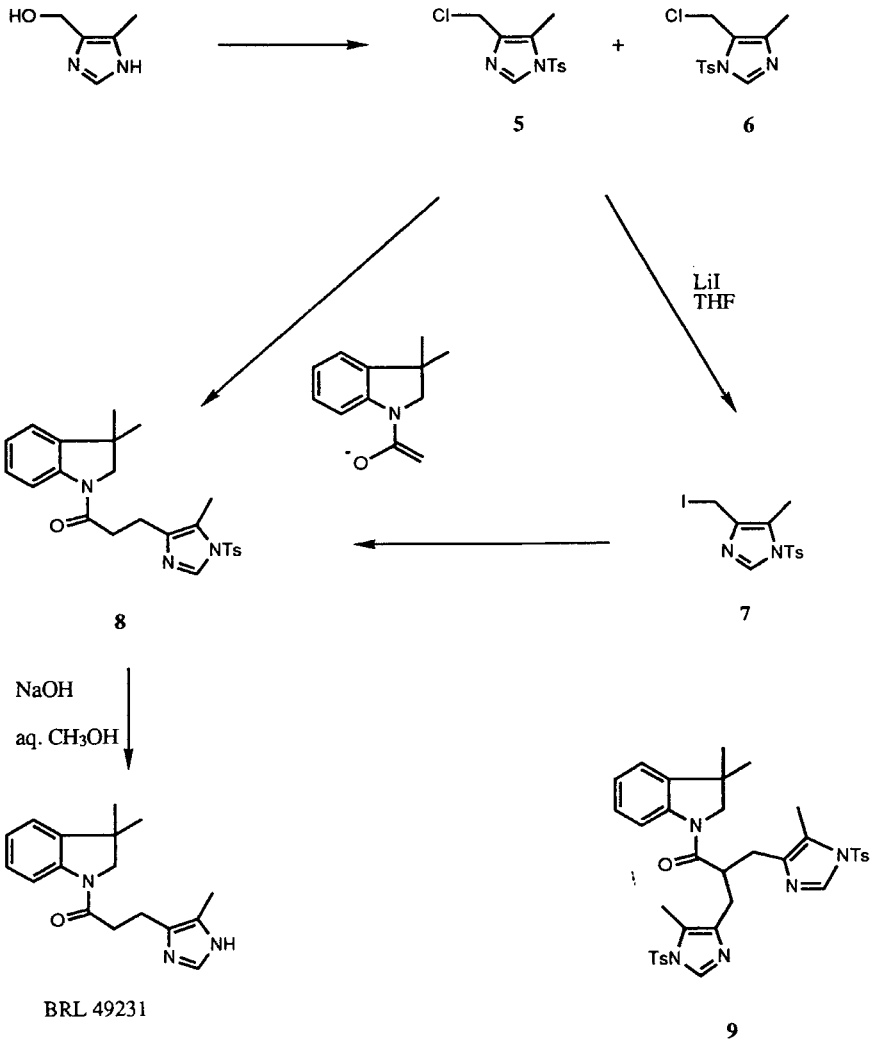
We were more concerned initially with keeping the amount of base to a minimum to prevent deprotonation of the imidazole substrates.

With regard to the imidazole substrates, we envisaged that the ditosylate **2**, X=OTs, R=Ts, would be an attractive alkylating agent for the amide enolate of **1** as it should be easily prepared from the commercially available alcohol **2**, X=OH, R=H. In addition, it was envisaged that the protecting group could be removed at the end of a synthesis by a simple hydrolysis. In the event, treatment of **2**, X=OH, R=H with 2 molar equivalents of TsCl in CH_2Cl_2 in the presence of Hunig's base (or NEt_3) gave the chlorides **5** and **6** in 41% yield after chromatography[10]. See Scheme 3. The structures of the isomers were assigned by n.O.e. studies and it is the chloride **5** that predominates in the mixture.

The preparation of **5** is conveniently carried out using DMF as solvent with 2 molar equivalent of TsCl and 4 equivalents of Hunig's base. A simple aqueous work-up gives **5** in 42% yield. The isomer **6** is not observed in the isolated product from this method.

Alkylation of the amide enolate of **1** with the chloride **5** was next attempted. The chloride was added to a solution of the enolate at -78°C and after stirring for 1h at this temperature, the mixture was allowed to warm to room

Scheme 3



temperature. This gave the required product **8** in 12% yield after chromatography. Also isolated was the bisalkylated product **9** in 7% yield and the starting materials **5** and **1** in 12 and 50% yield respectively. These results proved to be reproducible and it is of interest that only trace amounts of **3**

were observed in the reactions. Presumably deprotonation of **5** by the amide enolate is the major reaction pathway.

To increase the rate of alkylation, the leaving group was changed from chloride to iodide. Treatment of **5** with LiI in THF gave a 54% yield of the iodide **7** containing approximately 5% of the starting material **5**. Alkylation of the amide enolate with this substrate under the usual conditions gave **8** in an improved yield of 33%. In this experiment, the bisalkylated product **9** and **1** were each obtained in 23% yield. It may be possible to repress the amount of bisalkylation by inverse additon of the reactants, however, this approach has not been investigated.

To complete the synthesis of BRL 49231, a selective hydrolysis of **8** was required and was readily achieved. Thus treatment of **8** with aq. NaOH in CH_3OH gave a product in 85% yield which was identical (^1H NMR, tlc) to an authentic sample of BRL 49231.

In conclusion, our preliminary results on alkylation of the amide enolate of **1** with imidazole substrates[11] form the basis of a new, short convergent approach to BRL 49231.

Experimental

Preparation of 4-chloromethyl-5-methyl-1-(4-methylbenzenesulphonyl)-imidazole (5)

A solution of 4-methyl-5-imidazolemethanol hydrochloride (10.0g, 67 mmole) and diisopropylethylamine (34.7g, 269 mmole) in DMF (40 ml) was added to a solution of tosyl chloride (25.7g, 134 mmole) also in DMF (40 ml). The

reaction mixture was stirred at ambient temperature, under nitrogen, overnight, then poured into water (1L), and the product was extracted with Et_2O (2 x 300 ml). The combined ether layers were washed with water, 2.5N HCl and dried over sodium sulphate. The solvent was evaporated to give 8.0g (42%) of a white solid, which was used without further purification. A small portion of this was recrystallised from Et_2O/hexane.

Anal $C_{12}H_{13}N_2O_2SCl$ calc C50.61 H4.60 N9.84 found C50.59 H4.68 N9.84. ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H); 7.78 (d, J=9Hz, 2H); 7.37 (d, J=9Hz, 2H); 4.46 (s, 2H); 2.46 (s, 3H); 2.28 (s, 3H). IR (KBr Disc) υ 1360 (SO_2); 1200 cm^{-1} (SO_2). MS (70 eV) EI m/z (rel intensity) MH$^+$ 285 (27); 249 (100); 185 (6); 155 (82); 91 (95); 89 (11); 77 (3); 65 (28); 53 (7); 39 (9); 36 (5). Acc mass calc for $C_{12}H_{13}N_2O_2SCl$ 284.0386 actual 284.0395.

Preparation of 4-iodomethyl-5-methyl-1-(4-methylbenzenesulphonyl)-imidazole (7)

4-Chloromethyl-5-methyl-1-(4-methylbenzenesulphonyl)imidazole (4.1g, 14.3 mmole) was dissolved in THF and stirred, under nitrogen, at ambient temperature. Lithium iodide (7.6g, 57.0 mmole) was added, portionwise, and the mixture was stirred for 2 hours, then filtered through a pad of silica gel. The solvent was evaporated, then the residue was triturated with hexane filtered and dried to give the product (2.9g) in 54% yield. The product was used without further purification. The NMR spectrum showed the product to contain about 5% of the starting material.

^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H); 7.78 (d, J=9Hz, 2H); 7.38 (d, J=9Hz 2H); 4.26 (s, 2H); 2.46 (s, 3H); 2.15 (s, 3H). MS (70 eV) EI m/z (rel intensity) MH$^+$ 377 (14); 278 (12); 254 (21); 249 (100); 246 (67); 218 (22); 214

(11); 185 (12); 155 (86); 139 (40); 123 (37); 91 (90); 89 (22); 77 (17); 65 (52); 53 (21); 39 (16). Acc mass calc for $C_{12}H_{13}N_2O_2SI$ 375.9741 actual 375.9744.

Preparation of 1-(3-(5-methyl-1-(4-methylbenzenesulphonyl)-3-imidazole)-propionyl)-3,3-dimethylindoline (8)

n-Butyllithium (1.2M in hexane, 8.3 ml, 9.8 mmol) was added to a stirred solution of diisopropylamine (0.99g, 1.4 ml, 9.8 mmole) in THF (10 ml) at 0°C, under nitrogen. The cooling bath was removed, and after stirring at ambient temperature for 10 mins, the LDA solution was cooled to -78°C. A solution of the acetyl indoline **1** (1.86g, 9.8 mmol) in THF (8 ml) was added, and after 30 minutes, the 4-iodomethyl-5-methyl-1-(4-methylbenzene-sulphonyl)imidazole (3.70g, 9.8 mmol) in THF (8 ml) was added. After stirring for 1 hour at -78°C, the reaction mixture was stirred at ambient temperature for a further hour, then was quenched with saturated ammonium chloride solution (250 ml). The organic products were extracted with dichloromethane (2 x 200 ml), then the combined extracts were dried over sodium sulphate and the solvent was evaporated. The product was purified by chromatography, (silica gel, eluant hexane/ether gradient system) to give the product as a white solid (1.42g) in 33% yield. (m.p. 152-154°C).

Anal $C_{24}H_{27}N_3O_3S$ calc C65.88 H6.22 N9.60 found C66.49 H6.28 N9.61. ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J=8Hz, 1H); 8.06 (s, 1H); 7.73 (d, J=8Hz, 2H); 7.31 (d, J=8Hz, 2H); 7.21 - 7.00 (m, 3H); 3.75 (s, 2H); 2.85 - 2.73 (m, 4H); 2.42 (s, 3H); 2.22 (s, 3H); 1.30 (s, 6H). IR (KBr disc) υ 1667 cm^{-1} (C=O). MS (70 eV) EI m/z (rel intensity) MH^+ 438 (20); 291 (98); 282 (46); 174 (21); 155 (52); 147 (65); 132 (100); 130 (49); 117 (22); 95

(29); 91 (75); 77 (73); 65 (11); 53 (11); 53 (6); 39 (6). Acc mass calc for $C_{24}H_{27}N_3O_3S$ 437.1772 ,actual 437.1784.

Also isolated in 23% yield was the bis-alkylated product **9**. A sample of this compound was recrystallised from ether/hexane. (m.p. 171-172°C). Anal $C_{36}H_{39}N_5O_5S_2$ calc C63.04 H5.73 N10.21 found C63.00 H5.68 N10.34. ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 2H); 7.94 (d, 1H); 7.56 (d, J=8Hz, 4H); 7.09 (d, J=8Hz, 4H); 7.06 - 7.02 (m, 3H); 3.60 - 3.53 (m, 1H); 3.49 (s, 2H); 2.87 (dd, J=10, 14Hz, 2H); 2.61 (dd, J=5, 14Hz, 2H); 2.35 (s, 6H); 2.12 (s, 6H); 1.04 (s, 6H). IR (nujol mull) υ 1650 cm^{-1} (C=O). MS (70 eV) CI MH$^+$ 686 EI m/z (rel intensity) 539 (13); 530 (20); 436 (12); 385 (10); 383 (16); 291 (21); 282 (27); 251 (22); 218 (100). Acc mass calc for $C_{36}H_{39}N_5O_2S_2$ 685.2392 actual 685.2428 .

Preparation of BRL 49231

1-[3-(5-methyl-4-(4-methylbenzenesulphonyl)-3-imidazole)propionyl]-3,3-dimethylindoline (0.19g, 0.44 mmole) was taken up in methanol (8 ml) and 2M NaOH solution (2 ml) was added. After stirring at ambient temperature for 1 hour, the solvent was evaporated. Dichloromethane and water were added to the residue. The organic layer was dried over sodium sulphate, and the solvent was evaporated, to give 0.11g (85%) of the product, which was identical to authentic material.

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9. The acetoacetate **3** can be purified by column chromatography and has been characterised by its ^{1}H NMR and mass spectra. It exists in solution as a mixture of keto-enol forms.

10. The chlorides (and iodides) are prone to decomposition on chromatography and on storage.

11. The use of **2**, X=Cl, R=Bn has also been examined in the alkylation reaction but its poor solubility in THF was a major problem and the required product was not obtained.

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