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A SYNTHESIS OF (±)-7-METHOXYCARBONYL-2-(3-METHOXYPHENYLMETHYLIDENE)-8-METHYL-3,8-DIAZABICYCLO[3.2.1]OCTAN-4-ONE (1b) USING DIPOLAR CYCLOADDITION TO A 3-OXIDOPYRAZINIUM

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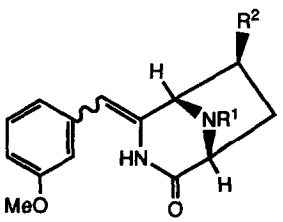
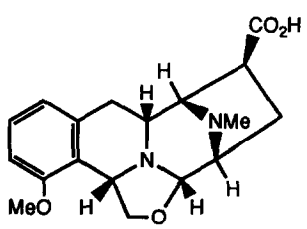
Summary : The 3-methoxybenzyl-substituted 3,8-diazabicyclo[3.2.1]octane **1b**, was prepared in 8 steps from 3-methoxybenzaldehyde, utilising, as the key step, the dipolar cycloaddition of methyl acrylate to a 5-benzyl-substituted 3-oxidopyrazinium, **5**.

A report[1] by Weinreb describing the synthesis of the 3-methoxyphenylmethylidene-substituted 3,8-diazabicyclo[3.2.1]octane **1a**, in homochiral form but in 23 steps, beginning with 3-methoxybenzaldehyde, as a late intermediate for the construction of antitumour

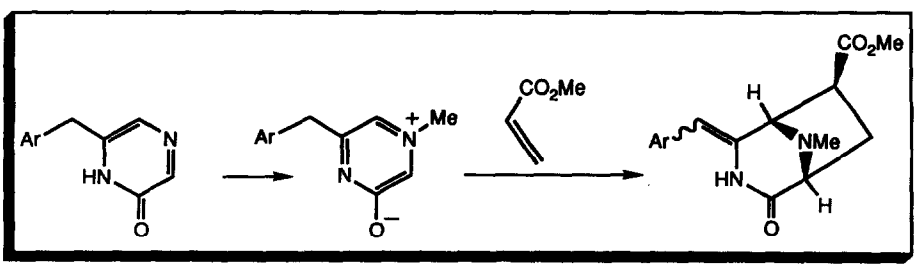
1	R^1	R^2
a	H	CH_2OH
b	Me	CO_2Me



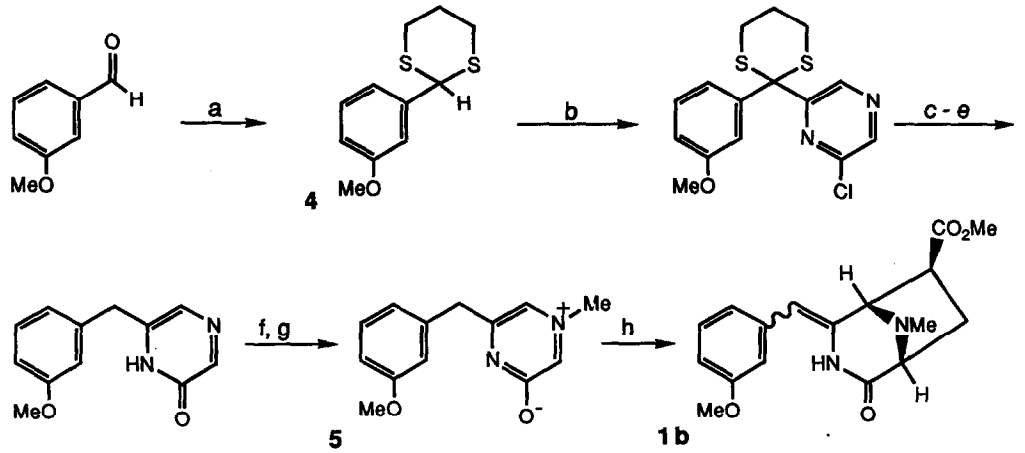


2 Quinocarcin

metabolite quinocarcin[2,3], **2**, prompts us to reveal how our approach[4], the essence of which is a dipolar cycloaddition to a 3-oxidopyrazinium (see box below), can be utilised for the synthesis of (±)-**1b**, in 8 steps from 3-methoxybenzaldehyde. Garner has also demonstrated[5] the utility of dipolar cycloadditions for the construction of the 3,8-diazabicyclo[3.2.1]octane system.



The synthesis of the requisite 3-methoxybenzylpyrazinone, **3**, began with the low temperature displacement of one halogen from 2,6-dichloropyrazine by the anion of dithiane, **4**. After subsequent displacement of a second chloride with benzyloxy, Raney nickel desulphurisation and BF_3/EtSH debenzylation[6] afforded **3**. Subsequent steps followed the earlier model work[4], quaternisation using iodomethane, deprotonation by passage down an anion exchange resin and dipolar cycloaddition of methyl acrylate to the resultant oxidopyrazinium, **5**, giving as a single geometrical isomer, bicycle **1b**[7]. In the simpler series[4] we showed that catalytic hydrogenation of enamides such as **1b** proceeds from the exo face of the bicycle, in the sense required for a synthesis of quinocarcin, and the recent Letter[1] reported the comparable reduction of **1a**.



Reagents : a, $HS(CH_2)_3SH$/HCl/$CHCl_3$/35°C[8], 92%; b, *n*-BuLi/TMEDA/2-methyl-THF/RT -> -100°C then 2,6-dichloropyrazine/2-methyl-THF -> RT, 14%; c, $PhCH_2OH$/NaH/THF/reflux, 78%; d, Raney Ni/EtOH/reflux, 40%; e, EtSH/$BF_3.Et_2O$/RT, 59%; f, MeI/EtOH/reflux, 40%; g, Amberlite IRA-400 (OH^-)/MeOH/RT, 93%; h, CH_2:$CHCO_2Me$/THF/reflux, 50%.

Acknowledgement

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References

1 T. A. Lesse, D. M. Demko, and S. M. Weinreb, *Tetrahedron Lett.*, 1990, **31**, 2105.

2 F. Tomita, K. Takahashi, and K.-I. Shimizu, *J. Antibiot.*, 1983, **36**, 463; K. Takahashi and F.Tomita, *ibid.*, 468; N. Hirayama and K. Shirahata, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1705; F.Tomita, K.Takahashi, and T. Tanaoki, *J. Antibiot.*, 1984, **37**, 1268.

3 For references to other synthetic approaches to quinocarcin (and quinocarcinol) see Ref. 1.

4 M. Kiss, J. Russell-Maynard, and J. A. Joule, *Tetrahedron Lett.*, 1987, **28**, 2187.

5 P. Garner, K. Sunitha, and T. Shanthilal, *Tetrahedron Lett.*, 1988, **29**, 3525; P. Garner, K. Sunitha, W.-B. Ho, W. J. Youngs, V. O. Kennedy, and A. Djebli, *J. Org. Chem.*, 1989, **54**, 2041; P. Garner, F. Arya, and W.-B. Ho, *J. Org. Chem.*, 1990, **55**, 412.

6 F. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, 1979, **44**, 1661.

7 Pale yellow gum, $\nu_{max.}$ 1738, 1690 cm^{-1}; δ_H ($CDCl_3$) 7.57 (1H, bs), 6.81 (3H, m), 6.73 (1H, m), 5.66 (1H, s), 4.07 (1H, s), 3.81 (3H, s), 3.78 (3H, s), 3.63 (1H, d, J 6.5 Hz), 3.13 (1H, dd, J 10, 6.5 Hz), 2.69 (1H, dt, J 13, 6.5 Hz), 2.53 (3H, s), 2.38 (1H, dd, J 13, 10 Hz); m/z 316 (M^+, 8%), 230 (100). $C_{17}H_{20}N_2O_4$ requires 316.1423. Found 316.1427.

8 R. Sarges, *J. Org. Chem.*, 1975, **40**, 1216.

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