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$Sn(II)Cl_2$-INDUCED REGIOSPECIFIC OPENING OF THE 1,3-BENZODIOXOLE RING SYSTEM: A ROUTE TO THE NOVEL DNA-INTERACTIVE LIGAND *ISO*-DC-81

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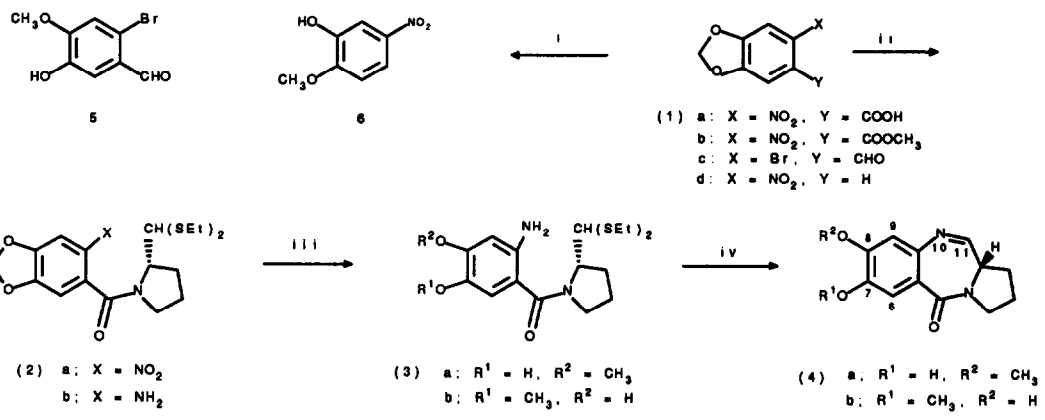
Abstract: *A novel tin-catalysed regiospecific cleavage of a 1,3-benzodioxole ring system is reported that has been applied to the synthesis of a uniquely-substituted DNA-binding pyrrolo[2,1-c][1,4]benzodiazepine antitumour agent, iso-DC-81(4a).*

Currently there is growing interest in the pyrrolo[2,1-c][1,4]benzodiazepine (PBD) family of antitumour antibiotics due to their ability to bind covalently to the N2 of guanine in the minor groove of DNA with marked sequence selectivity[1]. While investigating a new dioxolo[4,5-h]pyrrolo[2,1-c][1,4]benzodiazepine ring system, we found that the 1,3-benzodioxole intermediate **2a** cleaves completely regiospecifically upon treatment with $Sn(II)Cl_2$ in CH_3OH to afford **3a**. This intermediate could then be cyclized to **4a** which has aromatic hydroxy and methoxy substituents in the reverse positions (i.e. C7 and C8) to those in many known PBDs such as tomaymycin, neothramycin and DC-81 (**4b**). To our knowledge, this represents the first example of a regiospecific tin-catalysed cleavage of this type, and the first known PBD to possess a 7-hydroxy-8-methoxy substitution pattern.



Reagents: i, $NaOCH_3$, DMSO; ii, $(COCl)_2$, THF, DMF, 2(S)-pyrrolidinecarbaldehyde diethyl thioacetal[3], Et_3N, H_2O, 0°C, 30 min; iii, $SnCl_2{\cdot}2H_2O$, CH_3OH, reflux, 40 min; iv, $HgCl_2$, $CaCO_3$, CH_3CN-H_2O (4:1), 150 min.

Piperonylic acid was nitrated[2] to give **1a** and coupled to 2(S)-pyrrolidinecarbaldehyde diethyl thioacetal[3] to afford the amide **2a**. Based on past experience[3,4], **2a** was treated with $Sn(II)Cl_2$ in order to reduce the aromatic nitro group. Surprisingly, in addition to the expected reduction, the dioxole ring opened in a completely regiospecific fashion to give **3a**. The methylenedioxy proton signal in the ^{1}H-NMR spectrum of **2a** at δ6.2

disappeared and was replaced with a methoxy signal at δ3.9. Comparison of the NMR data with those of the DC-81 precursor **3b**[4b] indicated that the two molecules were similar but not identical, and suggested a difference in their A-ring substitution pattern. The H6 and H9 protons were still singlets (δ6.22 and δ6.85) but differed in chemical shift from the equivalent proton signals in the spectrum of **3b** (δ6.27 and δ6.79), suggesting a structure of type **3a**. As expected, catalytic hydrogenation (10% Pd-C/H_2/CH_3OH/atm.) of **2a** selectively reduced the aromatic nitro group to give **2b** in quantitative yield without cleavage of the dioxole ring. Cyclization of **3a** using $HgCl_2$[3] afforded a product with the same molecular weight as DC-81 (**4b**) (EI: $M^{+\cdot}$ 246), but ^{1}H-NMR indicated that, although the aromatic protons were in the para-relationship, they differed in chemical shift (δ6.81 and δ7.73) from those of DC-81 (δ6.90 and δ7.51)[4b]. A further feature of this compound was the downfield shift (δ7.73) of one aromatic proton (most likely H6) to a value lower than that for the H11 signal (δ7.67), which is usually the lowest-field non-exchangeable proton signal in PBDs. Based on these factors, the structure could be unambiguously assigned as *iso*-DC-81 (**4a**)[5]. This compound had a reduced binding affinity for pBR322 plasmid DNA compared to DC-81, but was significantly cytotoxic in three cell lines [IC_{50} (μM): L1210, 2.7; ADJ/PC6, 2.7; CH1, 0.2].

Interestingly, the analogous 1,3-benzodioxole ester (**1b**) failed to undergo a similar type of tin-catalysed cleavage; quantitative conversion to the corresponding amine occurred suggesting that the characteristics of other aromatic substituents may play a role in the reaction. Imakura and co-workers[6] have previously reported that similar benzodioxoles of type **1c** and **1d** cleave regiospecifically upon treatment with sodium methoxide/DMSO to afford **5** and **6**, respectively. However, both **1d** and **2a** have nitro substituents in the same position but cleave in different directions suggesting a fundamental difference in mechanism between the two cleavage processes. It is also noteworthy that $SnCl_2$ is a mild reagent and should not affect other functional groups in a molecule; for example, the amide group of **2a** would be highly susceptible to sodium methoxide. The difference in cleavage orientation observed between the similarly substituted intermediates **1d** and **2a** with the different reagents suggests that the regiospecificity of the mild tin-mediated cleavage reported here may have potential application in organic synthesis.

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5. **4a:** IR (Neat): 3050-3600, 2720-3000, 1610, 1515, 1450, 1275, 1215, 760 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.02-2.07 (m, 2H, H-1), 2.28-2.36 (m, 2H, H-2), 3.52-3.88 (m, 3H, H-3, H-11a), 3.92 (s, 3H, OCH_3), 6.82 (s, 1H, H-6), 7.28 (bs, 1H, 8-OH), 7.66 (d, 1H, J = 4.6Hz, H-11), and 7.73 (s, 1H, H-9). ^{13}C-NMR ($CDCl_3$): δ 24.2, 29.6, 46.7, 53.7, 56.1, 109.3, 115.6, 120.7, 139.9, 144.8, 149.8, 162.2, 164.7; MS (EI) m/z (relative intensity): 246 ($M^{+\cdot}$, 100), 217 (22), 177 (8), 150 (13), 122 (15), 107 (5), 89 (9), 70 (30), 45 (9); HRMS: Calc. for 246.1004 ($C_{13}H_{14}N_2O_3$), found 246.1041; $[\alpha]_D^{23}$ = +64 (c = 1.28, $CHCl_3$).
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