Crystal structure of 4-benzyloxy- and 4-hydroxy– (*Z*)-3-[(6-bromo-1, 3-benzodioxol-5-yl)methylene]-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-ones

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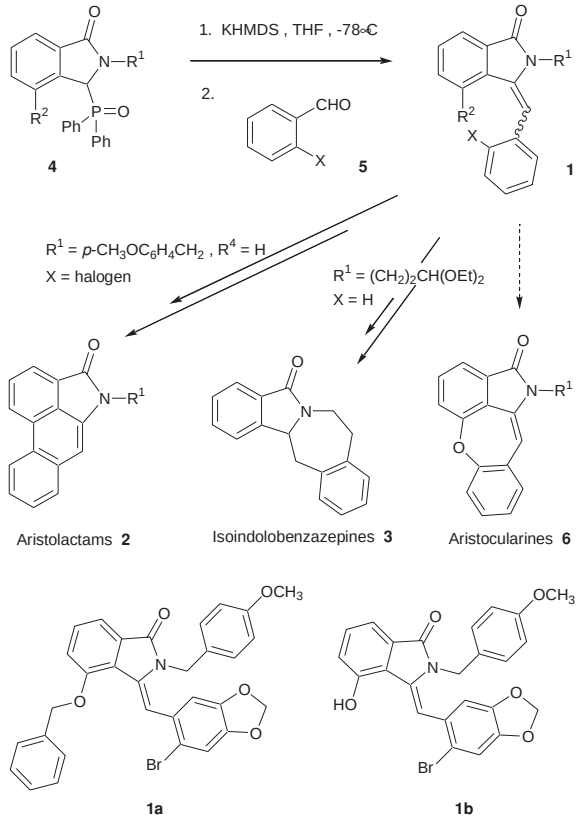
In contrast to unsubstituted models, the Horner reaction between phosphorylated 4-benzyloxyisoindolinone and *ortho*-bromobenzaldehyde gives rise selectively to the arylmethylene derivative with a *Z*-configuration.

Keywords: arylmethyleneisoindolinones, Horner reaction, stereoselection

Mesomerism endows the carboxamide function with a number of physical features such as planarity, absence of free rotation and high degree of double-bond character.[1] When such a functional group is further embedded in a lactam ring system fused with a stilbene (*i.e.* diaryl-1,2-ethylene) unit the resulting models are characterised by a high degree of conjugation. This is notably the case with arylmethylene isoindolinones **1**, a class of enelactams which have attracted much attention from the scientific community in the past few years.[2] They represent the core unit of a wide range of natural and bioactive substances[2] and may also be involved in a number of chemical transformations leading to structurally different alkaloids (Scheme 1). Thus radical-mediated cyclisation of halogenated models (X = Br, I) gives rise to aristolactams **2** (*e.g.* cepharanone, goniopedaline) a class of alkaloid structurally and biogenetically related to the aporphines[3], whereas construction of models with a dialkoxyalkyl chain on the lactam nitrogen has allowed the elaboration of isoindolobenzazepine alkaloids **3** (*e.g.* lennoxamine) after sequential hydrogenation and carbocationic cyclisation.[4]

Critical to the success of these synthetic approaches is the control of the stereochemistry of the exocyclic double bond of the pendant arylmethylene unit. The synthesis of arylmethylene isoindolinones **1**, involving the connection of the styrene unit to the isoindolinone framework, is usually ensured by reliance on the Horner protocol involving a suitably substituted phosphorylated isoindolinone **4** and an appropriate aromatic carboxaldehyde **5** (Scheme 1).[4,5] It has been unambiguously established in earlier reports that the stereochemical outcome of the stilbene double bond is strongly controlled by the bulk of the nitrogen lactam substituent. Thus the *E*-configured stereoisomers have been exclusively obtained with bulky substituents (R^1 = benzyl, *p*-methoxybenzyl, diethoxyethyl)[3,4] whereas *N*-methyl compounds have only been obtained in the *Z* form.[5] However, these studies have so far been carried out with rather uncongested models, namely with enelactams lacking substituents at the 4-position of the isoindolinone nucleus (R^2 = H). Substitution at this site is liable to alter the polyenic and planar character of the Horner products **1**.

In the course of our ongoing program on the synthesis of a variety of compounds comprising an arylmethylene isoindolinone embedded in fused models for subsequent biological evaluation we embarked recently on the construction of aristocularines **6** which further present a diaryl ether linkage.[6] A problematic aspect for the building of these structurally challenging alkaloids was the initial elaboration of the polysubstituted open models **1a** and **1b**, candidates for the annulation step giving rise to the target compounds.



Scheme 1

For structural determination, providing stereochemical assignment of the stilbenoid double bond and spatial arrangements for aromatic and heteroaromatic units making up these highly conjugated systems, X-ray diffraction appeared a method of choice, and we have therefore investigated the crystal structure of these two models.

The title compounds were synthesised by metalation of the parent phosphorylated isoindolinone **4a** (R^2 = OCH_2Ph) and subsequent trapping with 6-bromopiperonal. Usual work up afforded **1a**, the product of a Horner reaction. Retrieval of the phenolic hydroxy function was ensured by treatment with BCl_3 to provide the deprotected model **1b**. Recrystallisation of **1a,b** in EtOH gave crystals satisfactory for X-ray analysis.

The X-ray crystal analysis allowed the unambiguous assignment of the *Z* configuration to both models **1a** and **1b** which reveal a dramatic difference with the reaction performed with unalkoxylated models **1** (R^2 = H).[5] Interestingly, the stereochemistry of the exocyclic double bond was retained upon removal of the bulky benzyl phenolic protection.

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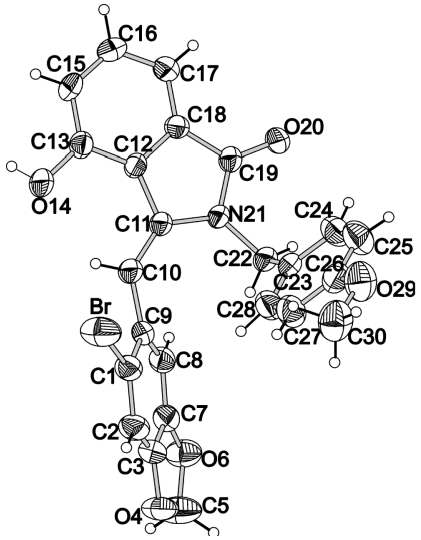

Fig. 1 Crystal structure of (*Z*)-3-(6-bromo-1,3-benzodioxol-5-ylmethylene)-4-hydroxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (**1b**).

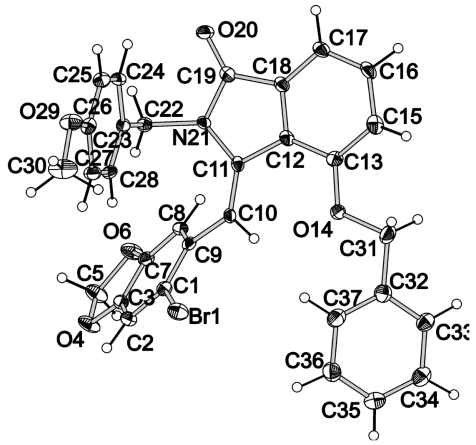

Fig. 2 Crystal structure of (*Z*)-4-benzyloxy-3-(6-bromo-1,3-benzodioxol-5-ylmethylene)-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (**1a**). First crystallographically independent molecule.

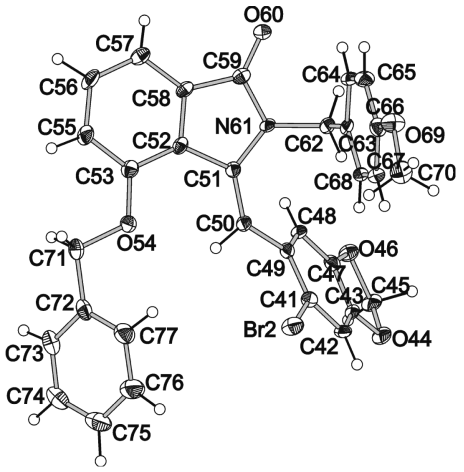

Fig. 3 Crystal structure of (*Z*)-4-benzyloxy-3-(6-bromo-1,3-benzodioxol-5-ylmethylene)-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (**1a**). Second crystallographically independent molecule.

From the X-ray data the torsion angle values for C12, C11, C10, C3 and N21, C11, C10, C9 are found to be –172.4° and 6.3° respectively, for compound **1b** (Fig. 1). For compound **1a**, the unit cell contains two crystallographically independent molecules with the corresponding torsion angles estimated at –162.5° and 14.1° and 155.4° and –19.5° for the two molecules (Figs 2 and 3). These results clearly demonstrate that the bulkiness of the aromatic substitution pattern has no steric impact on the planarity of these compounds which possess a very high degree of conjugation.

Experimental

(Z)-4-Benzyloxy-3-(6-bromobenzo[1,3]dioxol-5-ylmethylene)-2-(4-methoxybenzyl)-2,3-dihydro-1H-isoindol-1-one **1a**[7]: M.p. 160–161°C. Crystal data: $C_{31}H_{24}BrNO_5$, M_r = 570.42, F(000) = 2336, colourless crystal, monoclinic system, a = 11.329(3), b = 14.584(4), c = 31.859(9) Å, α = 90, β = 92.945(5), γ = 90°, V = 5257(3) Å^3, Space group P2(1)/n, Z = 8, D_c = 1.442 g cm^{-3}, B(Mo Kα) = 16.06 cm^{-1}.

(Z)-3-(6-Bromobenzo[1,3]dioxol-5-ylmethylene)-4-hydroxy-2-(4-methoxybenzyl)-2,3-dihydro-1H-isoindol-1-one **1b**[7]: M.p. 218–219°C. Crystal data: $C_{24}H_{18}BrNO_5$, M_r = 480.30, F(000) = 488, colourless crystal, triclinic system, a = 8.363(2), b = 8.973(2), c = 13.585(3) Å, α = 84.139(4), β = 83.300(4), γ = 81.418(4)°, V = 997.4(4) Å^3, Space group P-1, Z = 2, D_c = 1.599 g cm^{-3}, B(Mo Kα) = 0.21 cm^{-1}.

The intensity data were collected on a Bruker AXS SMART three-circle diffractometer with graphite monochromatised Mo Kα radiation (λ=0.71073 Å) and equipped with a CCD two-dimensional detector. Collection with ω and φ scans.

The structures were solved by direct methods and expanded using Fourier maps. All non hydrogen atoms were refined anisotropically. Hydrogen atoms positions were refined but their temperature coefficients were fixed to 1.2 times the U_{eq} of the atoms to which they are bound. The SHELXTL[8] crystallographic software package was used for all calculations.

For **1a** , 4366 independent reflections were used –15< h <15, –19< k <18, –42< l < 42 , θ max =28.7°, R_1 = 0.0515, Rw_2 = 0.1031; the estimated standard deviations for non-hydrogen atoms were in the range 0.0002–0.0006 Å for the bond lengths and 0.3-0.5° for the bond angles.

For **1b** , 4100 independent reflections were used –10< h <11, –12< k <11, –18< l <18 , θ max =28.75°, R_1 = 0.042, Rw_2 = 0.095; the estimated standard deviations for non-hydrogen atoms were in the range 0.0003–0.0005 Å for the bond lengths and 0.3–0.4° for the bond angles

Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre, quoting deposition numbers CCDC 244873 (**1a**) and 244874 (**1b**).

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References

1 M.B. Robin, F.A. Bovey and H. Basch, *Molecular and Electronic Structure of the Amide Group*, in *The Chemistry of Amides*, eds S. Patai and J. Zabicky, John Wiley & Sons, London, 1970, pp. 1-72.
2 Z.-L. Chang and D.-Y. Zhu, in *The Alkaloids*, eds A. Brossi, Academic Press, New York, 1978, Vol. 31, pp. 29-65.
3 A. Couture, E. Deniau, P. Grandclaudon and C. Hoarau, *J. Org. Chem.*, 1998, **63**, 3128.
4 A. Couture, E. Deniau, P. Grandclaudon and C. Hoarau, *Tetrahedron*, 2000, **56**, 1491-1499.
5 C. Hoarau, A. Couture, H. Cornet, E. Deniau and P. Grandclaudon, *J. Org. Chem.*, 2001, **66**, 8064-8069.
6 E. Tojo, D. Dominguez and L. Castedo, *Phytochemistry*, 1991, **30**, 1005-1010.
7 A. Moreau, A. Couture, E. Deniau and P. Grandclaudon, *J. Org. Chem.*, 2004, **69**, 4527-4530.
8 G.M. Sheldrick, SHELXTL, Program for Crystal Structure Solution and Refinement, Bruker AXS Inc., Madison, WI, 1997.