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A NOVEL REGIO- AND STEREOSELECTIVE SYNTHESIS OF ISOINDOLINES

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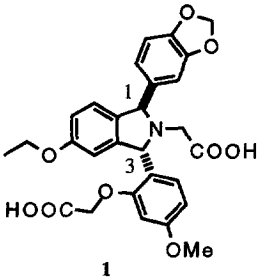
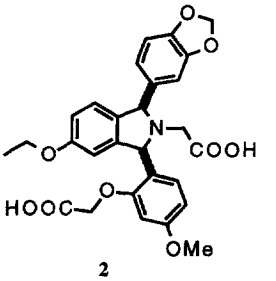
Abstract: The described synthesis of isomeric isoindoline dicarboxylic acid analogs **1** and **2**, two potent ET_A selective receptor antagonists, involves an efficient regioselective route to highly functionalized dibenzoylbenzenes and a novel methodology for the stereoselective preparation of *trans* and *cis* 1,3-disubstituted isoindolines. Copyright © 1996 Elsevier Science Ltd

Endothelins (ET-1, ET-2 and ET-3) are a family of potent vasoconstrictor and mitogenetic peptides originally isolated from vascular endothelial cells.[1] These peptides are known to elicit a number of biological effects contributing to cardiovascular and renal dysfunctions[2] through interaction with specific G-protein coupled receptors, of which two human subtypes, ET_A and ET_B, have been fully characterized.[3,4] In connection with our endothelin antagonist program we needed to develop a convenient synthetic route to highly fuctionalized isoindoline dicarboxylic acid analogs of type **1** and **2**, two potent ET_A selective receptor antagonists. Here, we describe a regio- and stereoselective synthesis for the efficient preparation of 1,3-disubstituted isoindolines.



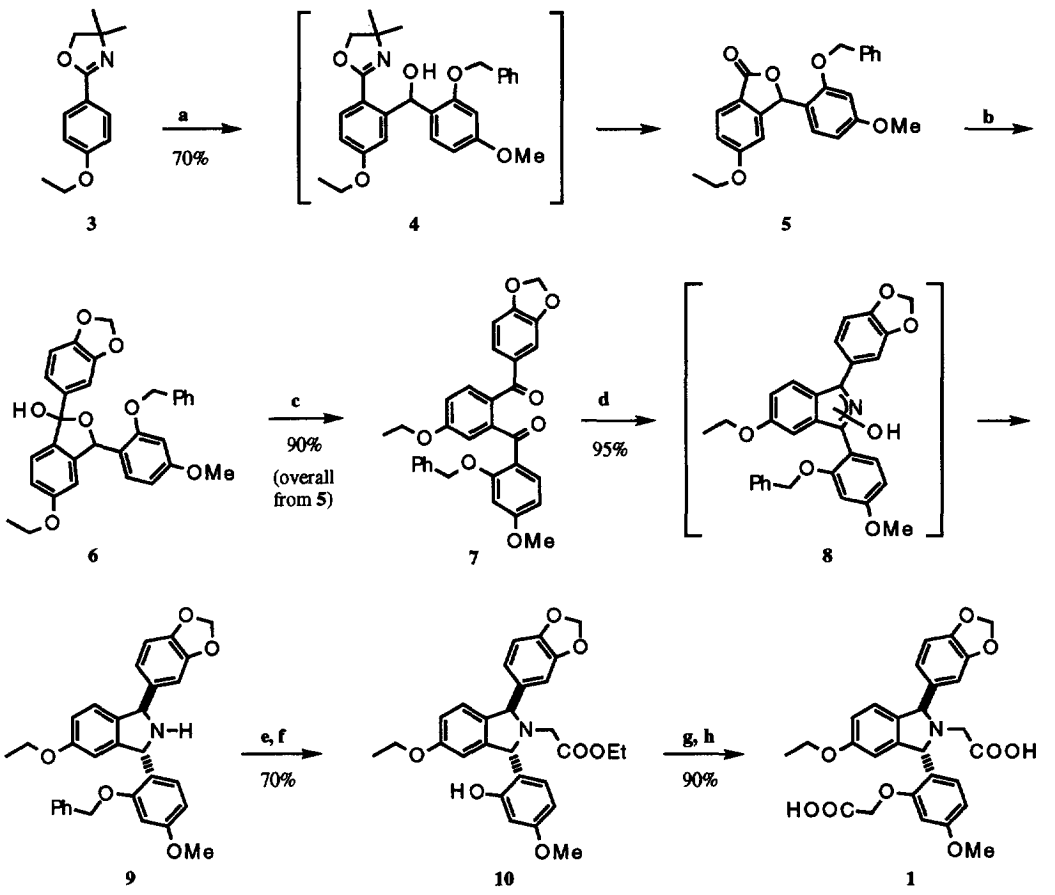
1



2

Previously, it has been reported by Carpino[5] that 1,3-diphenyl-3-hydroxyisoindole undergoes a stereoselective reduction to the corresponding *cis* 1,3-diphenylisoindoline upon treatment with zinc in acetic acid, whereas reduction with lithium aluminum hydride in the presence of aluminum chloride affords the *trans* isomer. However, in his later work Carpino[6] reversed his original assignment for the *cis* and *trans* stereochemistry, which is unequivocally confirmed by the present work. Accordingly, we envisoned that a regioselective synthesis of dibenzoylbenzene analog **7** (Scheme 1) and subsequent reaction with an ammonia equivalent would afford the key intermediate, hydroxyisoindole **8**. Functional group manipulation should then allow the stereoselective synthesis of isoindolines **1** and **2**. Indeed, the correct regiochemistry of the aromatic substituents in compound **7** was achieved through an oxazoline directed *o*-lithiation[7,8] followed by condensation with 2-benzyloxy-4-methoxybenzaldehyde.[9] The resulting hydroxyoxazoline intermediate **4** was hydrolyzed *in situ* to give the lactone **5** in 70% overall yield. A subsequent Grignard reaction[10] on this compound led to the formation of an unstable hemiketal intermediate **6** which, however, could be cleanly oxidized to the desired dibenzoylbenzene **7** by treatment with pyridinium chlorochromate (PCC).[11] Compound **7** reacted smoothly with an excess of ammonium acetate in refluxing ethanol containing a catalytic

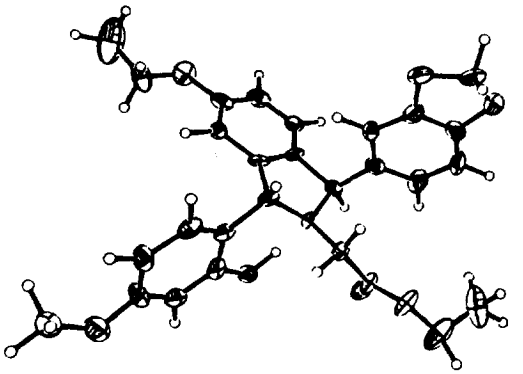
Scheme 1



a. *n*-BuLi, THF, -78 to 0°C; 2-Benzyloxy-4-methoxybenzaldehyde, -78°C; aq HCl, THF, -78°C to rt **b**. (3,4-methylenedioxyphenyl)magnesium bromide, THF, 0°C **c**. PCC, CH_2Cl_2, rt **d**. NH_4OAc, EtOH, Na (cat), Δ; Zn-Cu, AcOH, rt **e**. K_2CO_3, $BrCH_2CO_2Et$, DMF, rt **f**. Pd/C, H_2 (1 atm), EtOAc, rt **g**. NaH, $BrCH_2CO_2Et$, THF, rt **h**. NaOH, EtOH, 50°C

amount of sodium ethoxide and afforded the hydroxyisoindole derivative **8** as a 1:1 mixture of regioisomers. This mixture can be isolated or converted directly to the corresponding isoindoline analog **9** nearly quantitatively by *in situ* Zn-Cu reduction in the presence of glacial acetic acid. Compound **9** was obtained exclusively as the *trans* isomer and was used as such without purification in the following step. The relative stereochemistry of the substituents at the isoindoline C1 and C3 was determined by NOE experiments[12] and was confirmed by obtaining a crystal structure of the isoindoline analog **10** (Figure 1). Alkylation of **9** with ethyl bromoacetate was followed by removal of the benzyl protecting group using catalytic hydrogenation to give the *o*-hydroxyaryl isoindoline **10**. Finally, this compound was converted to the desired dicarboxylic acid analog **1** by an alkylation and hydrolysis sequence. Compound **1** was obtained in 37% overall yield from oxa-

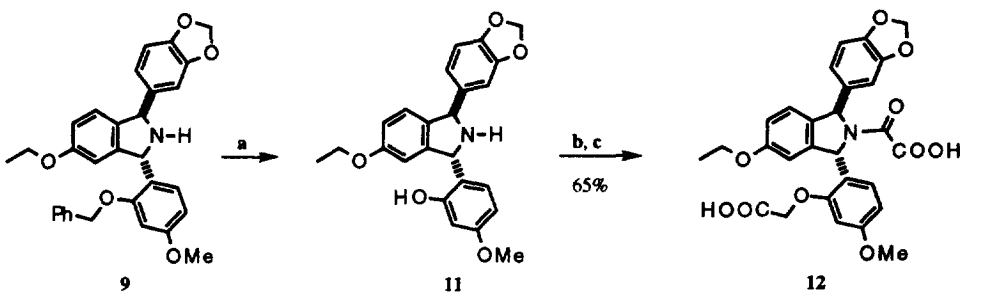
Figure 1. Crystal Structure of Isoindoline 10



zoline **3** in 8 steps. Furthermore, the two alkylation steps can be carried out simultaneously, e.g., when isoindoline **9** was first subjected to catalytic hydrogenation subsequent double alkylation followed by basic hydrolysis afforded compound **1** in good yield. In general, the phenol functionality can be selectively substituted prior to the sterically hindered isoindoline amino group. For example, as illustrated in Scheme 2, alkylation of the hydroxyl group and subsequent *N*-acylation, which can conveniently be carried out *in situ*, followed by hydrolysis gave the oxamic acid derivative **12** in 65% overall yield from the isoindoline **9**.

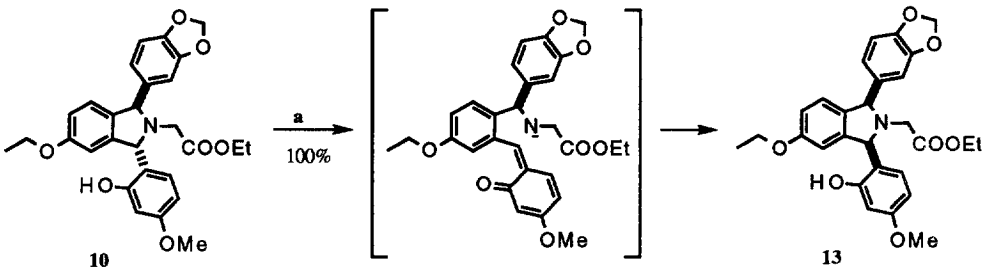
As reported by Carpino[5,6] hydroxyisoindoles can be reduced to the corresponding *cis* isoindolines by treatment with lithium aluminum hydride in the presence of aluminum chloride. However, in our hands this reaction gave only low yields (less than 30%) and was not always reproducible. Interestingly, when compound **10** was heated for an hour at 100 °C in DMF solution containing a catalytic amount of tetra-*n*-butylammonium iodide the *trans* isoindoline **10** was converted quantitatively to the thermodynamically more stable *cis* isomer **13** (Scheme 3).[12] This reaction most likely proceeds through a quinone-methide type of intermediate in which the benzylic carbon-nitrogen bond at the isoindoline C3 has been cleaved. Reclosure to form the isoindoline ring system then leads to the more stable *cis* isomer **13**. Compound **13** can be alkylated *in situ* and, finally, hydrolysis under standard conditions afforded the *cis* dicarboxylic acid analog **2**. Clearly, this method is limited to those compounds with *o*- or *p*-hydroxyaryl substituents either at C1 or C3. Furthermore, for the isomerization to proceed without severe side reactions the isoindoline nitrogen needs to bear an alkyl substituent, e.g., compound **11** (Scheme 2) gives the corresponding *cis* isomer in less than 10% yield. Similarly, amide derivatives of compound **11** also do not undergo isomerization cleanly.

Scheme 2



a. Pd/C, H_2 (1 atm), EtOAc, rt b. NaH, $BrCH_2CO_2Et$, THF, rt; *i*-Pr_2NEt, EtO_2CCOCl, -78°C c. NaOH, EtOH, rt

Scheme 3



a. Tetra-*n*-bytylammonium iodide, DMF, 100°C

In conlusion, several isoindoline analogs with different substitution patterns can be made using the described methodology. The synthesis allows an efficient, regio- and stereocontrolled route to many *trans* and *cis* isoindolines which are not easily accessible by the existing methods.[13] However, the *trans* to *cis* isomerization is limited to those isoindoline derivatives that have an *o*- or *p*-hydroxyaryl substituent either at C1 or C3. Whether a correctly positioned hydroxyl group at the isoindoline ring system itself would result in isomerization still needs to be examined.

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