

Regiospecific Synthesis of Mono-*N*-substituted Indolopyrrolocarbazoles

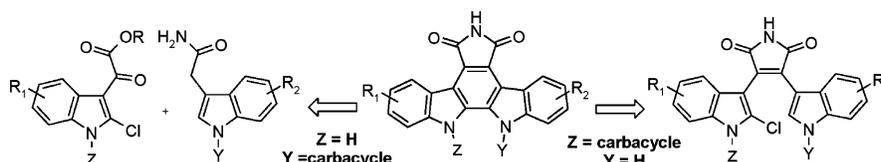
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ABSTRACT



Two complementary and efficient strategies have been developed for the regiospecific synthesis of unsymmetrical indolopyrrolocarbazoles (IPCs) mono-*N*-substituted with a pentacycle. A halogen in position 2 of the intermediate bisindolylmaleimides **3a–e** allows a selective Mitsunobu coupling by exploiting the increased acidity of the 2-chloro-substituted indole nitrogen. It also promotes an easier cyclization of bisindolylmaleimides **4a–e** and **7b–e** to IPCs. Alkylation of the 2-unsubstituted indole-3-carboxamides **2a,b** and further processing to the corresponding IPCs gives access to the opposite regioisomers.

The synthesis of indolopyrrolocarbazole (IPC) glycosides constitutes a hot topic for the chemistry community due to the wide range of biological activities covered by the representative natural products of this family (cf. Figure 1).

Monoglycosidated IPCs, such as rebeccamycin isolated in 1985,^{1a} have shown remarkable antiproliferative properties and inhibitory potency toward topoisomerase I.¹ A derivative of rebeccamycin, NB-506² (L-753000), and recently BMS-250749³ have entered clinical trials as antitumoral agents, and a third one, ED-749⁴ (J-107088), is currently in clinical

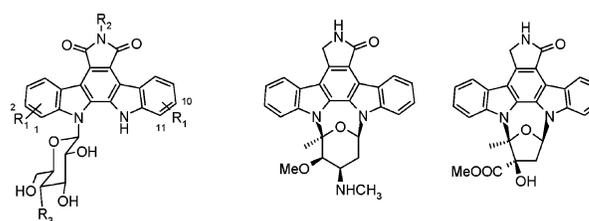
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Rebeccamycin: $R_1=1,11\text{-Cl}$, $R_2=H$, $R_3=OMe$
NB-506: $R_1=1,11\text{-OH}$, $R_2=NHCHO$, $R_3=OH$
BMS-250749: $R_1=3,9\text{-F}$, $R_2=H$, $R_3=F$
ED-749: $R_1=2,10\text{-OH}$, $R_2=CH(CH_2OH)_2$, $R_3=OH$

Staurosporine

K-252A

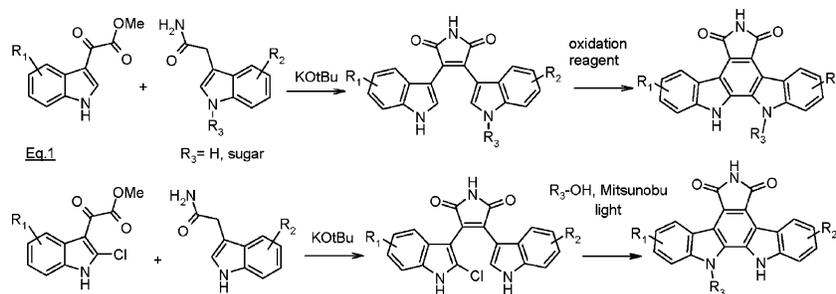
Figure 1. Representative indolopyrrolocarbazoles (IPC).

phase III for the treatment of solid tumors and glioblastoma. In contrast, *N,N'*-bis-substituted IPCs, such as staurosporine or K-252A, exhibit potent inhibition of various protein kinases.^{5,6}

We focused our attention on the synthesis of rebeccamycin-like IPC derivatives with an unsymmetrical substitution

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Scheme 1. Comparison of Strategies



pattern, wherein the carbohydrate moiety was replaced by a pentacyclic hydrocarbon derivative acting as a sugar analogue. Recently, related structures have been published having also pentacycle rings but related to K-252a and showing kinase inhibition activity.⁷

Two major challenges which have to be overcome during the synthesis of this class of compounds are (1) the relative low reactivity of the indole nitrogens within the aromatic system compared to the imidic nitrogen and (2) the selective functionalization of only one indole nitrogen in unsymmetrical aglycons.

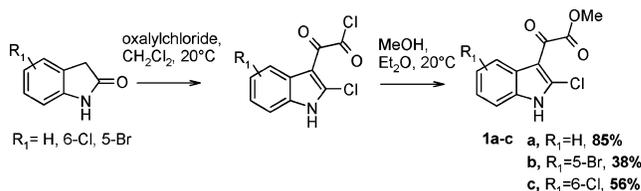
Different approaches have been published for the synthesis of unsymmetrical IPCs, by condensation of two 3-substituted indole derivatives⁸ or by Grignard reactions between two indole units and a protected maleimide.⁹ Oxidation of the intermediate products (bisindolylmaleimides, indole–indolines) to IPCs is mostly conducted with Pd salts or oxidation reagents such as DDQ. In some of these approaches, a protection strategy is required to achieve specific mono-functionalization of only one indole nitrogen.^{6,9,10}

Our synthetic approach is partially inspired by the strategy proposed by Faul et al.¹¹ who reported an improved synthesis of arcyciarubin A (bisindolylmaleimide) starting from methyl indole-3-glyoxylic acid and indole-3-acetamide (Scheme 1, eq 1).

Our fundamental modification was the introduction of a halogen atom in position 2 of the glyoxylic indole (Scheme

1, eq 2), which allows (1) a regioselective Mitsunobu reaction for the introduction of an allylic cyclopentenol in an unsymmetrical and completely deprotected aglycon and (2) leads to easier non-oxidative light-promoted cyclization of bisindolylmaleimides to IPCs in almost quantitative yield.

Scheme 2. Synthesis of Methyl 2-Chloroindole-3-glyoxylicates



Using Bergman's synthesis¹² (Scheme 2), oxindoles were converted to the corresponding methyl 2-chloroindole-3-glyoxylicates **1a–c**. All intermediates and products were isolated by precipitation as stable solids.

The starting materials oxindole and its 6-chloro derivative are commercially available. 5-Bromooxindole was obtained in 77% yield by simple bromination of commercial oxindole using Br₂ and KBr in boiling water.¹³

Intermolecular Perkin-type condensation of methyl 2-chloroindole-3-glyoxylicates **1a–c**¹⁴ with indole-3-acetamides **2a,b**¹⁵ in the presence of KOtBu in THF provided, after treatment with HCl, unsymmetrical bisindolylmaleimides **3a–e** in yields between 50 and 85% (Scheme 3) (**3d** was only isolated in 14% yield due to the low solubility of the product).

Subsequently, under classical Mitsunobu conditions we were able to functionalize regioselectively the 2-chloro-substituted indole nitrogen due to its increased acidity induced by the halogen.¹⁶ Thus, reaction of **3a–e** with an allylic cyclopentenol¹⁷ provided the corresponding bisindolylmaleimides **4a–e**. Although major products were always **4a–e** as seen by TLC analysis, the compounds were only isolated in modest yields (31–45%) as two subsequent

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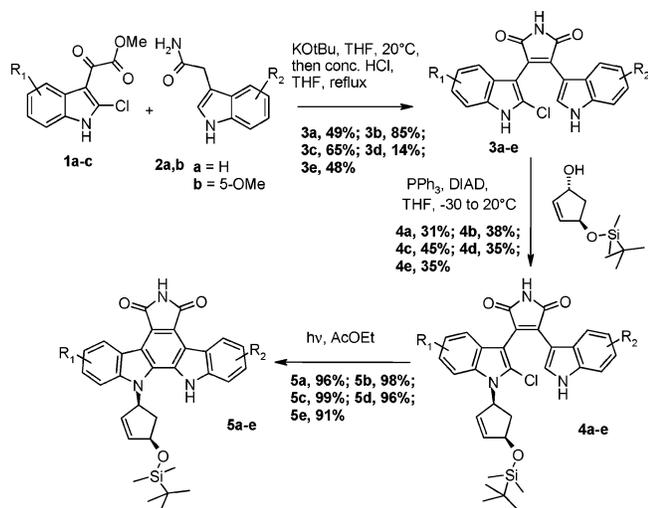
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Scheme 3. Synthesis of Compounds **5a–e** (Route A)



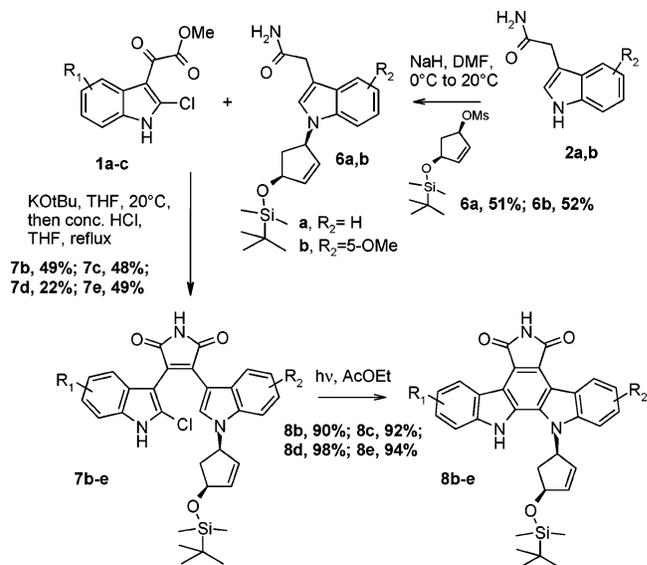
column chromatographies were necessary to eliminate small quantities of byproducts (5–10% of starting material and bisalkylated product), hydrazine dicarboxylate, and triphosphine-related substances.

This regioselectivity, in contrast, could not be obtained in our hands on arcylriarubin A, since the two indole nitrogens are undifferentiated. Instead, mixtures of mono-, bis-, and trisalkylated products resulted.

In our strategy, the enhanced reactivity of the chloro-substituted heterocycle directs the Mitsunobu alkylation selectively to the indole. In addition, unlike other syntheses,^{9,10,18} the method allows also the presence of all three unprotected nitrogens on the bisindolylmaleimide during the alkylation step.

Finally, subsequent cyclization of the monofunctionalized bisindolylmaleimides **4a–e** to IPCs **5a–e** was significantly facilitated by the presence of the 2-chloro substituent. Thus, compounds **4a–e** underwent smooth cyclization to the final IPCs **5a–e** in 91–99% yields by simple irradiation with a

Scheme 4. Synthesis of Compounds **8b–e** (Route B)



at the R_1 -substituted indole were obtained with complete regiocontrol (Table 1, entries 1–5).

This new mild method proved to be very useful for our purposes as some strategies from the literature were not suited for our targets. For example, we observed that the allylic pentacycle was lost when treated with acids (TFA/anisole or AlCl_3 used for PMB deprotection of the imide) or palladium salts (oxidation step).^{9,10}

Bisindolylmaleimide **3a** was also submitted to light-induced cyclization in which case arcylriarubin A was obtained in 95% yield. The total yield of the synthesis of this natural product was 40% starting from oxindole.

A second strategy was elaborated for the synthesis of the opposite regioisomers as shown in Scheme 4. In this case, the carbacycle unit was introduced at an earlier stage by direct alkylation of indole-3-acetamides **2a,b** using the cyclopentene mesylate. This reaction provides a mixture of cis and trans products, from which the cis isomers were isolated as the major product in around 50% yield. Subsequent condensation with methyl 2-chloroindole-3-glyoxylates **1a–c** provided the corresponding functionalized bisindolylmaleimides **7b–e** in around 50% yield, representing the regioisomers of **4b–e** (**7d** was only isolated in 22% yield due to low solubility of the product).

Cyclization to the complementary decorated IPCs was achieved as described before in very good yields (90–98%), and compounds **8b–e** were obtained in three steps as single isomers in moderate overall yields (Table 1, entries 6–9).

Table 1. Yields of Compounds **5a–e** and **8b–e**

entry	IPC	route	R_1	R_2	yield ^a (%)	yield ^c (%)
1	5a	A	H	H	15	31
2	5b	A	5-Br	H	32	38
3	5c	A	6-Cl	H	29	45
4	5d	A	H	5-OMe	5 ^b	35
5	5e	A	5-Br	5-OMe	15	35
6	8b	B	5-Br	H	22	NA
7	8c	B	6-Cl	H	23	NA
8	8d	B	H	5-OMe	11 ^b	NA
9	8e	B	5-Br	5-OMe	24	NA

^a Overall yield according to Schemes 3 or 4. ^b Decreased yield due to low solubility of **3d** or **7d**. ^c Yield for the Mitsunobu reaction to access intermediates **4**.

strong light source (halogen lamp 1000 W). Usage of purification procedures is not needed, and products alkylated

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In conclusion, exploiting the possibility to combine indole-derived building blocks with different substitution pattern, the two complementary strategies (routes A and B) allow the direct regiocontrolled synthesis of *N*-indole-monosubstituted IPCs either on the R₁ substituted indole or opposite to it. Moreover, the presence of a chlorine atom allows a selective Mitsunobu reaction on an unprotected bisindolylmaleimide and affords higher yields for the oxidation step relative to literature procedures.

This method should prove to be extremely useful to access previously unreported members of this important class of biologically active compounds.

Supporting Information Available: Detailed description of experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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