Pergamon

Tetrahedron Letters 43 (2002) 2561–2564

TETRAHEDRON LETTERS

First synthesis of symmetrical and non-symmetrical aza indolocarbazoles derivatives

Sylvain Routier,[a,*] Gérard Coudert,[a] Jean-Yves Mérour[a] and Daniel Henri Caignard[b]

[a]*Institut de Chimie Organique et Analytique associé au CNRS, Université d'Orléans, BP 6759, 45067 Orléans Cédex 02, France*
[b]*ADIR, 1 rue Carle Hebert, 92415 Courbevoie Cedex, France*

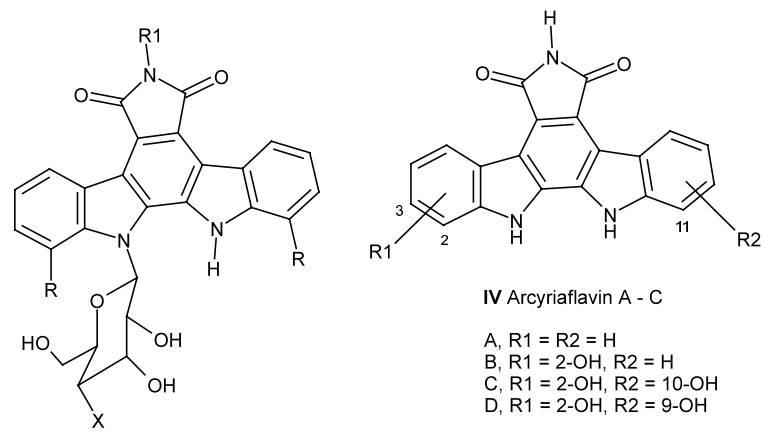
Received 5 February 2002; accepted 14 February 2002

Abstract—A new family of aza-indolocarbazoles **2**–**3** was built from protected 3-(3-indolyl)-4-bromo-*N*-methylmaleimide in a few efficient steps. Symmetrical and non-symmetrical products were obtained. Regioselectivity of anionic condensation was controlled. A possible selective deprotection between an *N*-Boc and *N*-benzenesulphonyl group using mild basic conditions was confirmed.

Indolocarbazoles are natural or synthetic products from which the Rebeccamycin **I**, a weak inhibitor of topoisomerase I is the archetype.[1,2] Development of new DNA topoisomerases I inhibitors as cancer chemotherapy agents is currently an active area of research. ED-110 **II** and NB-506 **III** are two representative products in this family.[3,4] Arcyriaflavin A–C **IV** are the major key intermediates in the preparation of symmetrical and non-symmetrical rebeccamycin analogues.[5] All these compounds possess an indolocarbazole backbone (Fig. 1).

Recently, several aglycone rebecamycin isosteres were described.[6] Structural modifications were realized on the heterocyclic core where the position and nature of the indolic substituents were changed. Related compounds lacking an indolic moiety such as granulatimide **V** were described.[7] For our own part, we chose to synthesize naphtho[3,4-*c*]carbazole **1** using the bioisoterism indole–naphthalene.[8] All these compounds are potential candidates for novel drug discovery (Fig. 2).

The most convenient synthesis of symmetric or non-symmetric bisindolylmaleimides generally uses indolyl Grignard reagents with dibromomaleimides.[1–8] A cyclisation between the two C-2 indolic carbon atoms com-



I : Rebeccamycin, X = OMe, R = Cl, R1 = H
II : ED-110, X = OH, R = OH, R1 = H
III : NB-506, X = OH, R = OH, R1 = NHCHO

IV Arcyriaflavin A - C

A, R1 = R2 = H
B, R1 = 2-OH, R2 = H
C, R1 = 2-OH, R2 = 10-OH
D, R1 = 2-OH, R2 = 9-OH

Figure 1. Most representative indolocarbazoles derivatives.

* Corresponding author. Tel.: (33) 2.38.49.48.53; fax: (33) 2.38.41.72.81; e-mail: sylvain.routier@univ-orleans.fr

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00315-5

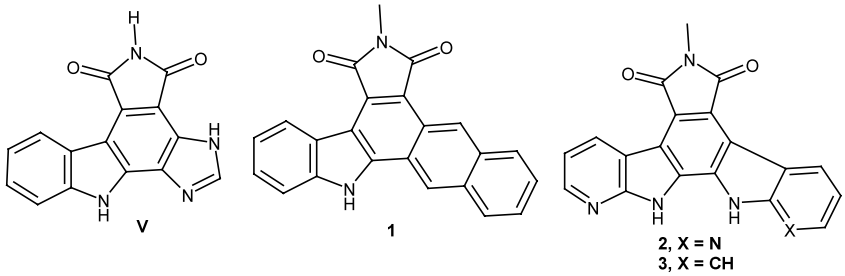


Figure 2. Some structural modification in indolocarbazoles series.

pletes the synthesis of the required derivatives. Several routes were described to perform this intramolecular ring closure: a photolytic activation[9] or the use of palladium-catalyzed cross-coupling reactions[10] were described. Suzuki reaction of a triflate derivative with 3-indoleboronic acid has also been reported[11] and more recently an oxidative cyclisation with a Wacker-type catalytic system was used in an industrial process.[12]

The huge synthetic effort developed in this area prompted us to report our work regarding a new series of related derivatives **2** and **3** containing one or two supplementary nitrogen atoms. In numerous antitumor series, the presence of a pyridine nitrogen atom reinforces the DNA binding properties.[13] This observation guided us to replace one or two indole moieties by a 7-azaindolic group in order to obtain the azaindolocabazoles **2** and **3**.

First, the reaction between 7-azaindole **4** and 2,3-dibromo-*N*-methylmaleimide **5** was performed (Table 1, Scheme 1) as previously described.[10] In our case, N1-alkylated product **6** was obtained (entry 1). Different conditions were attempted to direct the regioselectivity of the anionic reaction towards the C3-alkylated product **7**. For instance, if a mixture of THF and hexane was used, the yield of compound **6** decreased (entry 2) but no formation of **7** was observed.

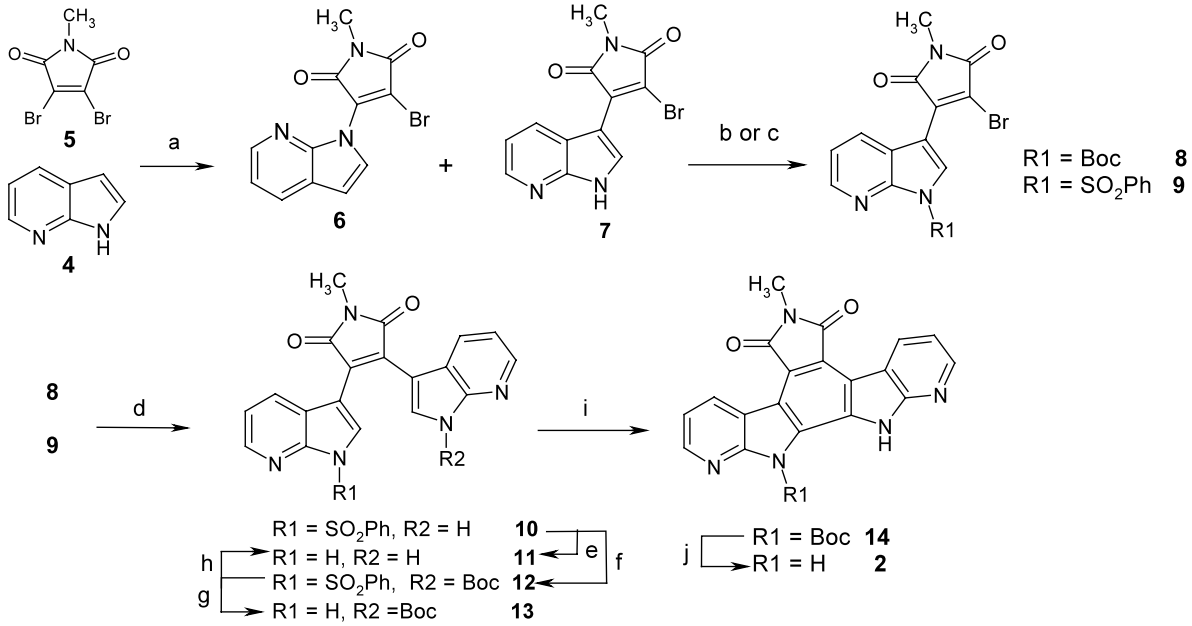
It was reported that 7-azaindolic Grignard reagent when condensed on furanose give C3-alkylated if the reaction was performed in CH_2Cl_2.[14] Thus, we used ethylmagnesium bromide as base (entry 3) in diethylether. After complete formation of the indolic Grignard reagent the diethylether was evaporated and replaced by dichloromethane (entry 3) in order to perform the condensation. For the first time, the regioselectivity was inverted, the C3-alkylation was observed and compound **7** was obtained in 14% yield. Solvent effect was studied with the use of chloroform, hexane and benzene but in all cases the reaction failed. The use of toluene at room temperature was unsuccessfull but at 50°C, compound **7** was obtained in a 15% yield (entries 4 and 5). Interestingly a mixture of toluene and dichloromethane afforded the desired compound **7** in 65% yield (entry 6) after one day of reaction. The heterogeneous reaction mixture load leads us to increase the reaction time to 4 days but the yield of **7** was not improved.

The next step consisted of the protection of indolic NH atom either by a *tert*-butyloxycarbonyl or a benzenesulphonyl group to afford compounds **8** and **9** in 66 and 74% yield, respectively. Anionic condensation of compound **8** with 7-azaindole **4** afforded, using previously described conditions (Table 1, entry 6), only *N*-Boc deprotection and compound **7** was recovered. *N*-Boc azaindole group was very sensitive to basic conditions. Another assay was performed using 2 equiv. of azaindole **4** and LiHMDS as base and only the deprotected compound **7** was obtained. On the other hand LiHMDS was used with **9** in toluene at room temperature, the reaction afforded, after 12 h, compound **10** in 64% yield. Increasing the amount of 7-azaindole **4** to 4 equiv., allowed the reaction time to be decreased to 6 h.

The coupling reaction performed on compound **10** using Pd $(OAc)_2$[15], Pd $(OCOCF_3)_2$[3,6] or DDQ in the presence[16] or absence[10] of APTS failed. We hypothesized that steric effects due to the protective group and its strong electron withdrawing effect inhibit the bond formation between the two indolic C-2 positions. To confort this hypothesis, compound **10** was deprotected using Bu_4NF in refluxing THF to afford compound **11** in 83% yield. Wathever the methods used, the cyclisation failed.

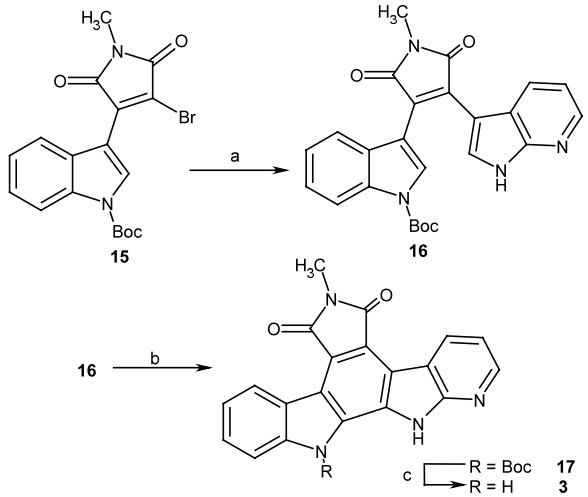
Table 1. Anionic condensation of **4** on 2,3-dibromo-*N*-methylmaleimide **5**

Entry	Reagents	Base	Solvent	Conditions	Product (yield)
1	**4** (1 equiv.), **5** (1.2 equiv.)	LiHMDS, (2 equiv.)	THF	0°C, 3 h	**6** (25)
2	**4** (1 equiv.), **5** (1.2 equiv.)	LiHMDS, (2 equiv.)	THF/hexane (3/2)	0°C, 3 h	**6** (15)
3	**4** (2 equiv.), **5** (1 equiv.)	EtMgBr, (2.05 equiv.)	Ether replaced by CH_2Cl_2	rt, 12 h	**7** (14)
4	**4** (2 equiv.), **5** (1 equiv.)	EtMgBr, (2.05 equiv.)	Toluene	rt, 12 h	No reaction
5	**4** (2 equiv.), **5** (1 equiv.)	EtMgBr, (2.05 equiv.)	Toluene	50°C, 12 h	**7** (15)
6	**4** (2 equiv.), **5** (1 equiv.)	EtMgBr, (2.05 equiv.)	Toluene/CH_2Cl_2 (2/1)	50°C, 24 h	**6** (65)



Scheme 1. *Reagents and conditions*: (a) Table 1; (b) Boc_2O, 2 equiv., 4-DMAP 0.1 equiv., CH_2Cl_2, rt, 1 h, 66%; (c) NaH 1.6 equiv., $PhSO_2Cl$ 1.4 equiv., THF 9/DMF 1, rt, 74%; (d) compound **4** 2 equiv., LiHMDS 3 equiv., toluene, rt, 12 h, 64%; (e) TBAF 2 equiv., THF, rflx, 2 h, 83%; (f) Boc_2O 2 equiv., 4-DMAP 0.1 equiv., THF, 30°C, 92%; (g) TBAF 2 equiv., THF, rt, 2 h, 80%; (h) TBAF 10 equiv., THF, rflx, 1 h, quant.; (i) hν, 500 W UV lamp TQ-718 DEMA, I_2 cat., benzene, 3 h 30, 74%; (j) formic acid, rt, 2 h, quant.

It has been reported that the presence of a mono *N*-Boc protected bis-indoylmaleimide compound seems to facilitate the photocyclisation.[17] By analogy, we realized the following sequence to prepare compound **13**: **10** was protected with a Boc group affording compound **12** in 92% yield. The *N*-benzenesulphonyl group cleavage was selectively performed on compound **12** by Bu_4NF in THF at room temperature to generate **13** in 80% yield.[18] This reaction was performed in refluxing THF with an excess of reagent to give compound **11** in a quantitative yield. Photoirradiation of compound **13** gave the desired product **14** in 74% yield. The final deprotection was performed using an excess of TBAF in refluxing THF to afford compound **2** in 88% yield. An acidic *N*-Boc deprotection using formic acid was realized and compound **2** was quantitatively obtained.



Scheme 2. Synthesis of the non-symmetrical aglycone **2**. (a) compound **4** 3 equiv., LiHMDS 4.1 equiv., toluene, rt, 24 h, 67%; (b) hν, I_2, benzene, 1.5 h, 85%; (c) TBAF 10 equiv., THF, rflx, 1 h, 88%.

The synthesis of the non-symmetrical compound **3** was straightforward (Scheme 2). The lithio derivative of 7-azaindole **4** was condensed on **15**[10] as described for compound **9** to afford **16** in 67% yield. No deprotection of the indolic nitrogen atom was observed. *N*-Boc azaindole was more sensitive than *N*-Boc indole to the basic conditions. The next step was performed by photocyclisation on **16** and compound **17** was obtained in 85% yield. Final deprotection was realized using TBAF in refluxing THF to give the non-symmetrical aglycone **3** in 88% yield. Identification of compounds **2** and **3** were realized by NMR and purity was determinated by microanalysis.[19]

In this summary, we have described a straightforward and efficient preparation of new symmetrical and non-symmetrical aza indolocarbazoles[19] using a photocyclisation procedure. The reactivity of 2,3-dibromo-*N*-methylmaleimide with 7-azaindole was explored in different anionic conditions and a regioselective C-3 alkylation was developped. Biological studies are in progress to evaluate the influence of the newly introduced nitrogen atoms.

Acknowledgements

We thank ADIR for financial support and J. Blu for technical assistance.

References

1. Pindur, U.; Kim, Y.-S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29–69.
2. Prudhomme, M. *Curr. Med. Chem.* **2000**, *7*, 1189–1212.
3. Ohkubo, M.; Nishimura, T.; Kawamoto, H.; Nakano, M.; Homna, T.; Yoshinari, T.; Arakawa, H.; Suda, H.; Morishima, H.; Nishimura, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 419–422.
4. Tanaka, S.; Ohkubo, M.; Kojiri, K.; Suda, H.; Yamada, A.; Uemura, D. *J. Antibiot.* **1992**, *44*, 1797–1798.
5. Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530–535.
6. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470.
7. Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850–9856.
8. Routier, S.; Coudert, G.; Mérour, J. Y. *Tetrahedron Lett.* **2001**, *42*, 7025–7028.
9. Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343–349.
10. Ohkubo, M.; Nishimura, T.; Homna, T.; Morishima, H. *Tetrahedron* **1996**, *52*, 8099–8112.
11. Neel, D. A.; Jirousek, M. R.; McDonald, J. H., III *Bioorg. Med. Chem. Lett.* **1998**, *8*, 47–50.
12. Wang, J.; Rosingana, M.; Watson, D. J.; Dowdy, E. D.; Discordia, R. P.; Soundarajan, N.; Li, W. S. *Tetrahedron Lett.* **2001**, *42*, 8935–8937.
13. Arimondo, P. B.; Baldeyrou, B.; Laine, W.; Bal, C.; Alphonse, F. A.; Routier, S.; Coudert, G.; Mérour, J. Y.; Colson, P.; Houssier, C.; Bailly, C. *Chem. Biol. Int.* **2001**, *138*, 59–75.
14. Cornia, M.; Casiraghi, G.; Zetta, L. *J. Org. Chem.* **1991**, *56*, 5466–5468.
15. Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361–8364.
16. Anizon, F.; Belin, L.; Moreau, P.; Sancelme, M.; Voldoire, A.; Prudhomme, M.; Ollier, M.; Sévère, D.; Riou, J. F.; Bailly, C.; Fabbro, D.; Meyer, T. *J. Med. Chem.* **1997**, *40*, 3456–3465.
17. Terpin, A.; Winkhofer, S.; Steglich, W. *Tetrahedron* **1998**, *54*, 1745–1752.
18. Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J. Y. *Tetrahedron Lett.* **2002**, *43*, 589–591.
19. *Synthesis of* ***3***: In a 10 mL flask, under argon, compound **17** (140 mg, 0.317 mmoles) was dissolved at room temperature in 5 mL of dry THF and 3 mL of Bu_4NF (1 M in THF, 3 mmoles) were added. The mixture was refluxed 1.5 h. After cooling, the solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography (petroleum ether/AcOEt 9/1) to afford compound **3** as a pale yellow solid (95 mg, 88%); mp 235°C dec. IR (KBr, cm^{-1}) ν 1383, 1694, 1749, 3932, 3357. ^1H NMR (DMSO-d_6) δ 2.98 (s, 3H), 7.26–7.33 (m, 2H), 7.50 (t, 1H, $J=7.5$ Hz), 7.70 (t, 1H, $J=7.5$ Hz), 8.49 (d, 1H, $J=5$ Hz), 8.81 (d, 1H, $J=5$ Hz), 8.94 (d, 1H, $J=7$ Hz), 11.30 (s, 1H), 11.92 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 23.7 (CH_3), 111.9 (Cq), 112.3 (CH), 113.2 (Cq), 115.9 (Cq), 116.3 (CH), 119.2 (Cq), 119.5 (Cq), 120.5 (CH), 121.5 (Cq), 124.4 (CH), 127.2 (CH), 127.8 (Cq), 128.8 (Cq), 132.3 (CH), 140.5 (Cq), 146.3 (CH), 152.4 (Cq), 169.6 (Cq), 169.7 (Cq). MS (IS) 341 $(M+H)^+$. Anal. calcd for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.34; H, 3.68; N, 16.62.