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Practical synthesis of the rebeccamycin aglycone and related analogs by oxidative cyclization of bisindolylmaleimides with a Wacker-type catalytic system

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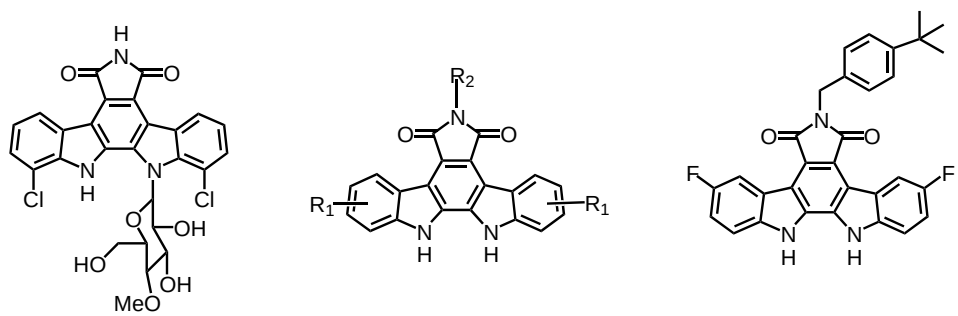
Abstract—Using atmospheric O_2 as the stoichiometric oxidant, Pd^{2+}/Cu^{2+}-catalyzed oxidative cyclization of the corresponding bisindolylmaleimides provides the rebeccamycin aglycone and related indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles in 58–88% yield. The method is operationally simple and utilizes readily prepared substrates, making the process amenable to scaleup. © 2001 Elsevier Science Ltd. All rights reserved.

Rebeccamycin **1**[1] and its family members[2] are potent antitumor agents. As part of a program for optimization of their biological activity by modification of the aglycone portion, we required an efficient route to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system **2**. In particular, we were interested in a practical synthesis of carbazole **2b**, which we needed in large quantities.

Several routes to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system **2** have been reported.[3–5] Among them, the approach via bisindolylmaleimides **3** is the most attractive because it is short and the starting materials are readily available. Conversion of the bisindolylmaleimides **3** to the corresponding carbazoles **2** has been achieved with DDQ,[5,6] I_2,[7–9] and $CuCl_2$.[10] However, in our case, with DDQ as the oxidant, the product was difficult to isolate due to poor solubility. With iodine and $CuCl_2$ as oxidants, by-products were formed during the reaction, resulting in poor quality and low yields. It has also been reported in the literature that $Pd(O_2CCF_3)_2$,[11,12] $PdCl_2$[6] and $Pd(OAc)_2$[13] may act as alternative oxidants. However, 1–5 equiv. of the palladium reagents were required to achieve the desired oxidation. We also found that $Pd(OAc)_2$ could oxidize bisindolylmaleimides **3** to carbazoles **2** in good yields, but the reactions required 2.5 equiv. of $Pd(OAc)_2$, which would not be amenable to large scale production due to the cost of the palladium reagent. In this communication we describe our efforts toward the construction of the central six-membered ring of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring systems (**2a–i**) using oxidative cyclization of the corresponding bisindolylmaleimides (**3a–i**) with a Wacker-type catalytic system,[14] resulting in the need for only 5 mol% of the Pd(II) catalyst (Scheme 1).



1 **2** **2b**

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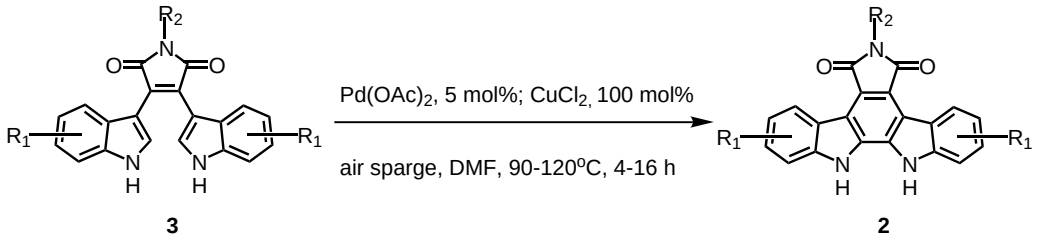


Scheme 1.

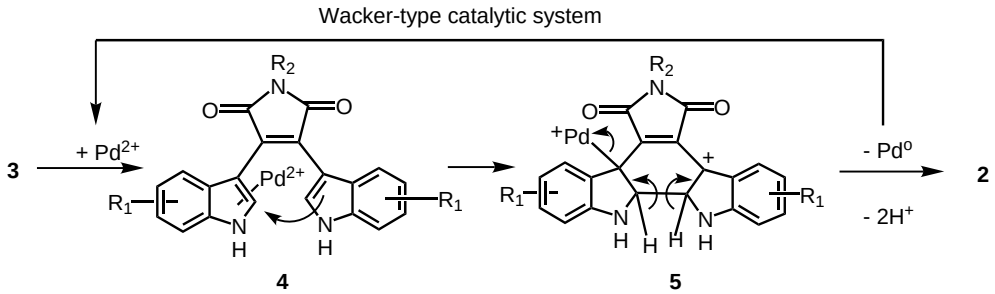
A series of bisindolylmaleimides **3a**–**i** were readily prepared by reaction of the appropriate substituted indolylmagnesium bromide with *N*-substituted 3,4-dihalomaleimides.[15] Oxidative cyclization of these bisindolylmaleimides under the reaction conditions described in Scheme 1 gave the desired indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **2a**–**i** in 58–88% yields (Table 1). It is noteworthy that even without protection of the imide N–H, the reaction still gives a satisfactory yield (**2d**, 78%). With an electron-rich system (**3f**,**h** and **i**), the reaction proceeds under milder conditions (90°C, 4–8 h). This observation could be attributable to the differences in the electron densities of the ring systems. As illustrated in Scheme 2, an electron-donating group (such as MeO) makes the ring system more electron rich and facilitates formation of complex **4**, presumably the turnover-limiting step, by stabilizing cation intermediate **5**. The reaction conditions and results are listed in Table 1.

Using this practical oxidation as a key step, we developed a scalable, three-step synthesis of carbazole **2b**, a key intermediate for our program, with an overall yield of 52% (Scheme 3). *N*-4-*t*-Butylbenzyl-protected dibromomaleimide **7** was prepared in 78% yield by the amidation of the readily available dibromomaleic acid **6** with 4-*t*-butylbenzyl amine mediated by EDCI (1.05 equiv.), followed by reflux in acetic acid for 3 h. Subsequently, reaction of 5-fluoroindolylmagnesium bromide, derived by treatment of 5-fluoroindole (2.2 equiv.) with EtMgBr (2.3 equiv.), gave bisindolylmaleimide **3b** in 82% yield. Finally, using our developed method, oxidative cyclization of **3b** afforded the desired indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole **2b** in 81% yield. This operation was carried out on greater than 3 kg scale, and proved to be operationally very practical.

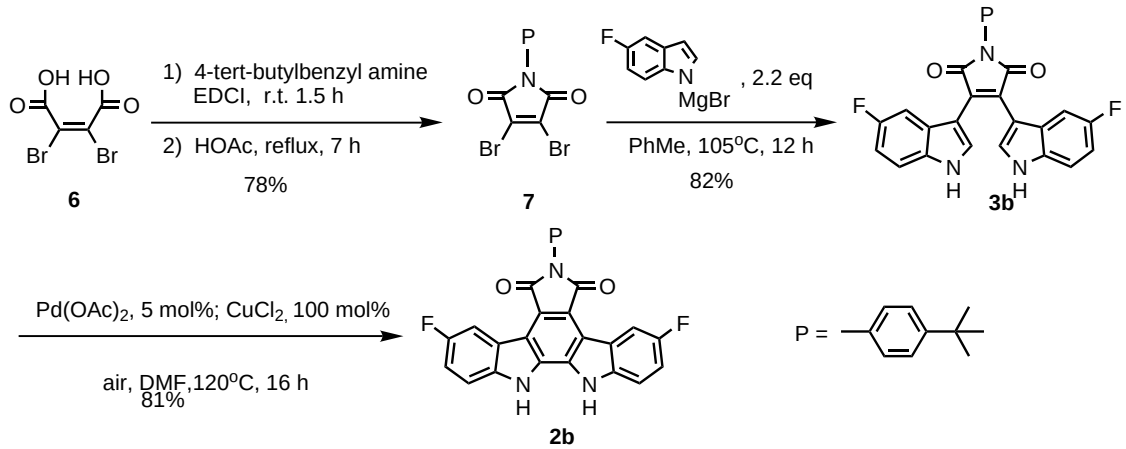
In conclusion, oxidative cyclization of bisindolylmaleimides facilitated by a Wacker-type catalytic system has been developed as a general and practical approach for the preparation of rebeccamycin aglycones and related analogs.

Table 1. Wacker-type oxidation of bisindolylmaleimides **3a**–**i** to carbazoles **2a**–**i**

Entry	Product	R_1; R_1	R_2	Temperature (°C)	Time (h)	Isolated yield (%)
1	**2a**	1-Cl; 11-Cl	*p*-*t*-Bu-Bn	120	12	88[16]
2	**2b**	3-F; 9-F	*p*-*t*-Bu-Bn	120	16	81
3	**2c**	3-Br; 9-Br	*p*-*t*-Bu-Bn	120	10	74
4	**2d**	3-F; 9-F	H	120	8	78
5	**2e**	2-F, 3-F; 9-F, 10-F	*p*-*t*-Bu-Bn	120	16	82
6	**2f**	3-OMe; 9-OMe	*p*-*t*-Bu-Bn	90	4	86
7	**2g**	H; H	*p*-*t*-Bu-Bn	90	8	79
8	**2h**	3-F; 9-F	*t*-Bu	90	6	62
9	**2i**	3-F; 9-F	DMB	90	5	58



Scheme 2. Proposed mechanism of oxidative cyclisation of bisindolylmaleimides **3a**–**i**.



Scheme 3. Three-step synthesis of **2b**.

Acknowledgements

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16. Representative procedure: To a 1 L, 3-necked flask equipped with a condenser and a thermocouple was charged **3b** (100 g, 0.196 mol), $Pd(OAc)_2$ (2.2 g, 0.0098 mol) and DMF (700 ml). The resulting brown-reddish solution was stirred at ambient temperature for 10 min. $CuCl_2$ (26.4 g, 0.196 mol) was added portionwise over 5 min. Air was sparged into the resulting suspension. The suspension was heated with stirring for 16 h. The oil bath temperature was controlled at 125°C and the internal temperature was 120°C. The reaction progress was monitored by HPLC. During this period, a greenish-yellow solid precipitated. The suspension was cooled to 5°C with an ice–water bath, and water (1 L) was added slowly (20 min). The resulting brownish suspension was kept at 5°C for 4 h, filtered through a sintered glass funnel (type C) and washed with water (2×50 ml) to give a crude product (170 g) as a brown solid. Recrystallization from *N*-methyl-2-pyrrolidinone (2 L) and water (100 ml) gave **2b** (81 g, 81%) as a greenish-yellow solid. (HPLC, AP 98). MS: $(M+H)^+$ 541; ^1H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 2H, N–H), 8.84 (d, $J=7.8$, 2H), 7.95 (s, 2H), 7.65 (d, $J=7.8$, 2H), 7.40–7.33 (m, 4H), 4.81 (s, 2H), 1.23 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 162.9, 149.6, 137.4, 134.5, 128.8, 127.9, 125.9, 124.9, 123.4, 120.9, 119.9, 116.4, 116.2, 41.0, 31.3169.1, 154.4, 149.3, 135.3, 134.9, 129.6, 127.5(2C), 124.9(2C), 122.8, 119.1, 116.4, 111.5, 106.4, 55.3, 40.9, 31.3 ppm.
Compound **2c**: MS: $(M+H)^+$ 630; ^1H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 2H, N–H), 9.27 (s, 2H), 7.58 (d, $J=7.8$, 2H), 7.52 (d, $J=7.8$, 2H), 7.44 (d, $J=8.3$, 2H), 7.09 (d, $J=8.3$, 2H), 4.81 (s, 2H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 149.5, 139.2, 134.6, 129.3, 129.2, 127.9, 127.2, 124.9, 123.8, 119.8, 115.8, 113.1, 112.8, 41.1, 34.7, 31.3 ppm.
Compound **2f**: MS: $(M+H)^+$ 534; ^1H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 2H, N–H), 8.74 (s, 2H), 7.43 (d, $J=7.7$, 2H), 7.42 (d, $J=7.3$, 2H), 7.34 (d, $J=7.7$, 2H), 7.09 (d, $J=7.3$, 2H), 4.91 (s, 2H), 3.95 (s, 6H), 1.27 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.1, 154.4, 149.3, 135.3, 134.9, 129.6, 127.5, 124.9, 122.8, 119.1, 116.4, 111.5, 106.4, 55.3, 40.9, 31.3 ppm.