HETEROCYCLES, Vol. 53, No10, 2000, pp. 2119 - 2122, Received, 30th June, 2000

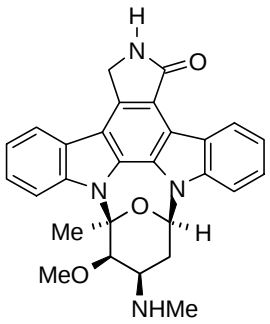
NEW SYNTHESIS OF KT5823 INDOLOCARBAZOLE AGLYCONE

Guillaume E. Burtin,* David J. Madge* and David L. Selwood

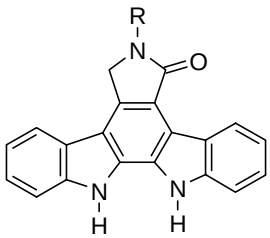
The Wolfson Institute for Biomedical Research, Biological and Medicinal Chemistry, University College London, Cruciform Building, Gower St., London WC1E 6AU, UK.

Abstract - The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole aglycone of the selective protein kinase G inhibitor KT5823 has been synthesised in four steps and 36% overall yield from 2,3-dichloro-*N*-methylmaleimide by utilising an efficient new two step reduction sequence for the key imide to amide transformation.

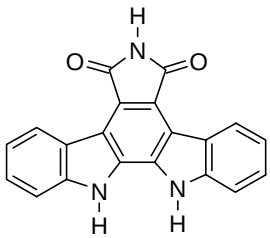
In 1977 the first indolocarbazole alkaloid, staurosporine **(1)** was isolated from *Streptomyces staurosporeus*.[1] Since then, the number of isolated and synthesised indolocarbazole glycosides has grown considerably due to their wide range of biological properties, from antifungal, antimicrobial, and antitumor through to antihypertensive effects.[2] Synthetic chemists have concentrated their efforts on the synthesis of the naturally occurring indolocarbazole K252c **(2)** and several strategies have been reported.[3]



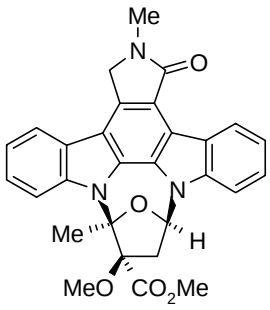
(1) : staurosporine



(2) : K252c (R = H)
(5) : KT5823 aglycone (R = Me)



(3) : arcyriaflavin A

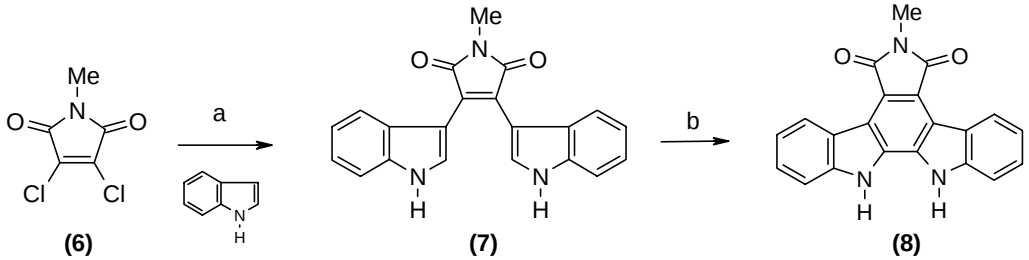


(4) : KT5823

For many years, the most widely used approaches to the aglycone **(2)** had involved the imide arcyriaflavin A **(3)** as a key intermediate, although its reduction to the lactam **(2)** proved to be difficult. [4] Several groups have recently developed new synthetic pathways to give direct access to analogues of **2**.[5]

As part of a program investigating the biological activity of (±)-KT5823 **(4)** towards the inhibition of protein kinase G,[6] we report here an efficient and high yielding synthesis of the KT5823 indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole aglycone **(5)**. Only one synthesis of lactam **(5)** has been described to date, with no experimental detail and in poor yield.[7] The strategy involving the *bis*-indolylmaleimide **(7)** was considered as the most convenient route to prepare large quantities of aglycone **(5)** (Scheme 1).[8]

Treatment of 2,3-dichloro-*N*-methylmaleimide[9] **(6)** with indole in presence of ethylmagnesium bromide afforded intermediate **(7)**.[10] In our hands, the utilisation of 3 equivalents of indole-MgBr gave higher yields. Oxidative cyclisation of the *bis*-indolylmaleimide **(7)** with a large excess of palladium chloride (5 eq.) in dimethylformamide provided product **(8)** in good yield.[11] The use of a 2:1 mixture of toluene and dimethylformamide allowed the reaction to go to completion with only 3.5 equivalents of expensive $PdCl_2$. Cyclisation using palladium acetate in acetic acid[12] gave poor results and $CuCl_2$ in methyl ethyl ketone[13] failed to provide the imide **(8)**. The product obtained with DDQ/TsOH[14] proved to be difficult to purify.



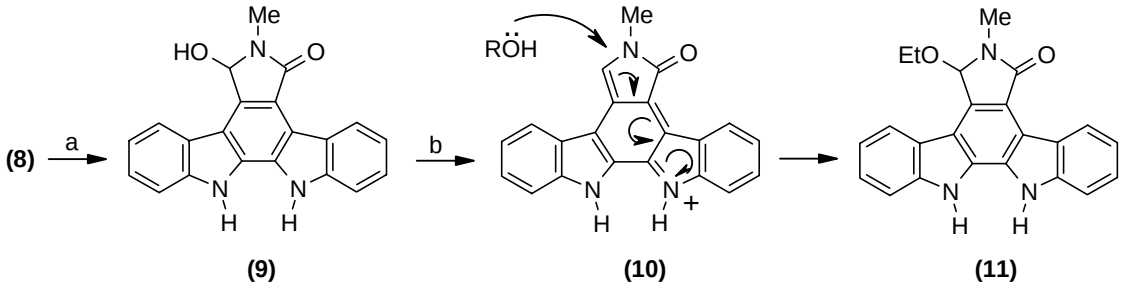
(6) **(7)** **(8)**

Scheme 1. (a) EtMgBr, toluene/THF, 90°C; 80%; (b) $PdCl_2$, toluene/DMF,105°C, 90%.

Final reduction of imide **(8)** to lactam **(5)** required more attention. Although Clemmensen type reduction of arcyriaflavin A **(3)** has been carried out by several groups to prepare K252c **(2)**,[4,15] treatment of (**8**) with acid activated zinc[16] in place of toxic zinc-amalgam gave the lactam **(5)** in poor yield. The use of BH_3.THF complex gave a mixture of reduced compounds.[17] The two step reduction sequence developed by Hill *et al.*[12] and used by Somei *et al.*[7] in the synthesis of aglycone **(2)** gave rise to the unexpected ethoxyindolocarbazole **(11)**[18] (Scheme 2). We assume that compound **11** results from the addition of ethanol to the iminium species **(10)**.

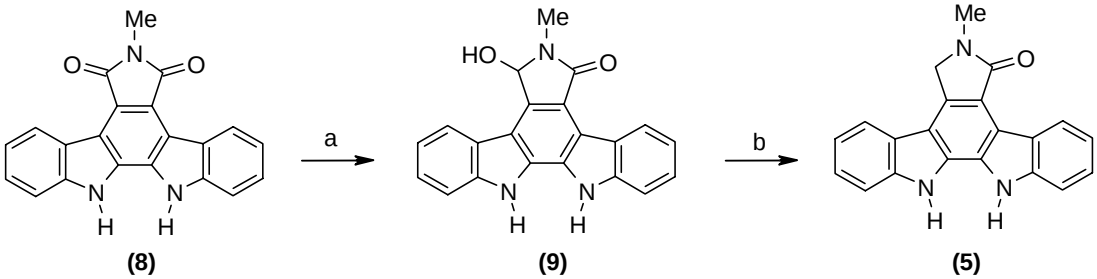
Formation of **10**, which presumably occurs by elimination of the hydroxyl from intermediate **(9)** due to the participation of indolic nitrogen, was also observed during attempts to purify crude **9** on silica gel

using a methanol-chloroform gradient. In this case partial elimination, followed by addition of methanol to **10**, led to a mixture of the alcohol **(9)** and the methoxy analogue of **11**. Although hydrogenolysis of compound **9** in ethyl acetate failed to give **5**, the use of ethanol-acetic acid afforded a separable mixture of **5** and **11**.



Scheme 2. (a) $NaBH_4$, DMF/MeOH; (b) 10% Pd/C, H_2, EtOH, rt, 42% two steps

Efficient reduction of imide **(8)** was finally achieved using the two step sequence shown in Scheme 3. Reduction of **8** with an excess of lithium aluminium hydride at room temperature yielded hydroxy derivative **(9)**. Treatment of crude hydroxy lactam **(9)** with a mixture of trifluoroacetic acid and triethylsilane[19,15b] at room temperature led to the KT5823 aglycone **(5)**[18] in 50% yield from **8**. Utilisation of toxic phenylselenol as a reducing agent of the hydroxy lactam has been avoided.[3]



Scheme 3. (a) $LiAlH_4$, THF, rt; (b) Et_3SiH, TFA, chloroform, rt, 50% two steps.

In summary, we have developed a new two step reduction sequence of indolopyrrolocarbazole giving access to the KT5823 aglycone **(5)** in four steps and 36% overall yield from *N*-methyl dichloromaleimide.

ACKNOWLEDGMENTS

This work was supported in part by *United Therapeutics Corp.* (Silver Spring, USA).

REFERENCES

* Corresponding author. Tel: (0044) 207 6796712; Fax: (0044) 207 6796799; e-mail: d.madge@ucl.ac.uk

1. (a) S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi, and R. Masuma, *J. Antibiot.*, 1977, **30**, 275. (b) A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai, and S. Omura, *J. Chem. Soc., Chem. Commun.*, 1978, 800.
2. For a review see G. W. Gribble and S. J. Berthel, 'Studies in Natural Products Chemistry', Vol. 12, ed. by Atta-ur-Rahman, Elsevier Science Publisher, New York, 1993, pp. 365-409.
3. For a short survey of the different strategies see: J. T. Link, S. Raghavan, M. Gallant, S. J. Danishefsky, T. C. Chou, and L. M. Ballas, *J. Am. Chem. Soc.*, 1996, **118**, 2825.
4. G. Xie and J. W. Lown, *Tetrahedron Lett.*, 1994, **35**, 5555.
5. (a) S. Mahboobi, E. Eibler, M. Koller, S. Sumar, and A. Popp, *J. Org Chem.*, 1999, **64**, 4697; (b) Y. Kobayashi, T. Fujimoto, and T. Fukuyama, *J. Am. Chem. Soc.*, 1999, **121**, 6501; (c) S. Eils and E. Winterfeldt, *Synthesis*, 1999, 275; (d) J. L. Wood, D. T. Petsch, B. M. Stoltz, E. M. Hawkins, D. Elbaum, and D. R. Stover, *Synthesis*, 1999, 1529.
6. H. Kase, K. Iwahashi, S. Nakanishi, Y. Matsuda, K. Yamada, M. Takahashi, C. Murakata, A. Sato, and M. Kaneko, *Biochem. Biophys. Res. Commun.*, 1987, **142**, 436.
7. M. Somei, H. Hayashi, T. Izumi, and S. Ohmoto, *Heterocycles*, 1995, **41**, 2161.
8. M. Brenner, H. Rexhausen, B. Steffan, and W. Steglich, *Tetrahedron*, 1988, **44**, 2887.
9. **6** was prepared in 60% yield using an adaptation of H. M. Relles, *J. Org Chem.*, 1972, **37**, 3630.
10. M. M. Faul, K. A. Sullivan, and L. L. Winneroski, *Synthesis*, 1995, 1511.
11. M. Ohkubo, T. Nishimura, H. Jona, T. Honma, and H. Morishima, *Tetrahedron*, 1996, **52**, 8099.
12. W. Harris, C. H. Hill, E. Keech, and P. Malsher, *Tetrahedron Lett.*, 1993, **34**, 8361.
13. (a) M. Ohkubo, T. Nishimura, H. Jona, T. Honma, S. Ito, and H. Morishima, *Tetrahedron*, 1997, **53**, 5937; (b) M. Ohkubo, T. Nishimura, T. Honma, I. Nishimura, S. Ito, T. Yoshinari, H. Arakawa, H. Suda, H. Morishima, and S. Nishimura, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3307.
14. R. P. Joyce, J. A. Gainor, and S. M. Weinreb, *J. Org Chem.*, 1987, **52**, 1177.
15. (a) D. Toullec, P. Pianetti, H. Coste, P. Bellevergue, T. Grand-Perret, M. Ajakane, V. Baudet, P. Boissin, E. Boursier, F. Loriolle, L. Duhamel, D. Charon, and J. Kirilovsky, *J. Biol. Chem.*, 1991, **266**, 15771; (b) I. Hughes, W. P. Nolan, and R. A. Raphael, *J. Chem. Soc., Perkin Trans I*, 1990, 2475.
16. S. Yamamura, M. Toda ,and Y. Hirata, *Org. Synth., Coll. Vol.*, 1988, **6**, 289.
17. S. W. McCombie, R. W. Bishop, D. Carr, E. Dobek, M. P. Kirkup, P. Kirschmeier, S.-I. Lin, J. Petrin, K. Rosinski, B. B. Shankar, and O. Wilson, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1537.
18. All new compounds gave satisfactory analytical and spectral data. *Compound* **(11)**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.53 (NH), 11.39 (NH), 9.17 (d, J = 7.9 Hz, 1H), 8.31 (d, J = 7.3 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.46 (q, J = 7.8 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 6.62 (s, 1H, C<u>H</u>OEt), 3.19-3.11 (m, 1H, C<u>H</u>$_2$CH$_3$), 3.11 (s, 3H, Me), 2.86-2.82 (m, 1H, C<u>H</u>$_2$CH$_3$), 0.97 (t, J = 7.0 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.6 (C=O), 139.6, 139.4, 129.0, 127.9, 126.4, 125.4, 124.8, 122.4, 122.0, 119.9, 119.2, 118.9, 115.2, 114.8, 111.8, 111.5, 87.3 (<u>C</u>HOEt), 56.4 (<u>C</u>H$_2$CH$_3$), 26.4 (Me), 15.1 (CH$_2$<u>C</u>H$_3$); Anal. Calcd for $C_{23}H_{20}N_3O_2$: C, 74.56; H, 5.45; N, 11.35. Found: C, 74.37; H, 5.68; N, 11.07. *Compound* **5**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (NH), 11.30 (NH), 9.23 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 5.02 (s, 2H, C<u>H</u>$_2$), 3.25 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.5 (C=O), 139.3, 139.1, 130.0, 127.6, 125.4, 125.0, 122.8, 122.4, 120.9, 119.8, 118.9, 118.7, 115.4, 113.9, 111.9, 111.3, 51.6 (<u>C</u>H$_2$), 29.2 (Me); MS (APCI+) m/z: 326 (M+H); Anal. Calcd for $C_{21}H_{15}N_3O.0.7H_2O$: C, 74.62; H, 4.90; N, 12.43. Found: C, 74.82; H, 4.62; N, 12.22.
19. D. Dube and A. A. Scolte, *Tetrahedron Lett.*, 1999, **40**, 2295 and references therein.