NEW SYNTHESIS OF KT5823 INDOLOCARBAZOLE AGLYCONE

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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. 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. Synthetic chemists have concentrated their efforts on the synthesis of the naturally occurring indolocarbazole K252c (2) and several strategies have been reported.4

For many years, the most widely used approaches to the aglycone (2) had involved the imide arcryiaflavin A (3) as a key intermediate, although its reduction to the lactam (2) proved to be difficult. Several groups have recently developed new synthetic pathways to give direct access to analogues of 2.
As part of a program investigating the biological activity of (±)-KT5823 (4) towards the inhibition of protein kinase G, 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. 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 (6) with indole in presence of ethylmagnesium bromide afforded intermediate (7). 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. 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 PdCl2. Cyclisation using palladium acetate in acetic acid gave poor results and CuCl2 in methyl ethyl ketone failed to provide the imide (8). The product obtained with DDQ/TsOH proved to be difficult to purify.

\[
\begin{align*}
&\text{(6)} & &\text{Me} & &\text{(7)} & &\text{Me} \\
&\text{Cl} & &\text{Cl} & &\text{N} & &\text{O} \\
&\text{N} & &\text{O} & &\text{Me} & &\text{Cl} \\
&\text{Cl} & &\text{Cl} & &\text{N} & &\text{O} \\
\end{align*}
\]

Scheme 1. (a) EtMgBr, toluene/THF, 90°C; 80%; (b) PdCl2, 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), treatment of (8) with acid activated zinc in place of toxic zinc-amalgam gave the lactam (5) in poor yield. The use of BH3.THF complex gave a mixture of reduced compounds. The two step reduction sequence developed by Hill et al. and used by Somei et al. in the synthesis of aglycone (2) gave rise to the unexpected ethoxyindolocarbazole (11) (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.

\[ \text{Scheme 2. (a) NaBH}_4, \text{DMF/MeOH; (b) 10\% Pd/C, H}_2, \text{EtOH, rt, 42\% two steps} \]

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\(^\text{19,15b}\) at room temperature led to the KT5823 aglycone (5)\(^\text{18}\) in 50\% yield from 8. Utilisation of toxic phenylselenol as a reducing agent of the hydroxy lactam has been avoided.\(^3\)

\[ \text{Scheme 3. (a) LiAlH}_4, \text{THF, rt; (b) Et}_3\text{SiH, TFA, chloroform, rt, 50\% two steps.} \]

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.

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REFERENCES


9. 6 was prepared in 60% yield using an adaptation of H. M. Relles, *J. Org Chem.*, 1972, 37, 3630.


18. All new compounds gave satisfactory analytical and spectral data. Compound (11): 1H NMR (DMSO-d6, 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, CHOEt), 3.19-3.11 (m, 1H, CH2CH3), 3.11 (s, 3H, Me), 2.86-2.82 (m, 1H, CH2CH3), 0.97 (t, J = 7.0 Hz, 3H, CH2CH3); 13C NMR (DMSO-d6, 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 (CHOEt), 56.4 (CH2CH3), 26.4 (Me), 15.1 (CH2CH3); Anal. Calcd for C23H20N3O2: C, 74.56; H, 5.45; N, 11.35. Found: C, 74.37; H, 5.68; N, 11.07. Compound 5: 1H NMR (DMSO-d6, 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, CH2), 3.25 (s, 3H, Me); 13C NMR (DMSO-d6, 100 MHz) δ 160.5 (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 (CH2), 29.2 (Me); MS (APCI+) m/z: 326 (M+H); Anal. Calcd for C23H26N2O0.7H2O: C, 74.62; H, 4.90; N, 12.43. Found: C, 74.82; H, 4.62; N, 12.22.