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Tetrahedron Letters 45 (2004) 4643–4647
Tetrahedron Letters

Synthesis of a staurosporine analogue possessing a 7-azaindole unit instead of an indole moiety

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Received 16 April 2004; revised 19 April 2004; accepted 20 April 2004

Abstract—The synthesis of a new staurosporine analogue possessing a 7-azaindole unit instead of an indole moiety is described. This synthesis could be achieved by coupling a sugar moiety previously tosylated in 2′ position to the azaindolocarbazole aglycone. Nucleophilic substitution on the carbon bearing the tosyl group yielded to the key cyclization leading to a compound in which the carbohydrate part is linked to both indole and azaindole nitrogens.

1. Introduction

Staurosporine, a microbial metabolite isolated from cultures of *Streptomyces staurosporeus*, has been extensively studied as a potent and nonselective kinase inhibitor.[1–3] Several academic and industrial groups have synthesized a large number of staurosporine analogues to obtain compounds exhibiting more selectivity toward the various kinases.[4] In the search for new staurosporine analogues, we have previously synthesized rebeccamycin derivatives in which the carbohydrate moiety is linked to both indole nitrogens (Fig. 1).[5,6] Rebeccamycin is an antitumor antibiotic produced from cultures of *Saccharothrix aerocolonigenes*. Rebeccamycin possesses an indolocarbazole framework onto which is attached via a β-*N*-glycosidic bond a 4-*O*-methoxyglucose. Its antitumor activity is linked to its capacity to inhibit topoisomerase I by forming a ternary DNA-topoisomerase I-drug complex that prevents the religation of the DNA strand cleaved by the enzyme.[7,8] Contrary to rebeccamycin, staurosporine has no effect on topoisomerase I. Our staurosporine analogues previously obtained by semi-synthesis from rebeccamycin seem to have multiple targets and in contrast with rebeccamycin, they exhibit high selectivity toward the different tumor cell lines tested.

Azaindoles, as biosters for indoles, present considerable biological importance. We have recently synthesized rebeccamycin analogues in which one or both indole moieties have been replaced by a 7-azaindole unit (Fig. 1).[9,10] The newly introduced nitrogen atom(s) could modify the interactions with the target(s) enzyme(s).

In this Letter, we report the synthesis of a 7-aza-staurosporine analogue **1** bearing a methyl group on the imide nitrogen (Fig. 1).

2. Results and discussion

The previously achieved semi-synthesis of a staurosporine analogue in three steps from rebeccamycin is outlined in Scheme 1.[5] Tosylation at 2′ position on the sugar part was carried out before reaction using sodium azide, which led to two compounds, the major product of the reaction was the bridged compound obtained via deprotonation of the indole nitrogen followed by nucleophilic substitution at C2′. The minor product, 3′-azide, was formed via 2′-3′-epoxide. The last step was the removal of the chlorine atoms.

Keywords: Staurosporine; Rebeccamycin; 7-Azaindole; Antitumor compounds; Enzyme inhibitors.
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doi:10.1016/j.tetlet.2004.04.102

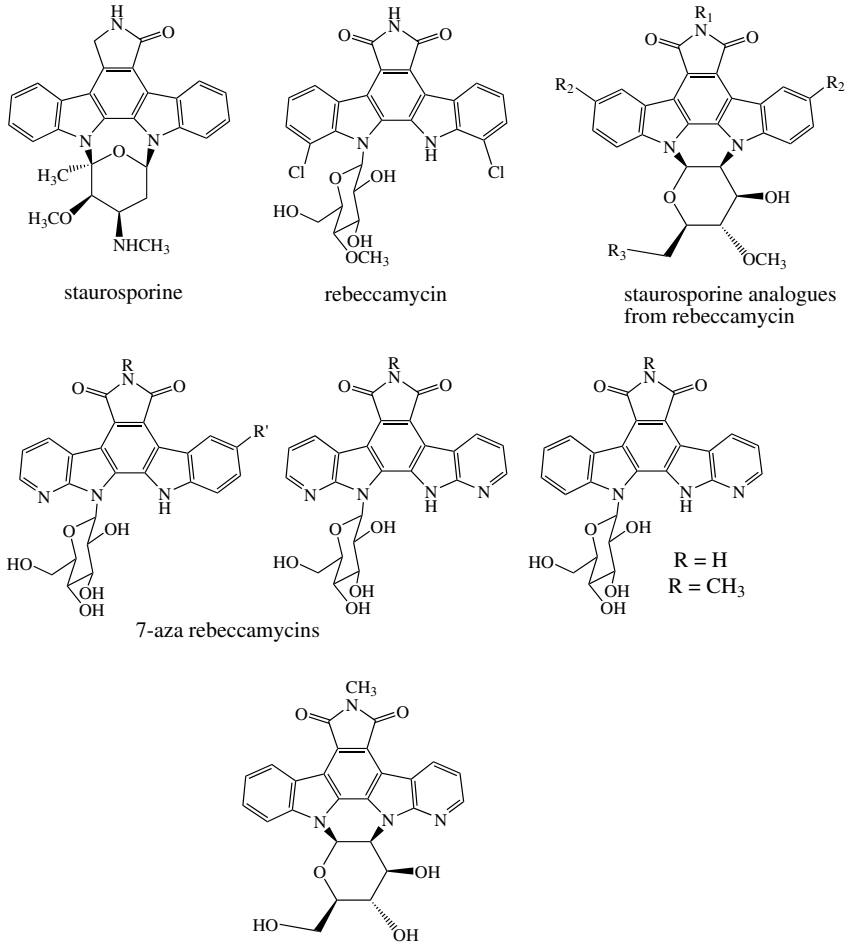
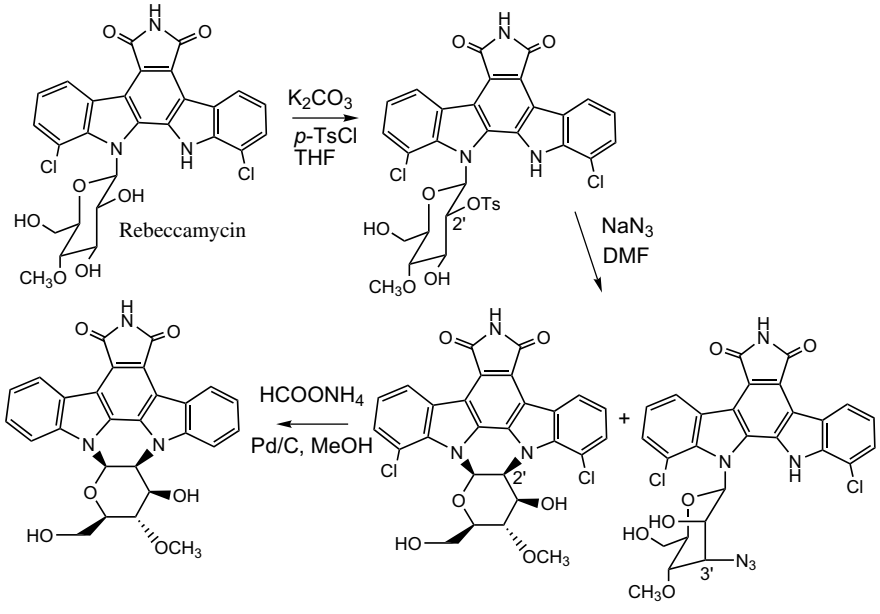
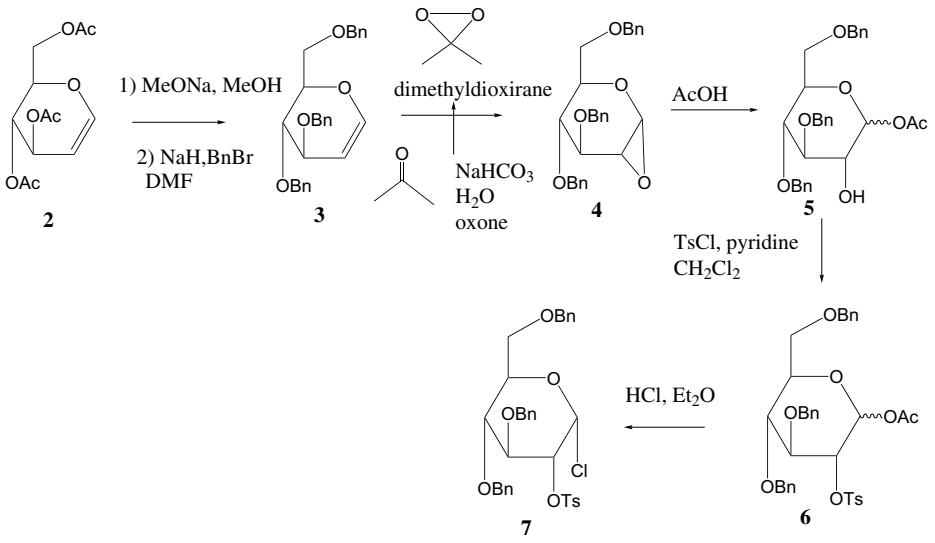


Figure 1.



Scheme 1.

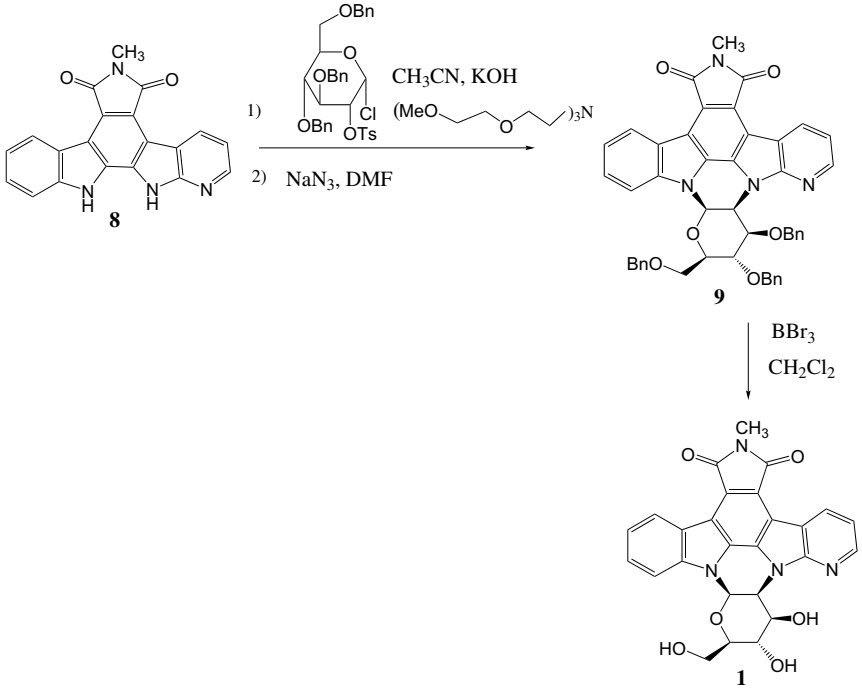
For the synthesis of compound **1**, we chose to use α-1-chloro-1-deoxy-2-*O*-tosyl-3,4,6-tri-*O*-benzyl glucopyranose **7**, prepared from triacetylated glycal **2** as shown in Scheme 2. Tribenzylated compound **3** was prepared



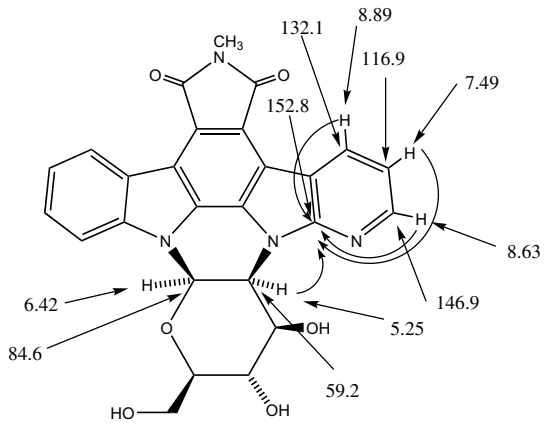
Scheme 2.

from commercial triacetylated glycal **2** according to a known method.[11] Epoxidation of **3** with dimethyldioxirane[12] provided the anhydro-sugar **4**. Reaction of **4** with glacial acetic acid led to compound **5** in 55% yield as a mixture of both α and β anomers in 3:10 ratio, respectively.[13,14] Tosylation of **5** gave **6**[15] in 84% yield as a mixture of the α and β anomers in 5:8 ratio, respectively, together with unreacted β anomer **5**. The anomeric mixture of **6** dissolved in diethylether was treated with HCl gas according to a method previously described in altro- and allo-pyranosyl series,[16] to yield compound **7**[17] in 66% yield as the α chloro anomer, the unreacted α **6** was recovered.

Coupling of the chloro-sugar **7** with the aglycone **8**[18] was achieved in a heterogeneous medium. The reaction did not occur using KOH, Na_2SO_4 in acetonitrile as described by Ohkubo et al.[19,20] for the synthesis of rebeccamycin analogues. The coupling reaction was carried out in acetonitrile, using KOH and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a phase transfer catalyst, according to the method described by Seela and Bourgeois[21] for the synthesis of nucleosides, to yield a mixture, which was partly purified by chromatography. The next step was the reaction with sodium azide in dimethylformamide leading to the bridged compound **9**[22] in only 12% yield for the two steps, however in the



Scheme 3.



Scheme 4. Correlations observed in NMR experiments (chemical shifts in ppm).

coupling step, the unreacted aglycone **8** could be recovered (Scheme 3). The last step was the removal of the benzyl groups on the carbohydrate moiety using boron tribromide in dichloromethane.[23] Compound **1**[24] was obtained in 90% yield. The structure of compound **1** was assigned from ^{1}H COSY, HSQC, and HMBC NMR experiments (Scheme 4). These experiments allowed the assignment of the protons of the azaindole moiety. The correlations allowed the identification of the quaternary carbon at 152.8 ppm. A correlation was observed between this carbon and $H_{2'}$. The regioselectivity of the coupling reaction with the sugar moiety is consistent with that already observed in the coupling using a heterogeneous medium in 7-azaindole series: the compound in which the sugar part is linked to the indole moiety was the major product of the reaction.[10]

In conclusion, we have successfully developed a method for the synthesis of 7-aza staurosporine analogues, which will be applied to prepare a new series by modifying the substituent at the imide nitrogen and/or by various substitutions on the aromatic rings and on the sugar moiety. The biological properties of these new azaindolocarbazoles will be evaluated.

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15. Spectral data of **6**: IR (film, NaCl) $\nu_{c=o}$ 1739, 1760 cm^{-1}. HRMS (FAB+) $(M+Na)^+$ calcd for $C_{36}H_{38}NaO_9S$ 669.2134, found 669.2147.
^{1}H NMR (400 MHz, $CDCl_3$) $^{\beta}$major anomer, $^{\alpha}$minor anomer:
1.92 ($3H^{\beta}$, s, CH_3), 2.11 ($3H^{\alpha}$, s, CH_3), 2.35 ($3H^{\beta}$, s, CH_3 of OTs), 2.39 ($3H^{\alpha}$, s, CH_3 of OTs), 3.54–3.86 (m, $5H^{\beta}$+$5H^{\alpha}$), 4.43–4.82 (m, $7H^{\beta}$+$7H^{\alpha}$), 5.65 ($1H^{\beta}$, d, $J = 8.0$ Hz, H_1^{β}), 6.18 ($1H^{\alpha}$, d, $J = 3.5$ Hz, H_1^{α}), 7.04–7.10 (m, $2H^{\beta}$+$2H^{\alpha}$), 7.14–7.36 ($15H^{\beta}$+$15H^{\alpha}$), 7.73–7.79 (m, $2H^{\beta}$+$2H^{\alpha}$).
^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.9, 21.6, 21.8 (CH_3), 67.7, 67.8 (C_6), 73.6, 73.7, 75.2, 75.4, 75.5, 75.7 (CH_2 of OBn), 72.6, 75.8, 77.0, 77.4, 78.1, 79.5, 79.7, 82.4, 89.6, 91.5 (C_1, C_2, C_3, C_4, C_5), 127.6–128.6, 129.7, 130.0 (C tert arom), 133.2, 134.7, 137.6, 137.7, 137.8, 137.9, 144.7, 145.3 (C quat arom), 168.6, 169.3 (C=O).
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17. Spectral data of **7**: IR (film, NaCl) $\nu_{c=o}$ 1739 cm^{-1}. HRMS (FAB+) $(M+Na)^+$ calcd for $C_{34}H_{35}ClNaO_7S$ 645.1690, found 645.1699.
^{1}H NMR (400 MHz, $CDCl_3$): 2.39 (3H, s, CH_3), 3.66 (1H, dd, $J_1 = 11.0$ Hz, $J_2 = 2.0$ Hz), 3.76–3.83 (2H, m), 4.05 (1H, t, $J = 9.5$ Hz), 4.10 (1H, m), 4.48 (1H, d, $J = 10.5$ Hz), 4.48 (1H, d, $J = 12,0$ Hz), 4.60 (1H, d, $J = 12.0$ Hz), 4.60 (1H, dd, $J_1 = 9.5$ Hz, $J_2 = 4.0$ Hz), 4.69 (1H, d, $J = 11.0$ Hz), 4.74 (1H, d, $J = 11.0$ Hz), 4.75 (1H, d, $J = 10.5$ Hz), 6.21 (1H, d, $J = 4.0$ Hz, H_1), 7.08–7.11 (2H, m), 7.16–7.23 (4H, m), 7.25–7.37 (11H), 7.80 (2H, d, $J = 8.5$ Hz).
^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3 of OTs), 67.4 (C_6), 73.6, 75.4, 75.6 (CH_2 of OBn), 73.4, 76.6, 78.6, 79.1, 91.8 (C_1, C_2, C_3, C_4, C_5), 127.7, 127.8–128.1, 128.3, 128.4, 128.5 (C tert arom), 133.0, 137.5, 137.6, 137.7, 145.3 (C quat arom).
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22. Spectral data of **9**: Mp 67–69 °C.
IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}.
HRMS (FAB+) $(M+H)^+$ calcd for $C_{47}H_{39}N_4O_6$ 755.2870, found 755.2871.

^{1}H NMR signals of the sugar part were assigned from ^{1}H–^{1}H COSY.

^{1}H NMR (400 MHz, $CDCl_3$): 3.30 (3H, s, CH_3), 3.79 (1H, d, $J = 11.0$ Hz), 3. 91 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 5.5$ Hz, $H_{6'}$), 3.96–4.03 (2H, m, $H_{3'}$, $H_{6'}$), 4.09 (1H, t, $J = 9.5$ Hz, $H_{4'}$), 4.42 (1H, m, $H_{5'}$), 4.44 (1H, d, $J = 10.5$ Hz), 4.65 (1H, d, $J = 11.0$ Hz), 4.67 (1H, d, $J = 12.0$ Hz), 4.75 (1H, d, $J = 12.0$ Hz), 4.92 (1H, d, $J = 11.0$ Hz), 5.53 (1H, m, $H_{2'}$), 6.15 (1H, d, $J = 3.5$ Hz, $H_{1'}$), 6.45 (2H, d, $J = 7.0$ Hz), 6.89 (2H, t, $J = 7.5$ Hz), 7.03 (1H, t, $J = 7.5$ Hz), 7.14–7.18 (2H, m), 7.24–7.28 (3H, m), 7.32–7.39 (2H, m), 7.40–7.49 (6H, m), 8.00 (1H, m), 8.52 (1H, d, $J = 4,0$ Hz), 8.82 (1H, m), 8.95 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 1.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 23.9 (NCH_3), 58.3, 74.5, 78.3, 80.4, 85.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 68.9 ($C_{6'}$), 73.8, 75.1, 75.9 (CH_2 of OBn), 110.4, 113.3, 116.5, 117.7, 121.9, 125.3, 127.4, 130.2, 136.1, 137.6, 137.9, 143.3, 152.3 (C quat arom), 113.6, 117.3, 122.9, 125.6, 127.7–128.7, 134.1, 146.5 (C tert arom), 170.0, 170.1 (C=O).

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24. Spectral data for **1**: Mp 245–250 °C (decomposition)
IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}, ν_{OH} 3040–3680 cm^{-1}.
HRMS (FAB+) $(M+H)^+$ calcd for $C_{26}H_{21}N_4O_6$ 485.1461, found 485.1465.
^{1}H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.59–3.66 (2H, m), 3.79 (1H, m), 3.95–3.98 (1H, m), 4.06 (1H, m), 5.18–5.28 (3H, m, 2OH+$H_{2'}$), 5.40 (1H, d, $J = 5.5$ Hz, OH), 6.42 (1H, d, $J = 4.0$ Hz, $H_{1'}$), 7.49 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 5.0$ Hz), 7.51 (1H, t, $J = 7.5$ Hz), 7.64 (1H, dt, $J_1 = 7.5$ Hz, $J_2 = 1.0$ Hz), 8.24 (1H, d, $J = 8.0$ Hz), 8.63 (1H, dd, $J_1 = 5.0$ Hz, $J_2 = 1.5$ Hz), 8.72 (1H, d, $J = 7.5$ Hz), 8.89 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz).
^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (CH_3), 61.1 ($C_{6'}$), 59.2 ($C_{2'}$), 70.1, 73.6, 76.8 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 84.6 ($C_{1'}$), 109.2, 114.6, 116.1, 120.1, 120.9, 124.4, 127.6, 130.2, 143.0, 152.8 (C quat arom), 114.1, 116.9, 122.1, 124.2, 127.7, 132.1, 146.9 (C tert arom), 169.5, 169.6 (C=O).