Pergamon

*Tetrahedron Letters*, Vol. 38, No. 6, pp. 915-918, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02512-9

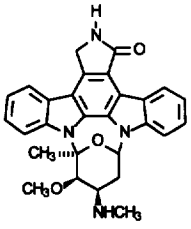
# Synthesis Of The Staurosporine Aglycone (K-252c) Lactam Regioisomer

*Robert L. Hudkins* and James L. Diebold*

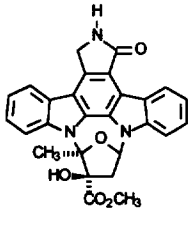
*Department of Chemistry, Cephalon, Inc.*
*145 Brandywine Parkway, West Chester, PA 19380 USA*

**Abstract:** The 6-oxo lactam regioisomer of the staurosporine aglycone was prepared from 2-(2-indolyl)indole and maleimide or ethyl *cis*-β-cyanoacrylate. The mechanism proceeds by a novel tandem Michael-acid catalyzed condensation sequence. 

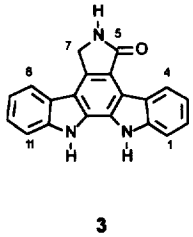
The indolocarbazole alkaloids, represented by the glycosylated derivatives staurosporine (**1**) and K-252a (**2**) are a biologically interesting class of natural products. Staurosporine was isolated from *Streptomyces staurosporeus* in 1977[1a] and K-252a was initially isolated from *Actinomadura* in 1985[1b] and later from the culture broth of *Nocardiopsis* sp. K-252[1c] in 1986. Another *Nocardiopsis* strain K-290 produced K-252c[1d] (**3**). Structure elucidation showed K-252c (**3**) to contain the same aglycone structure contained in staurosporine and K-252a.[1e] The indolocarbazole K-252c is commonly referred to as the staurosporine aglycone, or now sometimes as staurosporinone. The indolocarbazoles are biologically active and display properties ranging from antifungal, antimicrobial, antitumor and antihypertensive activities as well as inhibition of various serine-threonine and tyrosine specific protein kinases. Primary interest has focused on the protein kinase C (PKC) activity of compounds related to K-252c.[2]



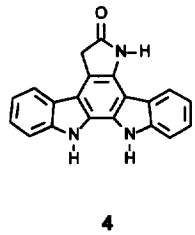

**1**




**2**




**3**



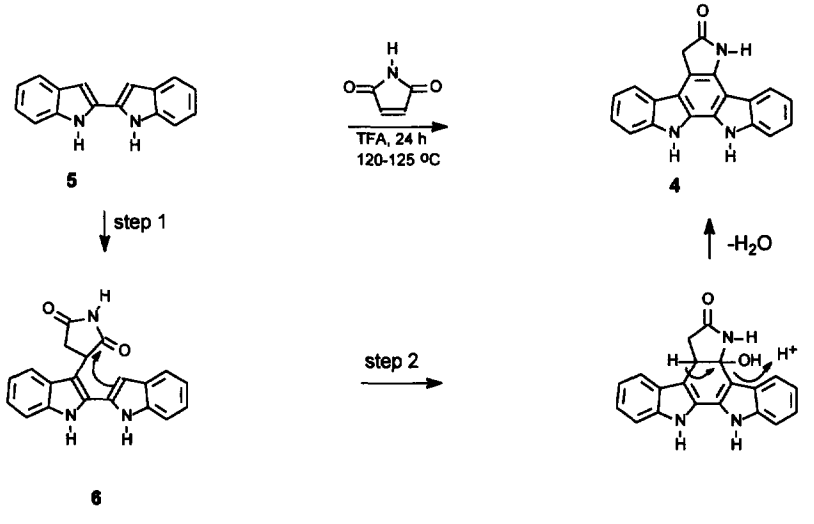

**4**

A number of diverse synthetic approaches have been developed to prepare the aglycone **3**.[3] An important component of K-252a and K-252c is the pyrrolo[3,4-c]carbazole 5-one ring fused system. The development of synthetic approaches to **3** have required addressing this critical pyrrole ring fusion. Due to the synthetic and biological interest in K-252c we sought to synthesize the unnatural K-252c lactam regioisomer, 5H, 12H, 13H-indolo-[2,3-a]pyrrolo[2,3-c]carbazole-6-one. We report here the first synthesis

of the corresponding 6-oxo lactam regioisomer **4** of the staurosporine aglycone. The approach to construction of the unnatural isomer is based on sequential electrophilic reactions at the C-3 positions of symmetrical 2,2'-biindole **5**. The indole C-3 position is known to be susceptible to electrophilic reactions such as Michael additions[4a,b] and acid catalyzed carbonyl condensations.[4a,c] Michael reaction of indoles with N-phenylmaleimide are known to give 3-substituted succinimides.[4b,d] 2,2'-Biindole has been utilized unsuccessfully in the cycloaddition approach to prepare the aglycone **3**.[4d,5a,b] Wood et. al[5c] described a successful method to **3** by coupling biindole **5** with a diazolactam which initiates a cycloaromatization via an indole C-3 carbonyl condensation as the last step.

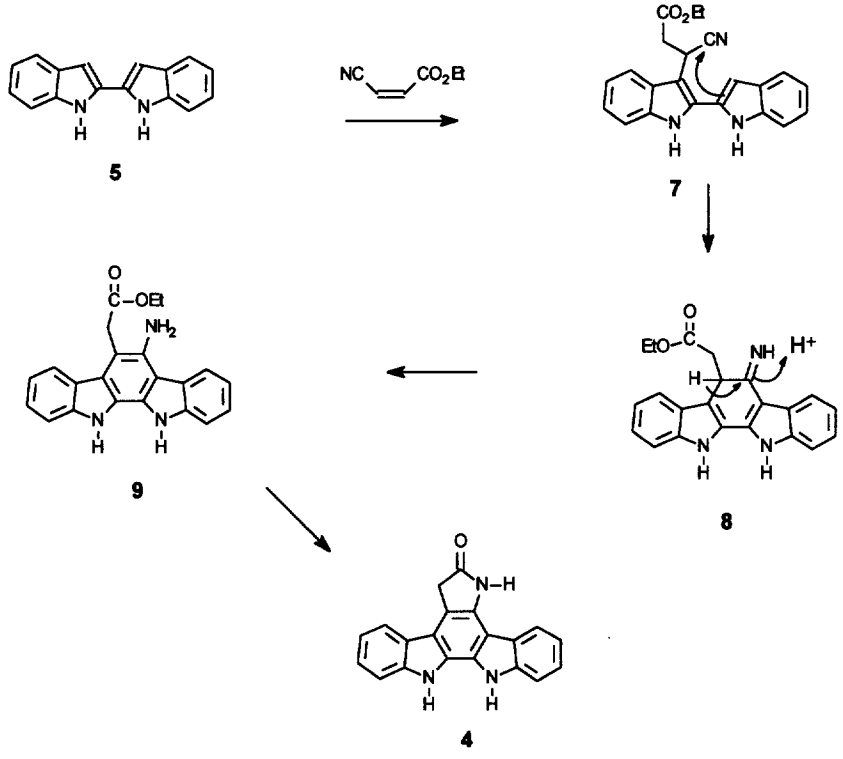
2,2'-Biindole (**5**) was prepared in high yield by Stille coupling of 2-iodoindole with 1-carboxy-2-(tributylstannyl)indole[6] (1-CSI). Treatment of **5** with maleimide in the presence of TFA failed to give the Michael adduct **6** below temperatures of 75 °C. Low yields of **6** (< 20%) could be isolated under these conditions as it was found difficult to halt the reaction after the initial Michael step occured. Conducting the reaction at toluene reflux in the presence of TFA, or in a sealed reaction vial (TFA, 110-115 °C, 14-24 h) the second acid catalyzed condensation step readily occurs at the succinimide C-2 carbonyl (scheme 1, step 2) resulting in dehydration to give the 6-oxo lactam regioisomer **4** (mp > 320 °C, 55-65%). Structural assignment of **4**[7] was based on $^1$H NMR, $^{13}$C NMR, IR, mass spectral and C,H,N analysis. The proton spectra (300 MHz, DMSO-$d_6$) of the aglycone **3**[8] reveals indole N-H singlets at δ 11.34 and 11.50, while the lactam NH chemical shift is at 8.52. A characteristic in the proton spectra of the aglycone **3** is the deshielding effect of the lactam carbonyl on the C-4 aryl proton. The chemical shift of H-4 is δ 9.22 (d, $J$ = 7.85 Hz) as opposed to H-8 which is at δ 8.05 (d, $J$ = 7.43 Hz). The lactam methylene hydrogens are at δ 4.97 (s, 2H). The proton spectra of the regioisomer **4** shows exchangeable NH singlets at δ 10.87, 10.92 and 11.18 and a two proton singlet (lactam $CH_2$) at δ 4.0. The protons adjacent to the lactam ring occur as a set of doublets at δ 8.03 ($J$ = 7.90 Hz) and δ 8.58 ($J$ = 8.27 Hz). The carbon spectra showed the lactam carbonyl at δ 179.16.[7]

**Scheme 1.**



During the course of these chemical studies we began to examine the use of ethyl *cis*-β-cyanoacrylate as the electrophile in the Michael reactions. Initial experiments with TFA as catalyst gave primarily decomposition or no reaction. When the reaction was run using $EtAlCl_2$ as a catalyst with an excess ethyl *cis*-β-cyanoacrylate, the pyrrolo[2,3-c]carbazole-6-one regioisomer **4** was formed in 27% yield (scheme 2). The use of additional Lewis acid catalysts ($SnCl_4$, $AlCl_3$, $Et_2AlCl$ or $TiCl_4$) generally gave lower yield and/or decomposition. The formation of carbazole **4** from maleimide or ethyl *cis*-β-cyanoacrylate occurs by similar tandem reaction sequences. The mechanism for the cyanoacrylate approach for the synthesis of **4** is proposed as shown in scheme 2. The initial step involves Michael addition at the α-carbon to the nitrile to give intermediate **7**. $EtAlCl_2$ catalysed indole C-3 addition to the nitrile leads to intermediate **8**. Tautomerization to the aromatized aniline **9**, followed by lactam ring closure, gives the pyrrolo[2,3-c]carbazole-6-one derivative **4**. The aniline-ester intermediate **9** has never been isolated from the reaction. The product which would be obtained from Michael addition to the ester α-carbon of cyano-acrylate has not been identified in the work-up and may result in decomposition products. Carbazole **4** prepared from biindole **5** and ethyl *cis*-β-cyanoacrylate was identical in its physical and spectral properties to that prepared from biindole **5** and maleimide.

**Scheme 2.**



In conclusion, the 6-oxo lactam regioisomer of the natural K-252c was prepared using a tandem Michael-acid catalyzed condensation sequence with 2,2'-biindole and maleimide or ethyl *cis*-β-cyanoacrylate.

**References**


1. (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275; (b) Sezaki, M.; Sasaki, T.; Nakazawa, T.; Takeda, U.; Iwata, M.; Watanabe, T.; Koyama, M.; Kai, F.; Shomura, T.; Kojima, M. *J. Antibiot.* **1985**, *38*, 143; (c) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059; (d) Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1066; (e) Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, N.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *39*, 1072.
2. (a) Davis, P.D.; Hill, C.H.; Lawton,G.; Nixon, J.S.; Wilkinson, S.E.; Hurst, S.A.; Keech, E.; Turner, S.E. *J. Med. Chem.* **1992**, *35*, 177. (b) Vice, S.F.; Bishop, W.R.; McCombie, S.W.; Dao, H.; Frank, E.; Ganguly, A.K. *BioMed. Chem. Lett.* **1994**, *4*, 1333. (c) McCombie, S.W.; Bishop, R.W.; Carr, D.; Dobek, E.; Kirkup, P.; Kirshmeier, P.; Lin, S.,; Petrin, J.; Rosinski, K.; Shankar, B.B.; Wilson, O. *BioMed. Chem. Lett.* **1993**, *3*, 1537. (d) Fabre S.; Prudhomme, M.; Rapp, M. *BioMed. Chem.* **1993**, *3*, 193.
3. (a) Bruning, J.; Hache, T.; Winterfildt, E. *Synthesis* **1994**, 25. (b) Moody, C.J.; Rahimtola, K.F.; Porter, B.; Ross, B.C. *J. Org. Chem.* **1992**, *57*, 2105. (c) Harris, W.; Hill, C.H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361. (d) Xie, G.; Lown, J.W. *Tetrahedron Lett.* **1994**, *35*, 5555.
4. (a) Reimers, W.A. In *Indoles Pt 1*; Houlihan, W.J. Ed.; Wiley: New York, 1972; (b) Colonna, M; Monti, A. *Gazz. Chim. Ital.* **1962**, *92*, 1401; (c) Appleton, J.E.; Dack, K.N.; Green, A.D.; Steel, J. *Tetrahedron Lett.* **1993**, *34*, 1529; (d) Barry, J.F.; Wallace, T.W.; Walshe, N.D.A. *Tetrahedron* **1995**, *47*, 12797.
5. (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015. (b) Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285. (c) Wood, J. L.; Stoltz, B. M.; Dietrich, H-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.
6. Hudkins, R.L.; Diebold, J.L.; Marsh, F.D. *J. Org. Chem.* **1995**, *60*, 6218.
7. $^1$H NMR 300 (MHz, DMSO-*d6*) δ 4.00 (s, 2H), 7.19 (t, 2H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 7.4 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 8.03 (d, 1H, *J* = 8.0 Hz), 8.58 (d, 1H, *J* = 7.7 Hz), 10.86 (s, 1H), 10.91 (s, 1H), 11.17 (s, 1H); $^{13}$C NMR (300 MHz, DMSO-*d6*) δ 35.79, 106.71, 107.16, 111.61, 111.95, 117.05, 119.14, 119.47, 121.52, 121.70, 121.87, 121.98, 123.10, 124.86, 125.22, 125.94, 129.97, 139.24, 139.94, 179.16; MS(FAB), (ES$^+$) m/z = 311(M$^+$). Anal. Calcd. for $C_{20}H_{13}N_3O \cdot 0.5\ H_2O$, (C, H, N ± 0.4%).
8. An authentic sample of the natural K-252c (**3**) was kindly provided by Dr. C. Murakata, Tokyo Researsh Labs, Kyowa Hakko Kogyo Co., Ltd.


(*Received in USA* 31 *October* 1996; *revised* 12 *December* 1996; *accepted* 13 *December* 1996)