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Synthesis of *N*-Protected Staurosporinones

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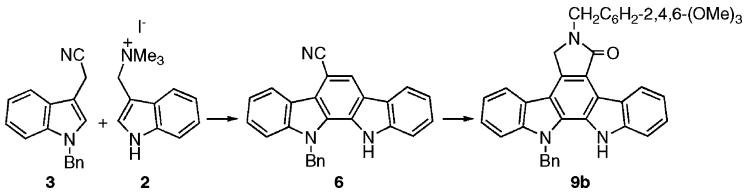

We report a method for the synthesis of *N*-protected staurosporinones, which are useful for the synthesis of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids and related compounds. An interaction of gramine methiodide (**2**) with 3-(*N*-benzyl)indolylacetonitrile (**3**) in the presence of *t*-BuLi, followed by a CF_3COOH-catalyzed intramolecular indole−indole coupling and dehydrogenation with DDQ, produced 5-cyanoindolo[2,3-*a*]carbazole **6** almost quantitatively. Reduction of its cyano group followed by *N*-benzylation produced *N*-benzylaminomethylindolo[2,3-*a*]carbazole **8b**, which was subjected to Pd-$(OAc)_2$-catalyzed direct aromatic carbonylation to give *N*-protected staurosporinone **9b**. Treatment with $AlCl_3$ in anisole removed *N*-benzyl groups to afford staurosporinone quantitatively.

Introduction

Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids have been isolated from soil organisms, blue-green algae, and slime molds.[1,2] Because of their unique diindole structure and remarkable biological activities,[3] such as potent protein kinase C inhibitory activity,[1c,3c,4] potent antitumor activities with topoisomerase inhibitory activities,[2c,5] platelet aggregation inhibitory activity,[4d,6] antimicrobial and hypotensive activities,[7] anti-HIV activitiy,[8] and immunosuppressive activity,[4i] many groups have made efforts toward achieving the synthesis of the alkaloids[9−17] and related compounds.[18−19] We report a new access to possible synthetic precursors of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids and staurosporinone (**1**) involving a $Pd(OAc)_2$-catalyzed direct aromatic carbonylation that was recently developed by us for preparation of five- or six-membered benzolactams.[20]

Results and Discussion

We first examined a synthetic route starting from a reaction of gramine methiodide (**2**) with 3-(*N*-benzylindolyl)acetonitrile

(1) For reviews (isolation), see: (a) Gill, M.; Steglich, W. *In Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Spriger: Wien, 1987; Vol. 51, pp 1−317. (b) Bergman, J. In *Studies in Natural Products Chemistry*, *Part A*; Elsevier Science: New York, 1988; Vol. 1, pp 3−30. (c) Steglich, W. *Pure Appl. Chem.* **1989**, *61*, 281−288. (d) Purdomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265−290.

(2) For staurosporine, see: (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R.; *J. Antibiot.* **1977**, *30*, 275−282.; Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A. A.; Iwai, Y.; Omura, S. *J. Chem. Soc., Chem. Commun.* **1978**, 800−801.; *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3681−3685. For arcyaflavin B and C, see: (b) Steilich, W.; Steffan, B.; Kopanski, L.; Eckhardt, G. *Angew. Chem., Int. Ed.* Engl. **1980**, *19*, 459−460. For Rebeccamycin, see: (c) Nettleton, D. E.; Doyle, T. W.; Kirshnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4011−4014. For K252a, see: (d) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059−1065. For K252c and d, see: (e) Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1066−1071. For holyrine A and B, see: (f) Williams, D. E.; Bernan, V. S.; Ritacco, F. V.; Maiese, W. M.; Greenstein, M.; Anderson, R. J. *Tetrahedron Lett.* **1999**, *40*, 7171−7174.

(3) For reviews (biological activities), see: (a) Gribble, G. W.; Berthel, S. J.; In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1993; Vol. 12, pp 365−409. (b) Sapi, J.; Massiot, G. In *The Alkaloids*; Cordell. G. A., Ed.; Academic Press: New York, 1995; Vol. 47, pp 173−226. (c) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshita, H. *J. Antibiot.* **1995**, *48*, 535−548. (d) Pindur, U.; Kim, Y.-S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29−69.

(4) (a) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397−402. (b) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059−1065. (c) Nakanishi, S.; Matsuda, Y.; Iwahashi, K. Kase, H. *J. Antibiot.* **1986**, *39*, 1066−1071. (d) Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, N.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *39*, 1072−1078. (e) Takahashi, I.; Saitoh, Y.; Yoshida, M.; Sano, H.; Nakano, H.; Morimoto, M.; Tamaoki, T. *J. Antibiot.* **1989**, *42*, 571−576. (f) Osada, H.; Takahashi, H.; Tsunoda, K.; Kusakabe, H.; Isono, K. *J. Antibiot.* **1990**, *43*, 163−167.; Takahashi, H.; Osada, H.; Uramoto, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 168−173. (g) Oikawa, T.; Shimamura, M.; Ashino, H.; Nakamura, O.; Nanayasu, T.; Morita, I. Murota, S.-I. *J. Antibiot.* **1992**, *45*, 1155−1160. (h) Fabre, S.; Prudhomme, M. *Bioorg. Med. Chem.* **1993**, *1*, 193−196. (i) McAlpine, J. B.; Karwowski, J. P.; Jackson, M.; Mullally, M. M.; Hochlowski, J. E.; Premachandran, U.; Burres, N. S. *J. Antibiot.* **1994**, *47*, 281−288. (j) Hoehn, P.; Ghisalba, O.; Moerker, T.; Peter, H. *J. Antibiot.* **1995**, *48*, 300−305.

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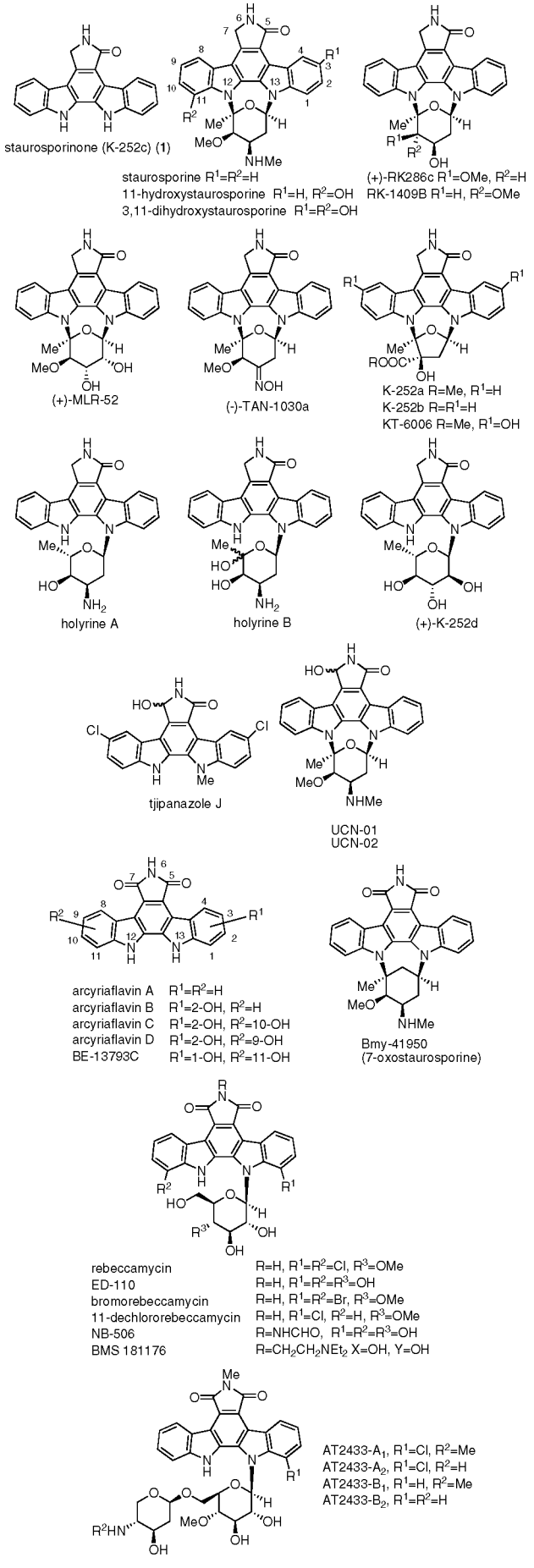


(**3**) via 3-methyleneindolenine (**2′**)[21,22] (Scheme 1). This coupling proceeded smoothly, when 2 equiv each of **3** and *t*-BuLi were used at −78 °C to room temperature (rt), to give a diindole **4** in 96% yield, 0.82 equiv of **3** being recovered. When the amount of acetonitrile **3** was less than 2 equiv, the reaction did not give

(5) (a) Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T. Tomita, K. *J. Antibiot.* **1987**, *40*, 668−678. (b) Kojiri, K.; Kondo, H.; Yoshinari, T.; Arakawa, H.; Nakajima, S.; Satoh, F.; Kawamura, K.; Okura, A.; Suda, H.; Okanishi, M. *J. Antibiot.* **1991**, *44*, 723−728. (c) Tanaka, S.; Ohkubo, M.; Kojiri, K.; Suda, H.; Yamada, A.; Uemura, D. *J. Antibiot.* **1992**, *45*, 1797−1798. (d) Yamashita, Y.; Fujii, N.; Murakata, C.; Ashizawa, T.; Okabe. M.; Nakano, H. *Biochemistry* **1992**, *31*, 12069−12075. (e) Merino, A.; Madden, K. R.; Lane, W. S.; Champoux, J. J.; Reinberg, D. *Nature* **1993**, *365*, 227−232. (f) Arakawa, H.; Iguchi, T.; Yoshinari, T.; Kojiri, K.; Suda, H.; Okura, A. *Jpn. J. Cancer Res.* **1993**, *84*, 574−581. (g) Arakawa, H.; Iguchi, T.; Morita, M.; Yoshinari, T.; Kojiri, K.; Suda, H.; Okura, A.; Nishimura, S. *Cancer Res*. **1995**, *55*, 1316−1320 and ref 16b.

(6) Oka, S.; Kodama, M.; Takeda, H.; Tomizuka, N.; Suzuki, H. *Agric. Biol. Chem.* **1986**, *50*, 2723−2727.

(7) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275−282.

(8) (a) Qatsha, K. A.; Rudolph, C.; Marmé, D.; Schächtele, C.; May, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 4674−4678. (b) Rashid, M. A.; Gustafson, K. R.; Kashman, Y.; Cardellina, J. H., II; McMahon, J. B.; Boyd, M. R. *Nat. Prod. Lett.* **1995**, *6*, 153−156.

(9) For reviews (synthesis), see: (a) Chakraborty, D. P. In *The Alkaloid*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, pp 257−364. (b) Moody, C. J. *Synlett* **1994**, 681−688. (c) Pindur, U.; Lemster, T. *Recent Res. Devel. Org. Bioorg. Chem*. **1997**, 33−54. (d) Knölker, H.-J.; Reddy, K. R. *Chem. Rev*. **2002**, *102*, 4303−4427 and refs 1b and 2b.

(10) For synthesis of staurosporinone, see: (a) Sarstedt, B.: Winterfeldt, E. *Heterocycles* **1983**, *20*, 469−476. (b) Hughes, I.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 1441−1444.; Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2475−2480. (c) Moody, C. J.; Rahimtoola, K. F. J. *Chem. Soc., Chem. Commun.* **1990**, 1667−1668.; Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105−2114. (d) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361−8364. (e) Xie, G.; Lown, J. W. *Tetrahedron Lett*. **1994**, *35*, 5555−5558. (f) Faul, M. M.; Sullivan, K. A.; Winneroski, L. L. *Synthesis*, **1995**, 1511−1516.; Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053−6058. (g) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Tetrahedron* **1998**, *54*, 6909−6918. (h) Mahboobi, S. Eibler, E.; Koller, M.; Kumar, S.; Popp, A. *J. Org. Chem.* **1999**, *64*, 4697−4704. (i) Reddy, G. M.; Chen, S.-Y.; Uang, B.-J. *Synthesis* **2003**, 497−500. (j) Guadêncio, S. P.; Santos, M. M. M.; Lobo, A. M.; Prabharkar, S. *Tetrahedron Lett*. **2003**, *44*, 2577−2578 and ref 11b.

(11) For synthesis of staurosporine, see: (a) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782−3783.; Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552−553.; Link, J. T.; Reghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825−2842. (b) Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656−10657.; Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652−9661. (c) Chen, S.-Y.: Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *J. Org. Chem.* **2001**, *66*, 5627−5628.

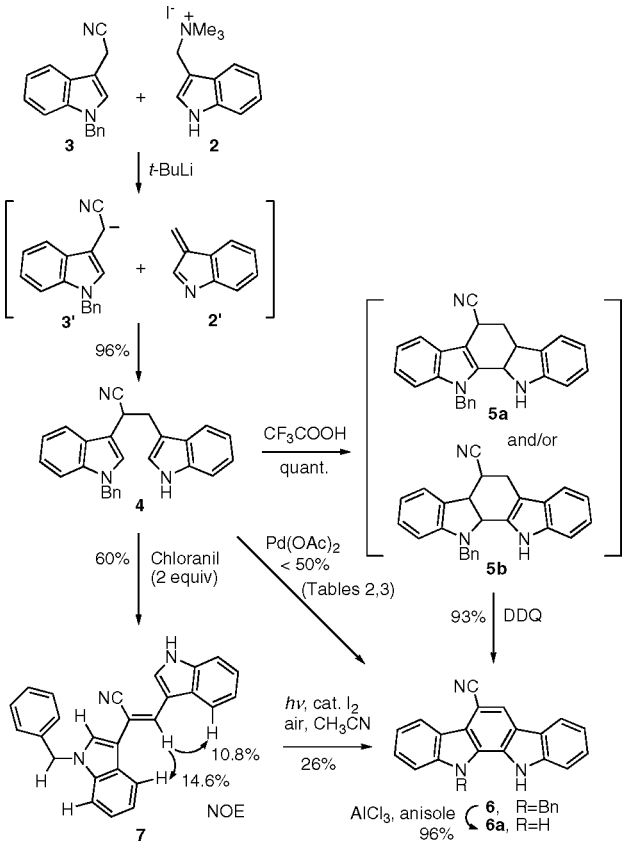
(12) For synthesis of K252a, see: (a) Wood, J. L.; Stoltz, B. M.: Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413−10414.; Wood, J. L.; Stoltz, B. M.: Dietrich, H.-J. Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641−9651. (b) Lowinger, T. B.; Chu, J.; Spence, P. L. *Tetrahedron Lett.* **1995**, *36*, 8383−8386. (c) Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501−6502.

(13) For synthesis of arcyriaflavin A, see: (a) Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824−828. (b) Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869−8880. (c) Fonseca, A. P.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1995**, *36*, 2689−2692.; Marques, M. M. B.; Lobo, A. M.; Prabhakar, S.; Branco, P. S. *Tetrahedron Lett.* **1999**, *40*, 3795−3796.; Marques, M. M. B.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2000**, *41*, 9835−9838. (d) Adeva, M.; Buono, F.; Caballero, E.; Medarde, M.; Tomé, F. *Synlett* **2000**, 832−834. (e) Bergman, J.; Koch, E.; Pelcman, B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2609−2614 and ref 10d.

(14) For synthesis of arcyriaflavin B, C, and D, see: Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Morishima, H. *Tetrahedron* **1996**, *52*, 8099−8112 and ref 10b.

(15) For synthesis of rebeccamycin, see: (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015−4018. (b) Gallant, M.; Link, J. Y.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343−349. (c) Faul, M. M.; Winneroske, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465−2470.

SCHEME 1. Preparation of 6-Cyanoindolo[2,3-*a*]carbazole 6



good results because of a competitive side reaction between **3** and pivalaldehyde or its equivalent **A** that was presumably formed by an interaction of *t*-BuLi with DMF, leading to an adduct **C**, as shown in Scheme 2 and Table 1. In fact, an interaction of nitrile **3** with pivalaldehyde itself in the presence of NaH gave **C**. The *cis*-*β*-alkylacrylonitrile structure of **C** was determined by ^{1}H NMR analysis using the nuclear Overhouser effect (NOE),[23] the values of which are shown in Scheme 2.

Oxidation of **4** with chloranil (2 equiv) in boiling xylene for 2 h[24] gave a single diindole **7** (60%), the trans structure of which was also determined by NOE analysis, as shown in Scheme 1. The application of stilbene photocyclization[10e,g,25,26] to **7** involving trans−cis isomerization in the presence of iodine was not very successful and afforded indolo[2,3-*a*]carbazole **6** in only 26% yield. On the basis of Hill's $Pd(OAc)_2$-induced oxidative

SCHEME 2. Formation of Byproduct C

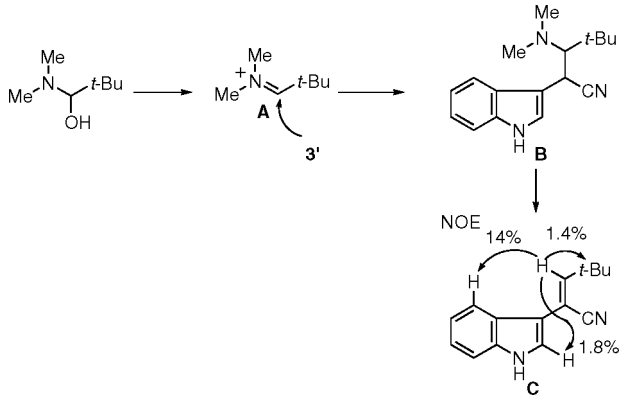


TABLE 1. Preparation of Diindole 4 from Methiodide 2 and Acetonitrile 3[a]

entry	**2**/**3** (equiv)	*t*-BuLi	ratio (**3**:**4**:**C**)[b]	yields of **4** and **C**
1	1/1	1.1	1:0.1:0	
2	1/1	2.2	1:1:1	33%, 23%
3	1/1.5	2.2	1:1.3:1	
4	1/2	2.2	1:1:0	96%, 0%

[a] To a mixture of **3** and *t*-BuLi in THF at −78 °C was added a solution of **2** in DMF, and the mixture was stirred at rt for 4 h. [b] Determined by ^{1}H NMR analysis.

(16) For synthesis of ED-110, see: (a) Tanaka, S.; Ohkubo, M.; Kojiri, K.; Suda, H. *J. Antibiot.* **1992**, *45*, 1797−1798. (b) Zembower, D. E.; Zhang, H.; Lineswala, J. P.; Kuffel, M. J.; Aytes, S. A.; Ames, M. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 145−150.

(17) For synthesis of NB-506, see: Ohkubo, M.; Kawamoto, H.; Ohno, T.; Nakano, M.; Morishima, H. *Tetrahedron* **1997**, *53*, 585−592.

(18) For other synthetic approaches to 5-oxoindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, see: (a) Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795−2797. (b) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309−324. (c) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177−1185. (d) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043−1055. (e) Wood, J. L.; Petsch, D. T.; Stoltz, B. M.; Hawkins, E. M.; Elbaum, D.; Stover, D. R. *Synthesis* **1999**, 1529−1533. (f) Eils, S.; Winterfeldt, E. *Synthesis* **1999**, 275−281. (g) Tamaki, K.; Shotewell, J. B.; White, R. D.; Drutu, I.; Petsch, D. T.; Nheu, T. V.; He, H.; Hirokawa, Y.; Maruta, H.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1689−1692. (h) Nomak, R.; Snyder, J. K. *Tetrahedron Lett.* **2001**, *42*, 7929−7933. (i) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005−2008. (j) Gingrich, D. E.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2829−2831. (k) Santos, M. M. M.; Lobo, A. M.; Prabhakar, S.; Maeques, M. M. B. *Tetrahedron Lett.* **2004**, *45*, 2347−2349.

(19) For other synthetic approaches to 5,7-dioxoindolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazoles, see: (a) Weinreb, S. M.; Garigipati, R. S.; Gainer, J. A. *Heterocycles* **1984**, *21*, 309−324. (b) Bergmann, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441−4444. (c) Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285−1288. (d) Pindur, U.; Kim, M. H. *Arch. Pharm.* **1992**, *325*, 353−356.; Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *Heterocycles* **1994**, *38*, 2267−2276.; *J. Heterocycl. Chem.* **1994**, *31*, 377−386.; **1995**, *32*, 1335−1339. (e) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Ito, S.; Morishima, H. *Tetrahedron* **1997**, *53*, 5937−5950. (f) Wood, J. L.; Petsch, D. T.; Stoltz, B. M.; Hawkins, E. M.; Elbaum, D.; Stover, D. R. *Synthesis* **1999**, 1529−1533. (g) Riley, D. A.; Simpkins, N. S.; Moffat, D. *Tetrahedron* **1999**, *40*, 3929−3932. (h) Wang, J.; Rosingama, M.; Watson, D. J.; Dowdy, E. D.; Discordia, R. P.; Soundarajan, N.; Li, W.-S. *Tetrahedron Lett.* **2001**, *42*, 8935−8937. (i) Akao, A.; Hiraga, S.; Iida, T.; Kamatani, A.; Kawasaki, M.; Mase, T.; Nemoto, T.; Satake, N.; Weissman, S. A.; Tschaen, D. M.; Rossen, K.; Petrillo, D.; Reamer, R. A.; Volante, R. P. *Tetrahedron* **2001**, *57*, 8917−8923. (j) Sanchez-Martinez, C.; Shih, C.; Zhu, G.; Li, T.; Brooks, H. B.; Patel, B. K. R.; Schltz, R. M.; DeHahn, T. B.; Spencer, C. D.; Watkins, S. A.; Ogg, C. A.; Considine, E.; Dempsey, J. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3841−3846. (k) Nichols, C. J.; Simpkins, N. S. *Tetrahedron Lett.* **2004**, *45*, 7469−7473. For synthesis of indolo[6,7-*a*]-pyrrolo[3,4-*c*]carbazoles, see: (l) Faul, M. M.; Engler, T. A.; Sullivan, K. A.; Grutsch, J. L.; Clayton, M. T.; Martinelli, M. J.; Pawlak, J. M.; LeTourneau, M.; Coffey, D. S.; Pedersen, S. W.; Kolis, S. P.; Furness, K.; Malhotra, S.; Al-awar, R. S.; Ray, J. E. *J. Org. Chem.* **2004**, *69*, 2967−2975.

(20) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H. Nagasaki, H.; Yuguchi, M; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342−14343. (b) Orito, K.; Miyazawa, M.; Nakamura, N.; Horibata, A.; Ushito, H. Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951−5958.

(21) (a) Lown, J. W.; Weir, G. L. *Can. J. Chem.* **1978**, *56*, 249−257. (b) Gelin, J. G.; Mortier, J.; Moyroud, J. *J. Org. Chem.* **1993**, *58*, 3473−3475.

(22) (a) Iwao, M. *Heterocycles* **1993**, *36*, 29−32.; Iwao, M.; Motoi, O. *Tetrahedron Lett.* **1995**, *36*, 5929−5932. (b) Iwao, M.; Ishibashi, F. *Tetrahedron* **1997**, *53*, 51−58.

(23) Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect: Chemical Applications*; Academic Press: New York, 1971.

(24) The use of DDQ instead of Chloranil resulted in the lower yield (<50%) of **8**.

(25) Mallory, F. B.; Mallory, C. W. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984; Vol. 30, pp 1−456.

TABLE 2. Preparation of Indolo[2,3-*a*]carbazole 6 by Oxidative Coupling of 4[a]

entry	PdX_2 (mol %)	solvent	atmosphere	ratio (**4**:**6**)[b]	yield of **6**
1	$Pd(OAc)_2$ (100)	AcOH	air	0:1	40%
2	$Pd(OAc)_2$ (200)	AcOH	air	c	
3	$Pd(OAc)_2$ (100)	dioxane	Ar	1:0.4	
4	$Pd(OAc)_2$ (100)	AcOH	N_2	1:1	
5	$PdCl_2$ (100)	DMF	air	1:0.5	

[a] A stirred mixture of **4** and PdX_2 (100 or 200 mol %) in AcOH, dioxane, or DMF was heated at 130 °C for 24 h. [b] Determined by ^{1}H NMR analysis. [c] A complex mixture was obtained.

TABLE 3. Preparation of Indolo[2,3-*a*]carbazole 6 by Pd-catalyzed Oxidative Coupling of 4[a]

entry	catalyst (mol %)	additive (mol %)	atm	ratio of **4**:**6**[b]	yield of **6**
1	$Pd(OAc)_2$ (5)	$CuCl_2$ (100)	O_2	1:0.1	
2	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (50)	Air	1:2.5	
3	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (50)	O_2	1:0.1	
4	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (900)		1:0.1	
5	$Pd(OAc)_2$ (5)	*t*-BuOOH (250)	Ar	0:1	31%
6	$Pd(OAc)_2$ (5)	$Sn(OAc)_2$ (10)	O_2	1:0	
7	$Pd(OOCCF_3)_2$ (5)	$Sn(OAc)_2$ (10)	O_2	1:3.3	47%
8	$Pd(OOCCF_3)_2$ (5)	$Sn(OAc)_2$ (50)	O_2	1:0.1	

[a] A stirred mixture of **4** and PdX_2 (5 mol %) in AcOH was heated at 130 °C for 24 h. [b] Determined by ^{1}H NMR analysis.

coupling of diindolylmaleimide,[10d] direct conversion of **4** to **6** was examined. As shown in Table 2, treatment of **4** with a stoichiometric amount of $Pd(OAc)_2$ afforded **6** in 40% yield after purification of a tarry reaction mixture (entry 1), although the addition of air (oxygen) accelerated the reaction (entry 1 vs entry 4). $PdCl_2$ was not suitable for this coupling (entry 5). As shown in Table 3, an alternative one-pot method based on Wang's catalytic procedure,[19h] using $Pd(OAc)_2$ (5 mol %) as a catalyst and $CuCl_2$,[27] $Cu(OAc)_2$[27] or $K_2S_2O_8$[28] as an oxidant, resulted in low yields of **6**. The use of *t*-BuOOH[29] led to the complete consumption of **4** after 2 h, but **6** was obtained in only 31% yield. The use of $Pd(OAc)_2$ (5 mol %)−$Sn(OAc)_2$[30] (10 mol %) in boiling AcOH under oxygen was not effective, but the use of $Pd(OCOCF_3)_2$ (5 mol %)-$Sn(OAc)_2$ gave a better result (47% yield) (entry 7).

On the other hand, by a modification of Gribble's and Vranken's methods,[31,32] cyclization of **4** by acid treatment with CF_3COOH in CH_2Cl_2 at rt for 2 h followed by DDQ oxidation of the resulting crude cyclization products **5a** and/or **5b** was successfully carried out to produce **6** in 93% yield.

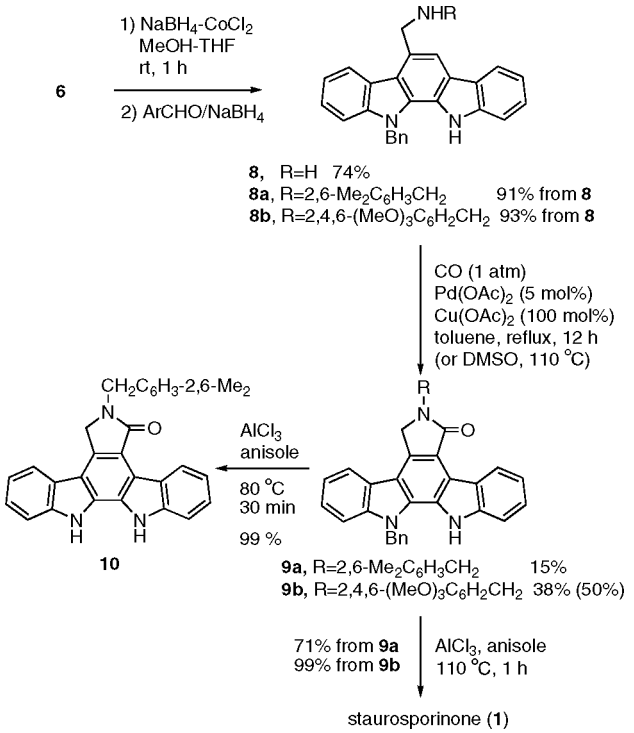
The cyano group of **6** was reduced with $NaBH_4$−$CoCl_2$ in MeOH−THF[33] at rt for 1 h to afford a primary amine **8** (74%), which was condensed with 2,6-dimethylbenzaldehyde in the presence of 4-Å molecular sieves (MS4 Å) in boiling THF for 24 h. The resultant imino bond was then treated with $NaBH_4$

TABLE 4. Preparation of *N*-Benzylamine 8b from 6

entry	reagent	solvent	temp.	time	yield of **8b**
1	MS4Å	THF	reflux	2 h	
	$NaBH_4$	MeOH	rt	1 h	93%
2	pyridine-BH_3, MS4 Å[34]	DMF	rt	17 h	a
3	$NaBH_4$CN-MS3 Å[35]	DMSO	rt	8 h	a
4	$NaB(OAc)_3H$−AcOH[36]	THF	rt	6 h	31%
5	$NaB(OAc)_3H$[36]	1,2-DCE	rt	8 h	40%

[a] A complex mixture was obtained.

SCHEME 3. Synthesis of *N*-Protected Staurosporinones, 9a,b and 10, and Staurosporinone (1)

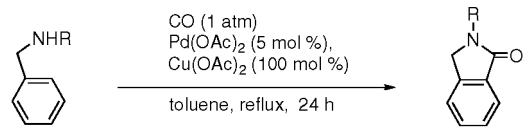


to afford *N*-(2,6-dimethyl)benzylamine **8a** in 91% yield in two steps. *N*-(2,4,6-Trimethoxy)benzylamine **8b** was also obtained in 93% yield (entry 1 in Table 4). However, the use of a one-pot procedure, so-called "reductive amination" using a pyridine−borane−MS4 Å complex,[34] $NaBH_3$CN-MS3 Å,[35] or $NaB(OAc)_3H$,[36] did not give satisfactory results (entries 2−5 in Table 4).

Benzylamine **8a** was subjected to carbonylation with $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (50 mol %)[20] in gently boiling toluene in an atmosphere of CO gas containing air corresponding to 0.5 molar equiv of O_2 delivered from a toy balloon for 2 h to give a lactam **9a** in 15% yield, although carbonylation of the model compounds **11a,b** to benzolactams **12a,b** gave better results (Scheme 4). Under the same conditions trimethoxybenzylamine **8b** was converted in 38% yield to benzolactam **9b**. The use of DMSO (110 °C) instead of gently boiling toluene enhanced the yield of benzolactam **9b** to 50%. Three nitrogen atoms of **9a**,**b** have different substituents. This should be useful for synthesis of staurosporine or related sugar-binding chiral

(26) (a) Liu, L. Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769−3775. (b) Lee, M. L.; Kudo, H.; Tedjamulia, M. L.; Castle, R. N. *J. Heterocycl. Chem.* **1984**, *21*, 185−192.
(27) Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49−52.
(28) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591−599.
(29) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097−2100.
(30) (a) Bryant, D. R.: Mckeon, J. E.; Ream, B. C. *J. Org. Chem.* **1968**, *28*, 4123−4127. (b) Hagelin, H.; Oslob, J. D.; Akermark, B. *Chem.−Eur. J.* **1999**, *5*, 2413−2416.
(31) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636−3642.
(32) Gilbert, E. J.; Van, Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500−5501.
(33) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555−4558.
(34) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995−5996.
(35) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904.
(36) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

SCHEME 4. Carbonylation of Benzylamines 11a,b



11a, R=Bn
11b, R=2,6-$Me_2C_6H_3CH_2$

12a, 67%
12b, 31%

alkaloids and optimization of their biological activity by modification of the aglycone portion, as described in some reports.[18d,f,h,i,k]

Deprotection of two benzyl groups of benzolactams **9a,b** was examined. Debenzylation of **6** via generation of a benzyl anion with *t*-BuOK in DMSO followed by treatment with O_2[37] did not work at all, probably due to the generation of a potassium salt on the indole NH. In contrast, the use of Murakami's procedure with a combination of $AlCl_3$ and anisole[38] at 110 °C for 1 h gave **6a** in 96% yield. Although Raphael reported that benzyl groups at the 6 position of staurosporinone derivatives could not be removed,[10b] a trimethoxybenzyl group of **9b** was also removed quantitatively under the latter conditions to give staurosporinone (**1**) in 99% yield [31% overall yield from gramine (**→4→6→8b→9b→1**)]. A similar debenzylation at 110 °C of **9a** proceeded more slowly to give **1** in 71% yield. Under milder conditions at 80 °C for 30 min, **9a** was successfully converted to 6-(2,6-dimethylbenzyl)staurosporinone **10** (99%).

In summary, *t*-BuLi-induced cross-coupling of grammine methiodide with *N*-benzyl-3-indolylacetonitrile produced *N*-benzyl-1,2-di-(3-indolyl)propionitrile, whose CF_3COOH-catalyzed cyclization followed by dehydrogenation produced 5-cyanoindolo[2,3-*a*]carbazole. Reduction of its CN group and benzylation of the resultant amine, followed by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation, provided indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole with two different benzyl groups at the 6 and 12 positions. Treatment with $AlCl_3$ and anisole resulted in efficient debenzylation to give staurosporinone quantitatively.

Experimental Section

All melting points were uncorrected. Mass spectrometric data were obtained by electron ionization at 70 eV. ^1H NMR spectra were obtained in $CDCl_3$ at 270 MHz using TMS as an internal reference, unless otherwise noted. Preparative thin-layer chromatography (TLC) was carried out on silica gel.

2-[3-(1-Benzyl)indolyl]-3-(3-indolyl)propionitrile (4) (Entry 4 in Table 1). To a stirred solution of 1-benzyl-3-indolylacetonitrile [**3**, almost quantitatively prepared using THF and benzyl bromide instead of benzene and benzyl chloride according to MacLean's procedure,[39] mp 94.5−95.5 °C (EtOH−CH_2Cl_2) (ref 39, mp 95−96 °C), 1.60 g, 6.5 mmol] in dry THF (25 mL) was added *t*-BuLi (1.62 M in pentane, 4.4 mL, 7.15 mmol) at −78 °C under argon. After being stirred at −78 °C for 1 h, a solution of gramine methiodide [**2** (1.06 g, 3.35 mmol), freshly and quantitatively prepared by Weir's procedure,[21a] mp 168−169 °C (ref 40, mp 167.5−170.5 °C; refs 41 and 42, mp 168−169 °C; ref 21a, 168−170 °C) in dry DMF (8 mL) was added dropwise. The mixture was stirred at rt for 4 h, quenched with water (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 layers were washed with water (5 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (starting with 1:1 hexane−CH_2Cl_2 and ending with CH_2Cl_2) to afford the unchanged nitrile **3** (0.65 g, 82%) as an oil and then **4** (1.20 g, 96%) as a white solid, mp 127−129 °C. Recrystallization from Et_2O−hexane afforded an analytical sample of **4**, mp 128.5−129 °C: IR (Nujol) 3354, 2248 cm^{-1}; ^1H NMR δ 3.39−3.55 (m, 2H), 4.39−4.45 (m, 1H), 5.24 (s, 2H), 7.02−7.46 (m, 14H), 7.71−7.74 (m, 1H), 8.02 (br. s, 1H); EI-MS *m*/*z* (relative intensity) 375 (M^+, 4.8), 130 (100), 91 (21.6). Anal. Calcd for $C_{26}H_{21}N_3$: C, 83.17; H, 5.64; N, 11.19. Found: C, 83.12; H, 5.58; N, 11.07.

Condensation of 2 with 3 in a 1:1 Ratio. Formation of (*Z*)-3-*tert*-Butyl-2-(*N*-benzyl-3-indolyl)acrylonitrile (C) (Entry 2 in Table 1). To a stirred solution of **3** (75 mg, 0.3 mmol) in dry THF (2 mL) was added *t*-BuLi (1.62 M in pentane, 0.4 mL, 0.65 mmol) at-78 °C under argon. After being stirred at-78 °C for 1 h, a solution of **2** (95 mg, 0.3 mmol) in dry DMF (1 mL) was added dropwise. The mixture was stirred at rt for 4 h, quenched with water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layers were washed with water (5 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue (134 mg) was purified by preparative TLC (30% hexane−CH_2Cl_2). A fraction with R_f = 0.7−0.8 gave **C** as yellow crystals (22 mg, 23%). Recrystallization from MeOH afforded an analytical sample of **C**, mp 79−80 °C: IR (Nujol) 2220 cm^{-1}; ^1H NMR δ 1.38 (s, 9H), 5.31 (s, 2H), 6.80 (s, 1H), 7.12−7.31 (m, 8H), 7.39 (s, 1H), 7.82−7.85 (m, 1H); EI-MS *m*/*z* (relative intensity) 314 (M^+, 30.5), 299 (30.3), 223 (5.4), 91 (100). Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.17; H, 7.04; N, 8.83. A less mobile fraction with R_f = 0.2−0.4 afforded **4** as colorless crystals (39 mg, 0.1 mmol, 33%), mp 127−129 °C (MeOH).

Preparation of Acetonitrile C by Condensation of 3 with Pivalaldehyde. A mixture of **3** (244 mg, 1.0 mmol), pivalaldehyde (103 mg, 1.2 mmol) and NaH (36 mg, 1.5 mmol) in dry THF (4 mL) was refluxed under nitrogen overnight. After being cooled to rt and quenched with water (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layers were washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue (293.2 mg) was purified by column chromatography on silica gel (30% hexane-CH_2Cl_2) to afford **C** (136 mg, 0.43 mmol, 44%), mp 79−80 °C (MeOH), as a yellow solid.

Preparation of 12-Benzyl-5-cyano-11,12-dihydroindolo[2,3-*a*]-carbazole (6) via an Acid-Catalyzed Cyclization of 4. A solution of **4** (111 mg, 0.3 mmol) in CF_3COOH (1 mL) was stirred at rt for 30 min and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aq $NaHCO_3$ (10 mL) and water (2 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated, and the residue (124.9 mg) was stirred with DDQ (173 mg, 0.76 mmol) in dry 1,4-dioxane (2 mL) at rt for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with saturated aq $NaHCO_3$ (3 × 50 mL) and water (2 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated, and the residue (123 mg) was purified by preparative TLC (CH_2Cl_2). A crystalline solid (112 mg) with R_f = 0.3−0.5 was recrystallized from benzene−CH_2Cl_2 to afford **6** as pale-yellow crystals (102.4 mg, 93%), mp 294−295 °C: IR (Nujol) 3392, 2204 cm^{-1}; ^1H NMR (DMSO−D_6) δ 6.19 (s, 2H), 7.12−7.40 (m, 7H), 7.48 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2, 1H), 8.33 (d, J = 7.6 Hz, 1H), 8.56 (d, J = 7.9 Hz, 1H), 8.68 (s, 1H), 12.01 (br. s, 1H); EI-MS *m*/*z* (relative intensity) 371 (M^+, 83.3), 280 (100), 91 (68.7). Anal. Calcd for $C_{26}H_{17}N_3$: C, 84.07; H, 4.61; N, 11.31. Found: C, 84.07; H, 4.83; N, 11.18.

(*Z*)-2-(*N*-Benzyl-3-indolyl)-3-(3-indolyl)acrylonitrile (7). A mixture of propionitrile **4** (372 mg, 1.0 mmol) and Chloranil (491

(37) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399−402.

(38) Watanabe, T.; Kobayashi, A.; Nishimura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, Y.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152−1156.

(39) Jahangtr; Brook, M, A.; MacLean, D, B.; Holland, H. L. *Tetrahedron* **1987**, *43*, 5761−5768.

(40) Melhado, L. L. *J. Org. Chem.* **1981**, *46*, 1920−1923.

(41) Geissman, T. A.; Armen, A. *J. Am. Chem. Soc.* **1952**, *74*, 3916−3919.

(42) Torralba, A. F.; Meyers, T. C. *J. Org. Chem.* **1957**, *22*, 972−975.

mg, 2 mmol) in *o*-xylene (10 mL) was refluxed under nitrogen for 4 h. The mixure was cooled to rt, diluted with CH_2Cl_2 (30 mL), washed with a 2 N NaOH solution (20 mL), water (2 × 20 mL), and brine (20 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography on silica gel (30 g) (CH_2Cl_2) afforded **7** as a solid (285 mg, 76%). Recrystallization from benzene afforded **7** as yellow crystals (223 mg, 60%), mp 201−202 °C: IR (Nujol) 3322, 2212 cm^{-1}; ^1H NMR δ 5.36 (s, 2H), 7.16−7.47 (m, 12H), 7.78−7.82 (m, 1H), 7.89 (s, 1H), 8.07−8.10 (m, 1H), 8.36 (d, J = 2.6 Hz, 1H), 8.56 (br. s, 1H); EI-MS *m*/*z* (relative intensity) 373 (M^+, 91.0), 282 (100), 91 (19.2). Anal. Calcd for $C_{26}H_{19}N_3$: C, 83.62; H, 5.13; N, 11.25. Found: C, 83.46; H, 5.19; N, 11.21.

A solution of **7** (238 mg, 0.64 mmol) in CH_3CN (35 mL) containing a catalytic amount of I_2 in a Pyrex tube without a stopper was irradiated with a 500-W high-pressure Hg arc lamp for 8 h. A 5% $Na_2S_2O_3$ solution (20 mL) was added to the mixture and was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (CH_2Cl_2). A band with R_f = 0.57−0.82 afforded **7** (62 mg, 0.17 mmol, 26%) as brown crystals, mp 292−294 °C (benzene−CH_2Cl_2).

Preparation of 6 from 4 Using 100 mol % of $Pd(OAc)_2$ (Entry 1 in Table 2). A mixture of **4** (35.4 mg, 0.09 mmol) and $Pd(OAc)_2$ (21.9 mg, 0.1 mmol) in AcOH (2 mL) was refluxed for 24 h. AcOH was evaporated. The residue was dissolved in dioxane (10 mL), and precipitates were removed by suction filtration through a thin pad of powdered $MgSO_4$. Dioxane was evaporated to afford an oily residue (35 mg), which was subjected to preparative TLC noted above to afford **6** (14 mg, 40%), mp 294−295 °C (benzene−CH_2Cl_2), as pale yellow crystals.

Preparation of 6 from 4 Using $Pd(OCOCF_3)_2$-$Sn(OAc)_2$ (Entry 7 in Table 3). A mixture of **4** (37.2 mg, 0.1 mmol), $Pd(OCOCF_3)_2$ (1.7 mg, 0.005 mmol), and $Sn(OAc)_2$ (2.4 mg, 0.01 mmol) in AcOH (2 mL) was refluxed under oxygen delivered from a toy balloon for 24 h. Preparative TLC of the crude product (37.8 mg) afforded **6** (17.3 mg, 47%), mp 294−295 °C (benzene−CH_2Cl_2), as pale-yellow crystals.

12-Benzyl-5-(aminomethyl)-11,12-dihydroindolo[2,3-*a*]carbazole (8). To a stirred mixture of carbazole **6** (1.86 g, 5 mmol) and $CoCl_2 \cdot 6H_2O$ (2.75 mg, 10 mmol) in MeOH (200 mL) and THF (80 mL) was added $NaBH_4$ (1.92 mg, 51 mmol). After 1 h, a 2 N HCl solution (100 mL) was added, and the mixture was stirred until black precipitates disappeared. The resultant solution was concentrated, and a 2 N NH_4OH solution was added. The basic solution was extracted with CH_2Cl_2 (2 L, 2 × 500 mL). The extracts were washed with water (3 × 300 mL) and dried (Na_2SO_4). The solvent was evaporated to give crude amine **8** (1.694 g, 90%). Recrystallization from THF−EtOH afforded an analytical sample of **8** (1.37 g, 3.7 mmol, 74%), mp 245−247 °C, as pale-yellow crystals: IR (Nujol) 3350 cm^{-1}; ^1H NMR δ 1.64 (br. s, 2H), 4.65 (s, 2H), 5.89 (s, 2H), 7.33−7.54 (m, 11H), 7.89 (s, 1H), 7.90 (br. s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H); EI-MS *m*/*z* (relative intensity) 375 (M^+, 100), 360 (57.3), 284 (35.6), 269 (93.8), 257 (49.5), 91 (31.6). Anal. Calcd for $C_{26}H_{17}N_3$: C, 83.17; H, 5.64; N, 11.19. Found: C, 82.96; H, 5.71; N, 11.09.

12-Benzyl-5-[*N*-(2,6-dimethylbenzyl)aminomethyl]-11,12-dihydroindolo[2,3 -*a*]carbazole (8a). A stirred suspension of 2,6-dimethylbenzaldehyde (134 mg, 1.0 mmol), amine **8** (455 mg, 1.2 mmol), and MS4 Å (4 g) in THF (36 mL) was refluxed for 24 h, then cooled, and filtered. The filtrate was concentrated to give an imine, which was dissolved in a mixture of CH_2Cl_2 (18 mL) and MeOH (18 mL). $NaBH_4$ (48 mg, 1.3 mmol) was added in portions, and the mixture was stirred at rt for 2 h, and the solvents were evaporated. The residue was dissolved in water (15 mL) and CH_2Cl_2 (15 mL). The water layer was separated and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 layers were washed with water (3 × 15 mL), dried over Na_2SO_4, and concentrated. The residue (574 mg) was purified by preparative TLC (3% MeOH−CH_2Cl_2). A fraction with R_f = 0.5−0.8 give a crystalline solid (532 mg), which was recrystallized from CH_2Cl_2−EtOH to give **8a** (448 mg, 91%), mp 189−190 °C (CH_2Cl_2−EtOH), as a pale-yellow solid: IR ($CHCl_3$) 3456, 3434 cm^{-1}; ^1H NMR δ 2.39 (s, 6H), 4.06 (s, 2H), 4.63 (s, 2H), 5.87 (s, 2H), 6.99−7.09 (m, 3H), 7.21−7.50 (m, 11H), 7.89 (br. s, 1H), 7.93 (s, 1H), 8.11(d, J = 7.9 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H); EI-MS *m*/*z* (relative intensity) 493 (M^+, 27.8), 374 (4.1), 360 (100), 282 (9.7), 269 (76.8), 255 (12.1), 132 (5.8), 118 (90.7), 91 (33.3). Anal. Calcd for $C_{26}H_{17}N_3$: C, 85.16; H, 6.33; N, 8.51. Found: C, 85.08; H, 6.56; N, 8.35.

12-Benzyl-6-(2,6-dimethylbenzyl)staurosporinone (9a). A stirred mixture of **8a** (49.5 mg, 0.1 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), and $Cu(OAc)_2$ (9.2 mg, 0.05 mmol) in toluene (2 mL) was gently refluxed in an oil bath in an atmosphere of CO gas (1 L) containing air (6 mL, 0.5 molar equiv of O_2) delivered from a toy balloon for 12 h. The reaction mixture was cooled to rt and filtered through a thin pad of powdered $MgSO_4$. Toluene was removed on a rotary evaporator. The residue (51.8 mg) was purified by preparative TLC, being developed 3 times with CH_2Cl_2. A fraction with R_f = 0.5−0.6 afforded **9a** as pale-yellow crystals (7.6 mg, 0.015 mmol, 15%) from benzene, mp >258 °C (dec): IR (Nujol) 3252, 1647 cm^{-1}; ^1H NMR δ 2.48 (s, 6H), 4.29 (s, 2H), 4.97 (s, 2H), 5.76 (s, 2H), 7.09−7.51 (m, 14H), 7.71 (d, J = 7.6 Hz, 1H), 7.79 (br, 1H), 9.59 (d, J = 7.6 Hz, 1H); EI-MS *m*/*z* (relative intensity) 519 (M^+, 100), 400 (43.9), 310 (17.7), 119 (23.0), 91 (14.0). Anal. Calcd. for $C_{37}H_{31}N_3O_4$: C, 83.21; H, 5.63; N, 8.09. Found: C, 83.25; H, 5.71; N, 8.06.

The carbonylation under compressed CO gas (20 atm) in an autoclave at 110 °C for 5 h resulted in recovery of **8a**.

12-Benzyl-6-(2,4,6-trimethoxybenzyl)indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole (9b). In a similar manner to the above, 2,4,6-trimethoxybenzylamine **8b** (55.6 mg, 0.1 mmol) was treated with $Pd(OAc)_2$ (1.2 mg, 0.005 mmol) and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) in DMSO (2 mL) in an atmosphere of CO gas (1 L) containing air (6 mL) at 110 °C for 12 h. A crude product (67.2 mg) was purified by preparative TLC (twice with 2% EtOAc−CH_2Cl_2). A fraction with R_f = 0.2 afforded **9b** (29.0 mg, 50%) from EtOAc, mp >207 °C (dec), as pale yellow crystals: IR (Nujol) 3218, 1653 cm^{-1}; ^1H NMR δ 3.86 (s, 3H), 3.88 (s, 6H), 4.45 (s, 2H), 4.97 (s, 2H), 5.75 (s, 2H), 6.21 (s, 2H) 7.16−7.46 (m, 11H), 7.72 (d, J = 7.9 Hz, 1H), 7.80 (br. s, 1H), 9.62 (d, J = 7.3 Hz, 1H); EI-MS *m*/*z* (relative intensity) 581 (M^+, 76.5), 413 (77.7), 401 (47.3), 310 (37.7), 181 (100), 151 (17.9), 121 (21.0), 91 (30.0). Anal. Calcd. for $C_{37}H_{31}N_3O_4$: C, 76.40; H, 5.37; N, 7.22. Found: C, 76.28; H, 5.53; N, 7.08.

Carbonylation of **8b** (55.6 mg) in boiling toluene afforded **9b** (22 mg, 38%).

5-Cyano-11,12-dihydroindolo[2,3-*a*]carbazole (6a). To a stirred suspension of $AlCl_3$ (80 mg, 0.6 mmol) in anisole (1 mL) in an ice bath was added a solution of carbazole **6** (36 mg, 0.096 mmol) in anisole (1 mL). The mixture was stirred at 110 °C for 50 min and worked up similarly to the above. The residue was purified by preparative TLC (5% EtOAc−CH_2Cl_2). A band with R_f = 0 .51−0.58 afforded **6a** (26 mg, 0.092 mmol, 96%), mp >300 °C (CH_2Cl_2−benzene), as pale-yellow crystals: IR (Nujol) 3368, 2220; ^1H NMR (DMSO-d_6) δ 7.28−7.38 (m, 2H), 7.46−7.56 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 8.46 (d, J = 7.9 Hz, 1H), 8.57 (s, 1H), 11.57 (s, 1H), 11.61 (s, 1H); EI-MS *m*/*z* (relative intensity) 281 (M^+, 100). Anal. Calcd for $C_{19}H_{11}N_3$: C, 81.12; H, 3.94; N, 14.94. Found: C, 81.09; H, 4.08; N, 14.97.

Staurosporinone (1). To a stirred suspension of $AlCl_3$ (41 mg, 0.3 mmol) in anisole (1 mL) in an ice bath was added a solution of **9b** (30 mg, 0.05 mmol) in anisole (1 mL). The mixture was stirred at 110 °C for 1 h. The reaction mixture was poured into water and extracted with AcOEt (3 × 10 mL). The organic layer was washed with 5% $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated, and the residue

was purified by preparative TLC (2:1 AcOEt/hexane). A band with R_f = 0.43−0.60 afforded **1** as pale-yellow crystals (16 mg, 0.05 mmol, quantitative), mp > 300 °C (acetone−benzene). Recrystallization from the same solvents afforded an analytical sample, mp > 300 °C (ref 10c, mp > 310 °C; refs 2e and 10b,g,h, mp >310 °C; ref 10a, mp 323−326 °C; ref 10j, mp > 350 °C): IR (Nujol) 3438, 3294, 1648 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.96 (s, 2H), 7.23, 7.31, 7.43, 7.48 (each t, J = 7.3 Hz, each 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.49 (s, 1H), 9.22 (d, J = 7.9 Hz, 1H), 11.32 (s, 1H), 11.49 (s, 1H); EI-MS *m*/*z* (relative intensity) 311 (M^+, 100), 282 (59.4), 255 (20.5), 156 (12.4), 128 (10.2). Anal. Calcd for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50. Found: C, 76.88; H, 4.16; N, 13.44. The NMR data were essentially identical with those obtained previously using the same solvent.[10b,g,h,j] Acetone-D_6 has also been used as solvent.[10c]

A similar debenzylation of **9a** (26 mg, 0.05 mmol) afforded **1** (11 mg, 71%).

6-(2,6-Dimethylbenzyl)staurosporinone (10). To a stirred suspension of $AlCl_3$ (40 mg, 0.3 mmol) in anisole (1 mL) in an ice bath was added a solution of lactam **8a** (27 mg, 0.05 mmol) in anisole (1 mL). The mixture was stirred at 80 °C for 30 min. The reaction mixture was poured into water (20 mL) and extracted with AcOEt (3 × 10 mL). The extracts were washed with 5% $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by preparative TLC (3% MeOH−CH_2Cl_2). A band with R_f = 0.5 afforded **10** as colorless crystals (23 mg, 0.05 mmol, 99%), mp >300 °C. Recrystallization from acetone−benzene afforded an analytical sample, mp > 300 °C: IR (Nujol) 3290, 1638 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.46 (s, 6H), 4.69 (s, 2H), 4.97 (s, 2H), 7.09−7.19 (m, 3H), 7.25 (t, J = 7.3 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.73 (d, J = 5.9 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 9.30 (d, J = 7.9 Hz, 1H), 11.37 (s, 1H), 11.52 (s, 1H); EI-MS *m*/*z* (relative intensity) 429 (M^+, 100), 323 (14.1), 310 (97.8), 282 (23.3), 119 (27.1). Anal. Calcd. for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, 80.88; H, 5.67; N, 9.65.

***N*-Benzyl-2,6-dimethylbenzylamine (11b).** To a stirred solution of benzylamine (109 mg, 1.01 mmol) and 2,6-dimethylbenzaldehyde (146 mg, 1.08 mmol) in CH_2Cl_2 (20 mL) at rt was added Na_2SO_4 (2 g). After 3 h, the solution was separated and concentrated. The oily imine was dissolved in MeOH (2 mL) and treated with $NaBH_4$ (76 mg, 2 mmol) for 2 h. MeOH was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (4 × 20 mL), dried over Na_2SO_4, and subjected to valve-to-valve distillation to give **11b** (211 mg, 87%), bp 150 °C/1.5 mmHg, as a colorless oil: IR (neat) 3318 cm^{-1}; ^1H NMR δ 1.28 (br. s, 1H), 2.34 (s, 6H), 3.75 (s, 2H), 3.88 (s, 2H), 6.97−7.08 (m, 3H), 7.22−7.39 (m, 5H); EI-MS (relative intensity) 225 (M^+, 17.1), 118 (100), 106 (26.7), 91 (44.3). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.09; H, 8.58; N, 6.17.

2-Benzylphthalimidine (12a). A stirred mixture of dibenzylamine (**11a**) (19.7 mg, 0.1 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol), and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) in toluene (2 mL) was gently refluxed under CO gas (1 atm) containing air (6 mL) delivered from a toy balloon for 24 h. The reaction mixture was filtered through a thin pad of powdered $MgSO_4$. The crude product was dissolved in CH_2Cl_2, washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent and crystallization of the residue (20 mg) from MeOH−Et_2O afforded **12a** (15.0 mg, 67%), mp 87−89 °C (MeOH−Et_2O) (ref 43, mp 90−91 °C; ref 44, mp 90−91.5 °C) as pale-yellow crystals. IR, ^1H NMR, and EIMS spectra were identical with the reported data.[43]

2-(2,6-Dimethylbenzyl)phthalimidine (12b). In a similar manner, carbonylation of **11b** (23 mg, 0.1 mmol) afforded **12b**, mp 152−152.5 °C (Et_2O−hexane) as pale-yellow crystals (8.5 mg, 33%); R_f = 0.7 (1:1 EtOAc/hexane): IR (Nujol) 1688 cm^{-1}; ^1H NMR δ 2.38 (s, 6H), 4.05 (s, 2H), 4.89 (s, 2H), 7.04−7.17 (m, 3H), 7.31−7.34 (m, 1H), 7.42−7.52 (m, 2H); EI-MS (relative intensity) 251 (M^+, 57.3), 145 (31.8), 118 (100), 91 (27.0). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.09; H, 8.58; N, 6.17.

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(43) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684−1687.
(44) Rivett, D. E.; Wilshire, J. F. K. *Org. Prep. Proc.* **1969**, *1*, 263−266.