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SYNTHESIS OF BISINDOLYLMALEIMIDES USING A PALLADIUM CATALYZED CROSS-COUPLING REACTION

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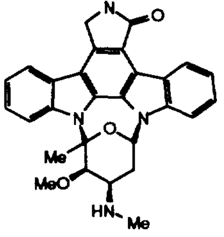
Abstract: Bisindolylmaleimides are known to be potent and selective PKC inhibitors. A new synthesis of this class of compound is reported. The key step is a Suzuki cross-coupling reaction using a readily available indolylmaleimide triflate intermediate.

Staurosporine (**1**) has shown itself to be a potent protein kinase inhibitor and in recent years it has been the focus of intense research synthetically and medicinally.[1] Staurosporine has limited selectivity in vitro among ATP dependent kinases. An antagonist that possessed selectivity for protein kinase C (PKC) could be a therapeutically useful agent. Recent SAR studies have resulted in dramatic improvements in potency and selectivity for PKC over other ATP dependent kinases with bisindolylmaleimides such as **2** (GF 109203X),[2] **3** (Ro 32-0432),[3] and **4** (LY333531).[4] The conformationally restricted analog **3** may be useful in the therapy of autoimmune diseases[5] and **4** is being developed as a candidate for diabetic retinopathy.[6]

As part of our program to develop synthetic methodology that would lead to an array of structurally diverse staurosporine analogs, we envisioned the triflate **8** as a key intermediate that would lend itself to addition-elimination chemistry with various nucleophiles. In addition, it should function as a suitable partner in palladium catalyzed cross-coupling reactions. Herein we report its use in a Suzuki reaction to provide a new synthesis of bisindolylmaleimides.



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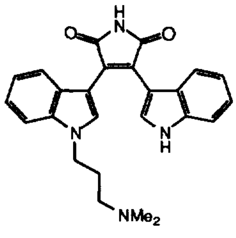

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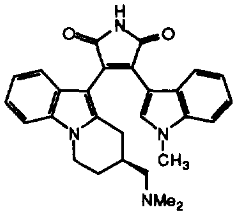

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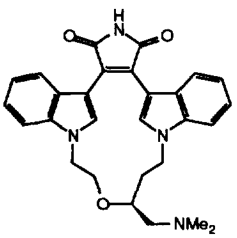

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Commonly used methods of constructing bisindolylmaleimides have employed indolyl Grignard reagents in reaction with dihalomaleimides.[7] The Roche group has reported a synthesis for bisindolylmaleic anhydride followed by mild conversion to the maleimide using hexamethyldisilazane[8] as well as direct construction of the maleimide through an indole-3-acetimidate and indole-3-glyoxylyl chloride.[9] Methodology

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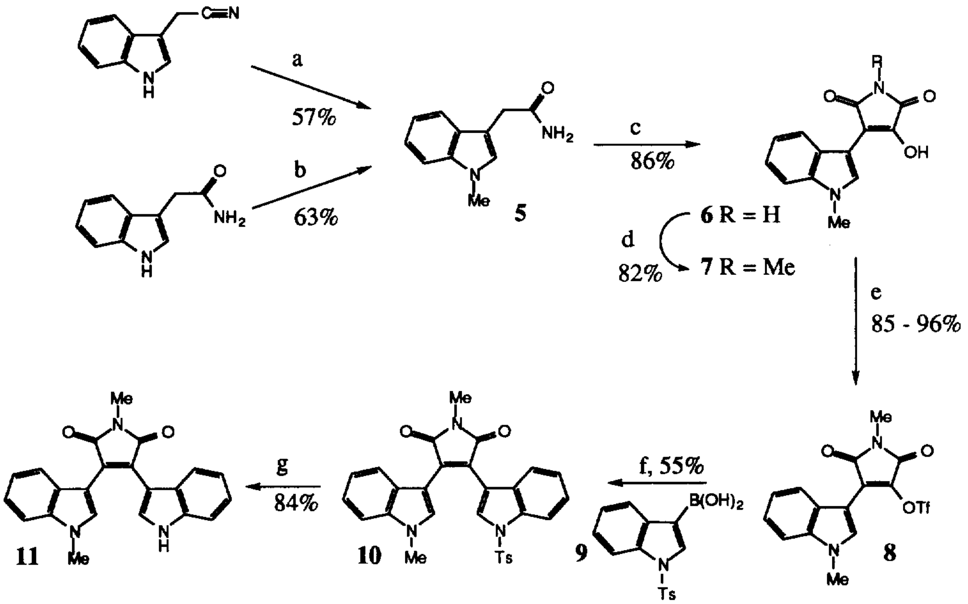
has also been developed using indolylacetate dianions in an oxidative coupling to obtain the bisindolesuccinic acid ester which can be transformed to the bisindolylmaleimide.[10] The proven utility and versatility of the Suzuki reaction[11] would provide an alternative means of entry into this system, allowing for a wide range of structural variation.

N-methylindole-3-acetamide **5** provided efficient access to the triflate **8** (Scheme). Compound **5** was obtained via alkylation of commercially available indole-3-acetamide or by alkylation of indole acetonitrile[12] and subsequent conversion to the amide.[13,14] Using a procedure described by Rooney and coworkers for the synthesis of aryl substituted hydroxymaleimide derivatives, **5** was cyclized in 86% yield with dimethyl oxalate and potassium t-butoxide in DMF to the enol **6**.[15] Selective alkylation of the maleimide was accomplished using 2 equivalents of NaH in DMF to provide **7**. Using standard conditions triflate **8** was obtained in 85–96% as analytically pure material,[16] setting the stage for the crucial Suzuki coupling with an appropriately metalated indole. A recent report by Martin wherein a 3-indole boronic acid **9**[17] was coupled to an alkene triflate lent credence to the feasibility of this approach.



Scheme: (a) i. KOH, MeI, acetone; ii. H_2O_2, K_2CO_3, DMSO; (b) NaH, MeI, DMF; (c) t-BuOK, MeOC(O)C(O)OMe, DMF; (d) NaH (2 equiv), MeI, DMF; (e) TEA, Tf_2O, CH_2Cl_2; (f) Pd_2dba_3-$CHCl_3$, CsF (3 equiv), CsBr (3 equiv), dioxane, 15 °C to rt; (g) K_2CO_3, $MeOH/H_2O$.

Initial attempts utilizing conditions such as $Pd(PPh_3)_4$ with K_3PO_4[18] or 2M $Na_2CO_3/LiCl$[17] provided <5% of the cross-coupled product **10**, together with 3,3'-bisindolyl by-products, *N*-tosylindole, and an intractable mixture of minor products. Under these conditions a large amount of the boronic acid was unreacted with the triflate apparently decomposing under the reaction conditions (dioxane or DME at 65 °C). Recently it has been reported that Suzuki cross-coupling reactions are improved by using phosphine free ligands.[19] In addition it has been observed that fluoride salts can be used to effect boronic acid coupling reactions under conditions that are compatible with base-sensitive functional groups.[20] On the basis of these observations, we found that the Pd_2dba_3 chloroform complex in the presence of cesium fluoride provided the desired bisindolylmaleimide **10** in 55% yield.[21] This combination of catalyst and base allowed the reaction to proceed at room temperature with acceptable conversion of starting material. The primary by-product of the reaction was enol **7**, presumably due to the limited stability of triflate **8**. In our experience the best results were obtained by maintaining the triflate at 15 °C in dioxane when adding the reagents. The tosyl group was subsequently removed with potassium carbonate in methanol/water[22] to give **11** in 84%. Conversion of *N*-methyl bisindolylmaleimides to the biologically active NH compounds has been previously reported.[4,8b]

In summary we have developed a new route for the formation of bisindolylmaleimides via the Suzuki cross-coupling reaction which allows for convenient differentiation between the two indoles. In addition, the triflate intermediate is quickly obtained and offers entry to compounds with a wide range of structural variation. Given the current interest in the biological activity of these compounds this methodology should prove to be useful in further analog synthesis.

Acknowledgments:

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References and Notes:

1. For example: (a) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177. Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555. Vice, S. F.; Bishop, W. R.; McCombie, S. W.; Dao, H.; Frank, E.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1333. Hendricks, R. T.; Sherman, D.; Strulovici, B.; Broka, C. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 67. Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825. Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656. (b) For a recent review of carbazole alkaloids and bisindolylmaleimides: Gribble, G. W.; Berthel, S. J. In *Studies in Natural Products Chemistry*, Atta-Ur-Rahman, Ed.; Elsevier: New York, 1993; Vol 12, pp 365-411.

2. Toullec, D.; Pianetti, P.; Coste, H.; Bellevergue, P.; Grand-Perret, T.; Ajakane, M.; Baudet, V.; Boissin, P.; Boursier, E.; Loriolle, F.; Duhamel, L.; Charon, D.; Kirilovsky, J. *J. Biol. Chem.* **1991**, *266*, 15771.

3. Bit, R. A.; Davis, P. D.; Elliott, L. H.; Harris, W.; Hill, C. H.; Keech, E.; Kumar, H.; Lawton, G.; Maw, A.; Nixon, J. S.; Vesey, D. R.; Wadsworth, J.; Wilkinson, S. E. *J. Med. Chem.* **1993**, *36*, 21.

4. Jirousek, M. R.; Gillig, J. R.; Gonzalez, C. M.; O'Bannon, D.; Heath, W. F.; McDonald III, J. H.; Neel, D. A.; Rito, C. J.; Singh, U.; Stramm, L. E.; Melikian-Badalian, A.; Baevsky, M.; Ballas, L. M.; Hall, S. E.; Winneroski, L. L.; Faul, M. M. *J. Med. Chem.* **1996**, *39*, 2664.

5. Wilkinson, S. E.; Nixon, J. S. *Curr. Pharm. Des.* **1996**, *2*, 596.

6. Ishii, H. ; Jirousek, M. R.; Koya, D.; Takagi, C.; Xia, P.; Clermont, A.; Bursell S. E.; Kern, T. S.; Ballas, L. M.; Heath W. F.; Stramm, L. E.; Feener E. P.; King, G. L. *Science* **1996**, *272*, 728.

7. (a) Brenner, M.; Rexhausen, H.; Steffen, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887. (b) Faul, M. M.; Sullivan, K. A.; Winneroski, L. L. *Synthesis* **1995**, 1511.

8. (a) Davis, P. D.; Bit, R. A.; Hurst, S. A. *Tetrahedron Lett.* **1990**, *31*, 2353. (b) Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201.

9. Bit, R. A.; Crackett, P. H.; Harris, W.; Hill, C. H. *Tetrahedron Lett.* **1993**, *34*, 5623.

10. Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441.

11. For reviews, see: (a) Martin, A. R.; Yang, Y. H. *Acta Chem. Scand.* **1993**, *47*, 221. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419.

12. Procedure adapted from: Kikugawa, Y.; Miyake, Y. *Synthesis* **1981**, 461.

13. Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949.

14. Literature methods for making primary and secondary indole acetamides include amination of the acid chloride or methyl ester. See: (a) Weller, L. E.; Sell, H. M. *J. Org. Chem.* **1958**, *23*, 1776. El-Gendy, A. A.; Osman, A. N.; Khalifa, M. *Pharmazie* **1982**, *37*, 481. (b) Hino, T.; Uehara, H.; Takashima, M.; Kawate, T.; Seki, H.; Hara, R.; Kuramochi, T.; *Nakagawa*, M. *Chem. Pharm. Bull.* **1990**, *38*, 2632.

15. Rooney, C. S.; Randall, W. C.; Streeter, K. B.; Ziegler, C.; Cragoe, E. J.; Schwam, H.; Michelson, S. R.; Williams, H. W. R.; Eichler, E.; Duggan, D. E.; Ulm, E. H.; Noll, R. M. *J. Med. Chem.* **1983**, *26*, 700. Fairly fresh potassium *t*-butoxide was necessary for the reaction to go to completion. The presence of hydroxide ion prevents complete reaction and **5** is difficult to separate from **6**. The reaction worked equally well on secondary amides (obtained from the succinimide ester of indole acetic acid).

16. To a CH_2Cl_2 (40 mL) suspension of the enol (506 mg, 1.97 mmol) under nitrogen at -78 °C was added triethylamine (690 uL, 4.93 mmol, 2.5 equiv) followed by slow addition of trifluoromethanesulfonic anhydride (500 uL, 2.96 mmol, 1.5 equiv). The reaction was stirred for 2 h at -78 °C with the solid material gradually dissolving. The CH_2Cl_2 was removed in vacuo and the resulting residue dissolved in EtOAc (150 mL). The EtOAc was washed with water (4 × 75 mL), brine (2 × 75 mL), dried ($MgSO_4$), and evaporated in vacuo to provide 732 mg (96%) of an orange solid. Sometimes it was necessary to triturate in ether/hexane to get analytically pure material in slightly lower yields. ^{1}H NMR (DMSO-d_6) δ 2.97 (s, 3H); 3.91 (s, 3H), 7.22–7.35 (m, 2H), 7.58 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 8.24 (s, 1H). MS (FD) *m/z* 388 (M^+). EA: Anal. calcd for $C_{15}H_{11}F_3N_2O_5S$: C, 46.40; H, 2.86 N, 7.21. Found: C, 46.65; H, 3.06; N, 7.05.

17. Zheng, Q.; Yang, Y.; Martin A. R. *Heterocycles* **1994**, *37*, 1761.

18. Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

19. Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

20. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

21. An anhydrous dioxane (15 mL) solution of triflate (**8**) (777 mg, 2.0 mmol) under nitrogen was placed in a water bath at 15 °C. Tris(dibenzylideneacetone) dipalladium chloroform complex (80 mg, 4 mol percent), *N*-tosyl-3-indolylboronic acid (693 mg, 2.2 mmol, 1.1 equiv), cesium fluoride (1.00 g, 6.6 mmol, 3 equiv to boronic acid) and cesium bromide (1.40 g, 6.6 mmol) were added and after 10 min the water bath was removed and the reaction allowed to warm to ambient temperature. After 5 h TLC (3 hexane/1 EtOAc) showed approximately 10–20% triflate remaining and so the reaction was allowed to continue for 18 h. The dioxane was removed in vacuo and the resulting residue partitioned between EtOAc (75 mL) and water (50 mL). The layers were separated and the aqueous portion was washed with EtOAc (2 × 50 mL). The combined EtOAc portion was washed with 0.1 N NaOH (2 × 50 mL) (NaOH backwashed with EtOAc), brine (2 × 50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to provide 1.21 g of a crude brown solid. The material was purified by flash chromatography by sequential elution with 9 hexane/1 EtOAc, 5/1, 3/1, 2/1 and 1 hexane/1 EtOAc to provide 559 mg (55%) of a yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.02 (s, 3H), 3.84 (s, 3H), 6.08 (m, 1H), 6.28 (d, J = 8 Hz, 1H), 6.84 (m, 2H), 6.92 (t, J = 8 Hz, 1H), 7.15 (m, 1H), 7.37 (m, 3H), 7.85 (m, 3H), 7.96 (s, 1H), 8.02 (s, 1H). MS (FD) *m/z* 509 (M^+). EA: Anal. calcd for $C_{29}H_{23}N_3O_4S$: C, 68.35; H, 4.55; N, 8.25. Found: C, 68.51; H, 4.60; N, 8.17.

22. Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2812.