A New, Efficient Method for the Synthesis of Bisindolylmaleimides

Margaret M. Faul,* Leonard L. Winneroski, and Christine A. Krumrich

Lilly Research Laboratories, A Division of Eli Lilly and Company, Chemical Process Research and Development Division, Indianapolis, Indiana 46285-4813

Received March 18, 1998

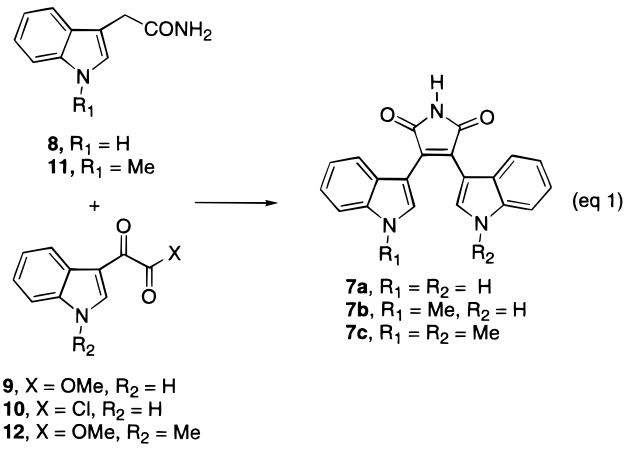
Introduction

Macrocyclic bisindolylmaleimides **1**−**4** have been identified as potent inhibitors of PKCβ and are currently under development for the treatment of diabetic complications (Chart 1).[1] The core structural framework required for the synthesis of **1**−**4** is the bisindolylmaleimide **7**,[2] which has also been employed in the synthesis of indolocarbazoles staurosporine **5**[3] and rebeccamycin **6**.[4] The most widely used method to prepare **7** involves reaction of indolylmagnesium bromide with a 2,3-dihalomaleimide.[5] Using this procedure the symmetrical bisindolylmaleimide **7a** ($R_1 = R_2 = H$), a natural product known as arcyriarubin A was prepared in two steps and 44% yield from 2,3-dichloromaleic anhydride.[6] However, for synthesis of unsymmetrical analogues (R_1 and/or $R_2 \neq H$) a six-step sequence is required, involving initial monoalkylation of indolylmagnesium bromide with the *N*-protected 2,3-dihalomaleimide, indole protection/alkylation followed by a second Grignard reaction, and a hydrolysis/ammonolysis sequence to incorporate the maleimide.[7]

Two alternative approaches to **7** have been developed that do not require maleimide protection. Perkin condensation of indole-3-acetic acid with indolyl-3-glyoxylyl chloride affords, in 24−64% yield, the bisindolylmaleic anhydrides,[8] which are converted into the desired bisindolylmaleimides (R_1, $R_2 \neq H$), upon treatment with an ammonium source.[9] Alternatively, direct access into **7** ($R_1 = H$, $R_2 \neq H$) can be achieved, in 42−75% yield, by condensation of an indolyl-3-glyoxylyl chloride with indole-3-acetimidate ester.[10] Although both of these methods afford access to **7**, the variable yields and the additional chemistry required to prepare the acetimidate or perform the ammonolysis reaction limited their potential in the development of a practical approach to **1**−**6**. Therefore to prepare this class of compounds we sought to identify a new, more efficient route that would afford high yields of product, employ readily available starting materials, and tolerate the variety of functional groups present in **1**−**6**. This paper describes a new, highly efficient method to prepare symmetrical and unsymmetrical bisindolylmaleimides **7** in 84−100% yield by reaction of the readily available indole-3-acetamides with methyl indolyl-3-glyoxylates using a 1.0 M solution of KOBu^t in THF. The reaction is successful in the presence of a variety of functional groups (H, alkyl, OH, NMe_2, OTr). The mechanism of this reaction is discussed.

Results and Discussion

It has been reported in the literature that 4-substituted 3-hydroxymaleimides can be prepared by reaction of a 2-substituted acetamide derivative with diethyl oxalate in strong base (KOBu^t) using a variety of solvents (DMF, EtOH, and benzene).[11] Encouraged by this report, we chose to examine a synthesis of bisindolylmaleimide **7a** by condensation of indole-3-acetamide **8**[12] with methyl indolyl-3-glyoxylate **9** using a variety of different bases and solvents (eq 1, Table 1). Upon condensation of **8** with



9 using KOBu^t in DMF, a 36% yield of **7a** was obtained (Table 1, entry 1). Use of NaH provided **7a** in 31% yield (Table 1, entry 2). Changing the solvent to THF, with NaH as base, improved the yield to 56% (Table 1, entry 3). However, when a 1.0 M solution of KOBu^t in THF was employed, **7a** was obtained in quantitative yield (Table 1, entry 4). The reaction was initially performed

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

(2) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A.; Sullivan, K. A.; Gillig, J. R.; Neel, D. A.; Rito, C. J.; Jirousek M. R. *J. Org. Chem.* **1998**, *63*, 1961.

(3) (a) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552. (b) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782.

(4) (a) Nettleton, D. E.; Doyle, T. W.; Kirshnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4011. (b) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015. (c) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.

(5) Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887.

(6) Faul, M. M.; Sullivan, K. A.; Winneroski, L. L. *Synthesis* **1995**, 1511.

(7) (a) Mayer, G.; Wille, G.; Steglich, W. *Tetrahedron Lett.* **1996**, *37*, 4483. (b) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Morishima, H. *Tetrahedron* **1996**, *52*, 8099.

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

(9) Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201.

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

(11) (a) Rooney, C. S.; Randall, W. C.; Streeter, K. B.; Ziegler, C.; Cragoe, E. J. Jr.; Schwam, H.; Michelson, S. R.; Williams, H. W. R.; Eichler, E.; Duiggan, D. E.; Ulm, E. H.; Noll, R. M. *J. Med. Chem.* **1983**, *26*, 700. (b) Neel, D. A.; Jirousek, M. R.; McDonald, J. H. III. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 47.

(12) Indole-3-acetamide can be purchased from the Aldrich Chemical Co. It is also readily prepared from indole-3-acetic acid or indole-3-acetonitrile by standard methods.

S0022-3263(98)00513-1 CCC: $15.00
Published on Web 07/24/1998

Chart 1

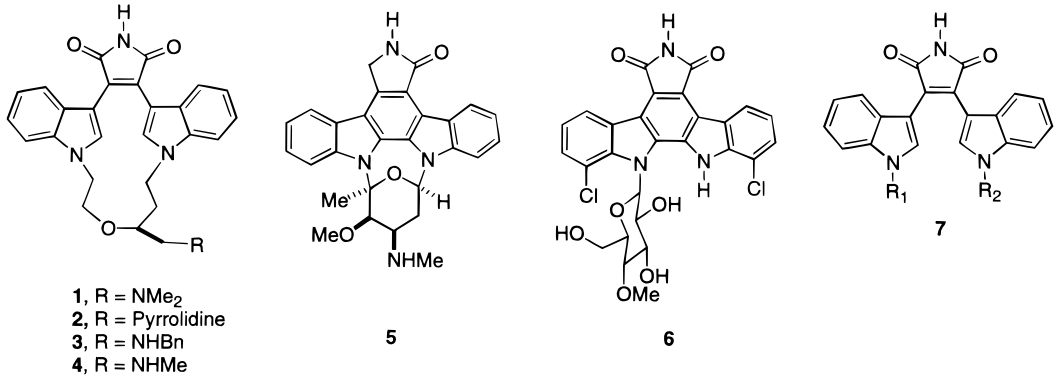


Table 1. Effect of Solvent, Base, and Addition Mode on Synthesis of 7a from 8 and 9 (eq 1)

entry	solvent	base	**9** (equiv)	addn mode[a]	yield (%)[b]
1	DMF	KOBu^t	1.1	B	36
2	DMF	NaH	1.2	B	31
3	THF	NaH	1.2	B	56
4	THF	KOBu^t	1.2	B	100
5	THF	KOBu^t	1.1	A	100

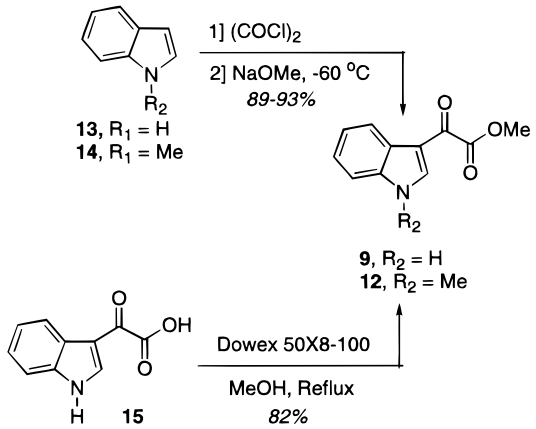
[a] Addition mode A = base added to reagents; B = reagents added to base. [b] Chromatography yields.

by addition of **8** and **9** to the KOBu^t solution at 0 °C (method B); however for ease of reaction, addition of the 1.0 M KOBu^t solution to a slurry of **8** and **9** in THF at 0 °C (method A) was preferred (Table 1, entries 4 and 5). All reactions were quenched with concentrated HCl vide infra and **7a** isolated either directly by crystallization from EtOH or by chromatographic purification.

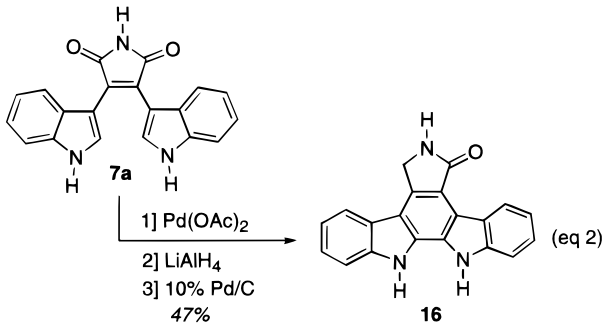
Since indolyl-3-glyoxylyl chlorides were successfully employed in the Perkin condensation, a comparison of indolyl-3-glyoxylyl ester **9** and indolyl-3-glyoxylyl chloride **10** in the synthesis of **7a** from **8** using 1.0 M KOBu^t in THF was performed. Although **7a** was prepared in 100% yield from **8** and **9**, the yield dropped to 68% when **10** was employed. Interestingly, Steglich has reported a synthesis of **7a** albeit in 11% yield by condensation of **8** with **10**, although the reaction conditions employed were not described.[13] Similarly, reaction of *N*-methylindole-3-acetamide **11** with **9** afforded a 92% yield of **7b** (eq 1), while the yield using **10** as the coupling partner was only 76%. In addition to affording higher yields in the condensation reaction indolyl-3-glyoxylyl esters are more stable than the corresponding indolyl-3-glyoxylyl chlorides and can be stored at room temperature for extended periods of time. This stability also means that they can be analyzed by HPLC facilitating monitoring of the reaction. In addition, substitution on the glyoxylyl ester was also tolerated and condensation of methyl (1-methylindolyl)-3-glyoxylate **12**[14] with **8** or **11** afforded an alternative approach to **7b** in 87% yield and the bismethylated bisindolylmaleimide **7c** in 99% yield.

Methyl indolyl-3-glyoxylyl esters **9** and **12** were prepared in >82% yield either by (i) treatment of indole **13** or **14** in Et_2O with oxalyl chloride, followed by sodium methoxide (25 wt % solution in MeOH) at low temperature (<60 °C),[15] or (ii) by refluxing the 3-indole glyoxylic acid **15** in MeOH with a Dowex 50X8100 ion-exchange resin (Scheme 1).

Scheme 1



Bisindolylmaleimide **7a** has been converted into the staurosporine aglycon **16** in 47% yield by a three-step oxidative cyclization/reduction sequence (eq 2).[16] Although previous syntheses of **16** have been limited by low yields and multiple steps,[17] this new high-yielding synthesis of **7a** will provide valuable access into this important indolocarbazole framework.



(13) Steglich, W. *Pure. Appl. Chem.* **1989**, *61*, 281.

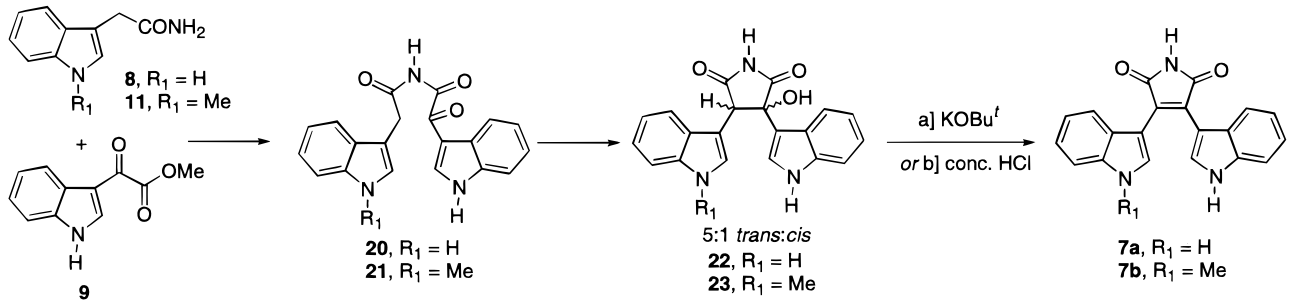
(14) Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.

(15) At higher temperatures a side reaction resulting in formation of the 3-indoleglyoxylic acid was observed.

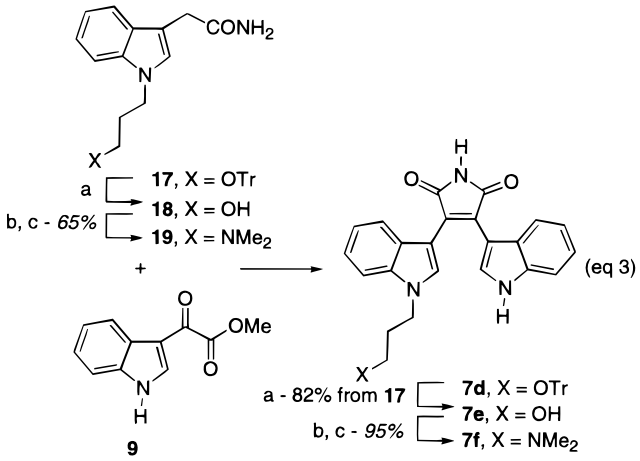
(16) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361.

(17) (a) Sarstedt, B.; Winterfeldt, F. *Heterocycles* **1983**, *20*, 469 (seven steps, 2% yield). (b) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. I* **1990**, 2475 (10 steps, 11% yield). (c) 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 (8% for last four steps, yield of coupling not reported). (d) Fabre, S.; Prudhomme, M.; Rapp, M. *Biomed. Chem. Lett.* **1992**, *2*, 449 (21% yield from degradation of rebeccamycin over three steps). (e) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105 (23% yield, five steps). (f) Reference 16 (14%, four steps from 2,3-dibromomaleimide).

Scheme 2



The sensitivity of functional groups to this chemistry was explored by examining a synthesis of unsymmetrical bisindolylmaleimide **7f**, a potent inhibitor of protein kinase C. A synthesis of this compound in five steps and 19% yield from 2,3-dichloromaleic anhydride, using the indole Grignard chemistry previously described, has been reported.[16c] We decided to examine a synthesis of **7f** by condensation of the *N*-substituted indole-3-acetamides **17**−**19** with methyl indolyl-3-glyoxylate **9** (eq 3). Reac-



(eq 3)

tion of *N*-trityloxypropylindole-3-acetamide **17** with **9** using 3.0 equiv of 1.0 M KOBu^t in THF afforded **7d** in 91% yield. Although **7d** can be deprotected to afford alcohol **7e**, it was found that **7e** could also be obtained directly, in quantitative yield, by condensation of **9** with *N*-hydroxypropylindole-3-acetamide **18** using 4.0 equiv of 1.0 M KOBu^t in THF. Bisindolylmaleimide **7e** can be converted into the desired bisindolylmaleimide **7f** by mesylation/amine displacement or **7f** can be prepared directly in 84% yield by condensation of *N*-dimethylaminopropylindole-3-acetamide **19**[18] with **9** using 4.0 equiv of 1.0 M KOBu^t in THF. Therefore, using this new methodology three alternative approaches to **7f** have been developed. The optimum synthesis affords **7f** in six steps and 51% overall yield from indole-3-acetamide **8** and indole **13** via **17**.

As described, these reactions were performed by addition of the 1.0 M solution of KOBu^t in THF into a pale yellow slurry of indole-3-acetamide and indole-3-glyoxylyl ester. During the addition of base, the reaction proceeded through a series of notable color changes to afford the final red solution of bisindolylmaleimide. Analysis of the reaction of **8** with **9** by HPLC indicated that three distinct intermediates were formed (Scheme 2). These intermediates were isolated and characterized. The first intermediate, which was short-lived (<5 min), was the tricarbonyl compound **20**.[19] This cyclized rapidly via an intramolecular Perkin type condensation to hydroxy imide **22**, generated as a 5:1 trans:cis isomeric mixture. The rate of dehydration of **22**, believed to be the rate-determining step, was found to be dependent on substitution of the indole-3-acetamide only and not the substitution of the indolyl glyoxylate. For example, on condensation of **8** and **9** using 3.0 equiv of 1.0 M KOBu^t in THF, dehydration of **22** in situ to bisindolylmaleimide **7a** was slow, giving only 13% of product after 3 h at room temperature. However, when *N*-methylindole-3-acetamide **11** was employed, under identical reaction conditions, dehydration of **23** was faster, affording 77% of **7b** after 3 h. For both hydroxy imides **22** and **23** dehydration can be enhanced either (i) by addition of concentrated HCl which facilitates dehydration by an E1 process or (ii) by use of excess base (5−10 equiv) causing dehydration via an E2 or E1cB mechanism. The latter is particularly important when acid sensitive functionality is present in either indole fragment.

In summary we have reported a new, efficient, and very general method to prepare symmetrical and unsymmetrical bisindolylmaleimides in 84−100% yield by condensation of indole-3-acetamides and methyl indole-3-glyoxylates using a 1.0 M solution of KOBu^t in THF. The reaction can tolerate a variety of functional groups (H, alkyl, OH, OTr, and NMe_2). Application of this methodology to the synthesis of macrocyclic bisindolylmaleimides **1**−**4**, staurosporne **5**, rebeccamycin **6**, and other members of the bisindolylmaleimide family are under active investigation and will be reported in due course.

Experimental Section

General. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in DMSO-d_6 unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral and combustion analyses were performed by the Eli Lilly and Co. Physical Chemistry Department.

Methyl Indolyl-3-glyoxylate (9). Preparation under basic conditions: to a solution of indole **13** (2.00 g, 17.1 mmol) in Et_2O (20 mL) at 0−5 °C was added dropwise oxalyl chloride (1.50 mL, 17.2 mmol). The resultant yellow slurry was stirred in an ice bath for 30 min and then cooled to −65 °C. A 25 wt % solution of sodium methoxide in MeOH (7.80 mL, 34.1 mmol) was added to this slurry, keeping the temperature below −60 °C. The reaction was allowed to warm to room temperature and quenched

(18) *N*-Dimethylaminopropylindole-3-acetamide **19** can be prepared in one step (approximately 60% yield) by alkylation of indole-3-acetamide using NaH in DMF; however, it was very difficult to purify.

(19) Isolated from the reaction by addition of 1.0 equiv of KOBu^t in THF followed by rapid quench with concentrated HCl (37%).

by addition of water (10 mL). A solid, which precipitated out of solution, was isolated by filtration and dried under vacuum at room temperature to give 3.21 g (93%) of **9**.

Preparation under acidic conditions: a 100 mL round-bottom flask, fitted with a Dean−Stark apparatus containing 4 Å molecular sieves, was charged with 3-indoleglyoxylic acid **15** (1.00 g, 5.29 mmol), anhydrous MeOH (40 mL), and Dowex 50X8-100 ion-exchange resin (1.00 g). After 1 h at reflux the reaction was cooled to room temperature. Acetone (20 mL) was added, and the reaction was reheated to dissolve the product. The resin was removed by filtration and the product crystallized from 20 mL of MeOH (0 °C) to afford 880 mg (82%) of **9**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.39 (bs, 1H), 8.41 (s, 1H), 8.16−8.10 (m, 1H), 7.55−7.49 (m, 1H), 7.29−7.21 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 179.5, 164.8, 139.1, 137.5, 126.3, 124.6, 123.6, 121.9, 113.5, 113.2, 53.2; IR (KBr) ν 3215, 1732 cm^{-1}; UV (EtOH) λ 324 nm (ϵ 9582), 267 (ϵ 9399), 255 nm (ϵ 9582); MS (FD) m/z 203 (M$^+$, 100%). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.93; H, 4.25; N, 7.03.

Methyl (1-Methylindolyl-3)-glyoxylate (12). To a solution of 1-methylindole **14** (2.00 g, 15.2 mmol) in Et_2O (20 mL) at 0−5 °C was added dropwise oxalyl chloride (1.30 mL, 14.9 mmol). The resultant yellow slurry was stirred in an ice bath for 30 min and then cooled to −65 °C. A 25 wt % solution of sodium methoxide in MeOH (7.0 mL, 30.6 mmol) was added to this slurry keeping the temperature below −60 °C. The reaction was allowed to warm to room temperature and quenched by addition of water (10 mL). The solid, which precipitated out of solution, was isolated by filtration and dried under vacuum at room temperature to give 2.93 g (89%) of **12**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.16−8.13 (m, 1H), 7.60−7.57 (m, 1H), 7.36−7.26 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.7, 164.6, 142.2, 138.1, 126.6, 124.5, 123.9, 121.9, 112.0, 111.8, 53.1, 34.1; IR (KBr) ν 1728 cm^{-1}; UV (EtOH) λ 327 nm (ϵ 10586), 260 nm (ϵ 10603); MS (FD) m/z 217 (M$^+$, 100%). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.29; H, 5.39; N, 6.65.

1-Methylindole-3-acetamide (11). To a suspension of NaH (3.33 g, 83.3 mmol, 60% mineral oil dispersion) in DMF (20 mL) was added dropwise a solution of 3-indolylacetonitrile (10.0 g, 64.0 mmol) in DMF (50 mL). The reaction was stirred at room temperature for 30 min and then cooled to 0−5 °C. A solution of methyl iodide (13.6 g, 95.8 mmol) in DMF (30 mL) was added dropwise. The reaction was stirred at room temperature for 3 h and then quenched with EtOAc (300 mL), washed with aqueous 0.5 N HCl (400 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 16.3 g (100%) of 1-methyl 3-indolylacetonitrile that was carried on without purification. To a solution of crude 1-methylindole-3-acetonitrile (16.3 g, 95.0 mmol) and tetrabutylammonium bromide (4.13 g, 12.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added a 30% aqueous solution of hydrogen peroxide (33 mL) followed by an aqueous 20 wt % solution of NaOH (26 mL). The reaction was stirred at room temperature overnight, diluted with CH_2Cl_2 (650 mL), and washed with aqueous 1 N HCl (500 mL) and water (500 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give a thick slurry to which was added hexanes (100 mL). Filtration using 1:1 CH_2Cl_2:hexanes (100 mL) as a rinse afforded 8.45 g (70%) of **11**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (d, 1H, J = 7.78 Hz), 7.32 (d, 1H, J = 8.21 Hz), 7.27 (bs, 1H), 7.11−7.05 (m, 2H), 6.95 (t, 1H, J = 7.40 Hz), 6.79 (bs, 1H), 3.68 (s, 3H), 3.4 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 137.5, 129.1, 128.6, 122.0, 119.9, 119.3, 110.4, 109.4, 22.2, 33.2; IR (KBr) ν 3436, 3175, 1624 cm^{-1}; UV (EtOH) λ 287 nm (ϵ 5853), 223 nm (ϵ 32896); MS (FD) m/z 188 (M$^+$, 100%). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.02; H, 6.17; N, 14.99.

General Procedure for the Preparation of Bisindolylmaleimides. To a suspension of the indole-3-acetamide and methyl indolyl-3-glyoxylate in THF at 0 °C was added 1.0 M KOBu^t in THF. The reaction was allowed to come to room temperature and stirred for 3 h. The reaction was quenched (for conditions see individual examples), extracted, and purified by flash chromatography.

3,4-(3-Indolyl)-1*H*-pyrrole-2,5-dione (7a). The general procedure was followed using **8** (1.00 g, 5.74 mmol) and **9** (1.28 g, 6.30 mmol) in THF (10 mL), with 1.0 M KOBu^t (17.2 mL, 17.2 mmol). The reaction was quenched with concentrated HCl (37%, 8 mL) and diluted with EtOAc (125 mL), and the organic layers were washed with water (2 × 100 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. Purification was achieved using a gradient of 2:1 to 1:1 hexanes:EtOAc to give 2.04 g (100%) of **7a** as dark red crystals. Crude 3,4-(3-indolyl)-1*H*-pyrrole-2,5-dione can also be crystallized directly from the reaction using EtOH to give a stiochiometric ethanol monosolvate in high purity (>99%) and yield (88%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (s, 2H), 10.9 (s, 1H), 7.70 (s, 1H), 7.69 (s, 1H), 7.33 (d, 2H, J = 8.07 Hz), 6.94 (t, 2H, J = 7.34 Hz), 6.77 (d, 2H, J = 8.00 Hz), 6.59 (t, 2H, J = 7.72 Hz), 4.33 (t, 1H, J = 5.04 Hz), 3.45−3.37 (m, 2H), 1.02 (t, 3H, J = 7.00 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 135.6, 128.7, 127.4, 125.1, 121.2, 120.5, 118.9, 111.3, 105.2, 30.2, 18.1; IR (KBr) ν 3395, 3353, 1701 cm^{-1}; UV (EtOH) λ 464 nm (ϵ 8443), 376 nm (ϵ 5591), 277 nm (ϵ 12176); MS (FD) m/z 327 (M$^+$, 100%). Anal. Calcd for the ethanol solvate $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.97; H, 5.22; N, 11.12.

3-[(1-Methyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione (7b). From 1-methyl indole-3-acetamide **11**: the general procedure was followed using **11** (1.00 g, 5.31 mmol) and **9** (1.30 g, 6.40 mmol) in THF (10 mL) with 1.0 M KOBu^t (15.9 mL, 15.9 mmol). The reaction was quenched with concentrated HCl (37%, 8 mL) and diluted with EtOAc (150 mL), and the organic layer was washed with water (100 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. Purification was achieved using a gradient of 2:1 to 1:1 hexanes:acetone to give 1.66 g (92%) of **7b**.

From methyl (1-methylindolyl-3)-glyoxylate **12**: the general procedure was followed using **8** (1.00 g, 5.74 mmol) and **12** (1.50 g, 6.91 mmol) in THF (10 mL), with 1.0 M KOBu^t (17.2 mL, 17.2 mmol). The reaction was quenched with concentrated HCl (37%, 8 mL) and diluted with EtOAc (150 mL) and the organic layer was washed with water (100 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. Purification was achieved using a gradient of 2:1 to 1:1 hexanes:acetone to give 1.71 g (87%) of **7b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (s, 1H, NH), 10.9 (s, 1H, NH), 7.79 (s, 1H), 7.69 (d, 1H, J = 2.55 Hz), 7.38 (d, 1H, J = 8.19 Hz), 7.34 (d, 1H, J = 8.11 Hz), 6.97 (qn, 2H), 6.81 (d, 1H, J = 7.98), 6.69 (d, 1H, J = 7.87), 6.63−6.57 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 137.9, 137.3, 134.4, 130.4, 128.8, 128.7, 127.1, 126.9, 123.0, 122.9, 122.5, 122.3, 120.9, 120.6, 113.1, 111.4, 107.0, 106.1, 34.2; IR (KBr) ν 3347, 3190, 1754, 1691 cm^{-1}; UV (EtOH) λ 466 nm (ϵ 8415), 376 nm (ϵ 5513), 278 nm (ϵ 10733); MS (FD) m/z 341 (M$^+$, 100%). Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.31; H, 4.57; N, 12.27.

3,4-[(1-Methyl)-3-indolyl]-1*H*-pyrrole-2,5-dione (7c). The general procedure was followed using **11** (1.00 g, 5.31 mmol) and **12** (1.38 g, 6.35 mmol) in THF (10 mL), with 1.0 M KOBu^t (15.9 mL, 15.9 mmol). The reaction was quenched with 1 N HCl (25 mL). The product precipitated out of solution and was isolated by filtration after 15 min to give 1.88 g (99%) of **7c**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 7.79 (s, 2H), 7.41 (d, 2H, J = 8.22 Hz), 7.02 (t, 2H, J = 7.06 Hz), 6.74 (d, 2H, J = 7.95), 6.63 (t, 2H, J = 7.54 Hz), 3.84 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 136.4, 132.9, 126.9, 125.8, 121.6, 121.0, 119.4, 109.9, 104.6, 32.8; IR (KBr) ν 3411, 3127, 3058, 1710 cm^{-1}; UV (EtOH) λ 470 nm (ϵ 6219), 376 nm (ϵ 3991), 283 nm (ϵ 7385); MS (FD) m/z 355 (M$^+$, 100%). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.25; H, 5.03; N, 11.55.

3-[1-(3-*O*′-Triphenylmethylpropyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione (7d). The general procedure was followed using **17** (1.00 g, 2.10 mmol) and **9** (0.51 g, 2.51 mmol) in THF (10 mL), with 1.0 M KOBu^t (6.30 mL, 6.30 mmol). The reaction was diluted with EtOAc (125 mL), washed with water (100 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. Purification was achieved using 1:1 hexanes:acetone to give 1.20 g (91%) of **7d** as a foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (bs, 1H), 10.87 (bs, 1H), 7.61 (d, 1H, J = 2.67 Hz), 7.50 (s, 1H), 7.37−7.15 (m, 17H), 6.91 (q, 2H, J = 8.15 Hz), 6.73 (d, 1H, J = 7.98 Hz), 6.61−6.55 (m, 2H), 6.42 (t, 1H, J = 7.75 Hz), 4.30 (t, 2H, J = 6.42 Hz), 2.93 (t, 2H, J = 5.62 Hz), 1.94−1.91 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 143.8, 135.9, 135.5, 131.9, 129.0, 128.1, 127.8, 127.6, 127.1,

126.9, 125.8, 125.1, 121.5, 121.4, 121.2, 121.0, 119.4, 119.1, 111.6, 110.0, 105.5, 104.8, 86.0, 59.8, 42.7, 29.8; IR (KBr) ν 3385, 3054, 1757, 1701 cm^{-1}; UV (EtOH) λ 465 nm (ϵ 7597), 377 nm (ϵ 4916), 278 nm (ϵ 9971); HRMS calcd for $C_{42}H_{33}N_3O_3$ 627.2522, found 627.2528.

3-[1-(3-Hydroxypropyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione (7e). From 1-(3-*O*′-triphenylmethylpropyl)indole-3-acetamide **17**: the general procedure was followed using **17** (1.00 g, 2.10 mmol) and **9** (510 mg, 2.51 mmol) in THF (10 mL), with 1.0 M KOBu^t (6.30 mL, 6.30 mmol). The reaction was quenched with concentrated HCl (37%, 8 mL), heated to reflux for 1 h to detritylate the alcohol, and diluted with EtOAc (125 mL). The organic layer was washed with water (100 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. Purification was achieved using 1:1 hexanes:acetone to give 660 mg (82%) of **7e**.

From 1-(3-hydroxypropyl)-indole-3-acetamide **18**: the general procedure was followed using **18** (1.56 g, 6.71 mmol) and **9** (2.73 g, 13.4 mmol) in THF (15 mL), with 1.0 M KOBu^t (26.9 mL, 26.9 mmol). The reaction was quenched with concentrated HCl (37%, 10 mL) and diluted with EtOAc (300 mL), and the organic layer was washed with water (2 × 200 mL) and saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$), and filtered. Purification was achieved using a gradient of 2:1 to 1:1 hexanes:acetone to give 2.55 g (100%) of **7e** as a foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (bs, 1H), 10.86 (bs, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 7.41 (d, 1H, J = 8.24 Hz), 7.31 (d, 1H, J = 8.11 Hz), 6.94 (qn, 2H), 6.78 (d, 1H, J = 7.91 Hz), 6.69 (d, 1H, J = 8.00 Hz), 6.63−6.52 (m, 2H), 4.58 (t, 1H, J = 4.95 Hz), 4.23 (t, 2H, J = 6.73 Hz), 3.35−3.26 (m, 2H), 1.81 (t, 2H, J = 6.35 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.0, 172.9, 136.0, 135.8, 132.2, 132.0, 129.2, 128.0, 127.2, 126.1, 125.3, 121.6, 121.2, 121.0, 119.5, 119.3, 111.8, 110.2, 105.6, 105.0, 42.8, 32.8, 29.7; IR (KBr) ν 3502, 3180, 3051, 1751, 1693, 1528 cm^{-1}; UV (EtOH) λ 466 nm (ϵ 8147), 378 nm (ϵ 5382), 278 nm (ϵ 10364); HRMS calcd for $C_{23}H_{19}N_3O_3$ 386.1505, found 386.1501.

3-[1-(3-Dimethylaminopropyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione (7f). From 1-(dimethylaminopropyl)-indole-3-acetamide **19**: the general procedure was followed using **19** (600 mg, 2.31 mmol) and **9** (940 mg, 4.63 mmol) in THF (10 mL), with 1.0 M KOBu^t (9.30 mL, 9.30 mmol). The reaction was diluted with EtOAc (100 mL) and the organic layer washed with water (2 × 75 mL) and saturated aqueous sodium chloride (25 mL), dried ($MgSO_4$), and filtered. The product was crystallized directly after workup with acetone (8 mL) to give 0.80 g (84%) of **7f**.

From 3-[1-(3-hydroxypropyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione (**7e**): a suspension of **7e** (41.8 g, 109 mmol) in CH_2Cl_2 (1.20 L) was treated with pyridine (26.3 mL, 326 mmol) and methanesulfonic anhydride (22.7 g, 130 mmol) and stirred for 2.5 h at room temperature. The reaction was then quenched using aqueous 0.1 N HCl (3.26 L), and the organic layer was washed with water (1500 mL) and saturated aqueous sodium chloride (500 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 50.0 g (99%) of 3-[1-(methanesulfonylpropyl)-3-indolyl]-4-(3-indolyl)-1*H*-pyrrole-2,5-dione that was used directly: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (bs, 1H), 10.88 (bs, 1H), 7.72 (d, 1H, J = 2.70 Hz), 7.71 (s, 1H), 7.44 (d, 1H, J = 8.25 Hz), 7.32 (d, 1H, J = 8.12 Hz), 6.99 (t, 1H, J = 7.63 Hz), 6.92 (t, 1H, J = 7.46 Hz), 6.81 (d, 1H, J = 7.98 Hz), 6.68−6.54 (m, 3H), 4.29 (t, 2H, J = 6.75 Hz), 4.10 (t, 2H, J = 6.09 Hz), 3.11 (s, 3H), 2.09 (t, 2H, J = 6.41 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 135.9, 135.6, 131.6, 129.2, 128.2, 126.8, 126.0, 125.1, 121.8, 121.6, 121.2, 120.8, 119.6, 119.2, 111.7, 110.0, 105.4, 105.3, 67.3, 42.0, 36.5, 29.2; IR (KBr) ν 3469, 1760, 1717, 1618, 1392, 1176 cm^{-1}; UV (EtOH) λ 462 nm (ϵ 7567), 379 nm (ϵ 5211), 279 nm (ϵ 11428), 207 nm (ϵ 49965); HRMS calcd for $C_{24}H_{21}N_3O_5S$ 463.1202, found 463.1191.

A suspension of mesylate (70.4 g, 152 mmol) in THF (1.02 L) was treated with a 40% aqueous solution of dimethylamine (423 mL, 3.75 mol), and the solids were dissolved immediately to give a solution which was stirred at room temperature for 16 h. The reaction was diluted with CH_2Cl_2 (1.50 L), and the organic layer was washed with water (2 × 1.00 mL). The solvent was removed in vacuo to give 60.0 g (96%) of **7f**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (bs, 1H), 10.88 (s, 1H), 7.75 (d, 1H, J = 2.58 Hz), 7.66 (s, 1H), 7.37 (d, 1H, J = 8.22 Hz), 7.16 (d, 1H, J = 8.12 Hz), 7.01−6.90 (m, 2H), 6.83 (d, 1H, J = 7.96 Hz), 6.69−6.61 (m, 2H), 6.54 (t, 1H, J = 7.54 Hz), 4.21 (t, 2H, J = 6.48 Hz), 2.06−2.03 (bs, 8H), 1.81−1.77 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.1, 173.0, 136.0, 135.8, 132.0, 129.3, 127.9, 127.1, 126.1, 125.2, 121.7, 121.6, 121.2, 120.9, 119.5, 119.2, 111.8, 110.1, 105.6, 105.0, 45.1, 43.6, 30.7, 27.5; IR (KBr) ν 3394, 1701 cm^{-1}; UV (EtOH) λ 466 nm (ϵ 4085), 378 nm (ϵ 2640), 347 nm (ϵ 1831), 277 nm (ϵ 5376); HRMS calcd for $C_{25}H_{25}N_4O_2$ 413.1978, found 413.1975.

***N*-(1*H*-Indol-3-ylacetyl)-α-oxo-1*H*-indole-3-acetamide (20).** A solution of **8** (1.00 g, 5.74 mmol) and **9** (1.28 g, 6.30 mmol) in THF (10 mL) was cooled to 0 °C under N_2, treated with 1.0 M KOBu^t (11.5 mL, 11.5 mmol), and then quenched immediately with concentrated HCl (8 mL). The reaction was worked up extractively using EtOAc and water, and the mixture was purified by chromatography using a gradient of 2:1 to 1:1 hexanes:acetone to give 0.25 g (13%) of the major HPLC product identified as **20** (R_f = 0.46, 1:1 hexanes:acetone): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.28 (bs, 1H), 12.27 (bs, 1H), 11.38 (bs, 1H), 8.29 (d, 1H, J = 2.82 Hz), 8.08 (d, 1H, J = 6.74 Hz), 7.51−7.46 (m, 2H), 7.32 (d, 1H, J = 8.04 Hz), 7.27−7.21 (m, 3H), 7.05 (t, 1H, J = 7.29 Hz), 6.95 (t, 1H, J = 7.35 Hz), 3.90 (s, 2H); ^{13}C (75 MHz, DMSO-d_6) δ 181.6, 171.3, 137.2, 136.6, 136.0, 127.2, 125.5, 124.3, 123.5, 122.5, 121.06, 120.9, 118.5, 118.4, 112.5, 111.7, 111.4, 106.6, 33.3; IR (KBr) ν 3348, 3217, 3058, 1762 cm^{-1}; MS (FAB) calcd for $C_{20}H_{15}N_3O_3$ 345, found [M + H]$^+$ of m/z 346 (100%).

(3*R*-*trans*)-3-Hydroxy-3,4-di-1*H*-indol-3-yl-2,5-pyrrolidinedione and (3*S*-*cis*)-3-Hydroxy-3,4-di-1*H*-indol-3-yl-2,5-pyrrolidinedione (22). A solution of **8** (1.00 g, 5.74 mmol) and **9** (1.28 g, 6.30 mmol) in THF (10 mL) was cooled to 0 °C under N_2, treated with 1.0 M KOBu^t (31.6 mL, 31.6 mmol), and then quenched with water after 15 min. The reaction was worked up extractively using EtOAc and water, and the mixture was purified by chromatography using CH_2Cl_2 treated with 0−5% MeOH to give 0.42 g (21%) of the major HPLC products[20] identified as **22** (R_f = 0.22, 9:1 CH_2Cl_2:MeOH). The diastereomers **22** were separated by preparative HPLC using a 25 cm Kromsil C18 (13 μm) DT0048 column with 40% ACN in a water mobile phase, 1.0 mL/min, 240 nm at ambient temperature to give 0.11 g of the major diastereomer and 0.02 g of the minor diastereomer as determined by HPLC. **22** (major-trans): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 11.06 (d, 1H, J = 2.09 Hz), 11.03 (d, 1H, J = 1.88 Hz), 7.61 (d, 1H, J = 7.93 Hz), 7.42−7.31(m, 3H), 7.24 (d, 1H, J = 2.42 Hz), 7.15−6.97 (m, 4H), 6.85 (dt, 1H, J = 7.49 Hz, 0.88 Hz), 6.19 (s, 1H), 4.77 (s, 1H); ^{13}C (75 MHz, DMSO-d_6) δ 178.9, 177.5, 136.8, 135.9, 127.9, 125.8, 124.9, 123.7, 121.2, 120.7, 120.1, 119.2, 118.7, 118.3, 115.2, 111.6, 111.3, 105.8, 77.0, 51.8; IR (KBr) ν 3405, 3400, 3059, 1781, 1719 cm^{-1}; MS (FAB) calcd for $C_{20}H_{15}N_3O_3$ 345, found [M + H]$^+$ of m/z 346 (100%). **22** (minor-cis): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 10.75 (d, 1H, J = 2.13 Hz), 10.59 (d, 1H, J = 1.91 Hz), 7.50 (d, 1H, J = 7.71 Hz), 7.37 (d, 1H, J = 8.01 Hz), 7.11 (t, 2H, J = 7.55 Hz), 7.00 (d, 1H, J = 2.60 Hz), 6.96−6.75 (m, 4H), 6.69 (d, 1H, J = 2.44 Hz), 6.61 (d, 1H), 4.79 (s, 1H); ^{13}C (75 MHz, DMSO-d_6) δ 179.3, 176.7, 136.0, 135.3, 127.4, 125.0, 124.1, 123.8, 120.6, 120.5, 120.0, 118.9, 118.2, 113.0, 111.3, 111.0, 106.8, 80.1, 53.6; MS (FAB) Calcd for $C_{20}H_{15}N_3O_3$ 345, found [M + H]$^+$ of m/z 346 (100%). Both compounds gave identical fragmentation pathways by positive ion EI-MS including loss of 18 mass units (H_2O). The minor diastereomer produced a cross-peak between the methine proton at 4.79 ppm and the hydroxyl proton at 6.61 ppm in the NOESY spectrum indicative of a cis-orientation, while no cross-peak was present in NOESY spectrum of the major trans-diastereomer.

Acknowledgment. We are grateful to Professors Marvin Miller and Bill Roush for helpful discussions during the course of this work. We would like to thank

(20) HPLC conditions: Zorbax SB-CN 4.6 mm × 25 cm column with 40/60 THF/0.1% trifluoroacetic acid in water mobile phase (isocratic, 22 °C) at 1 mL/min and 233 nm. Elution times: t_R **9** = 6.6 min, t_R **8** = 3.9 min, t_R **7a** = 11.7 min, t_R **22** (major trans-diastereomer) = 9.5 min, t_R **22** (minor c*is*-diastereomer) = 10.3 min, t_R **20** = 17.6 min.

Mr. Joe Kennedy and Mr. John Bowers for purification of cis and trans isomers **22**. Ms. Karen McCune, Mr. Gary Cooke, Dr. Doug Dorman, Mr. K. Wayne Taylor, Mr. David Reed, Mr. James Osbourne, and Mr. Craig Kemp, of Eli Lilly and Co. Pharmaceutical and Analytical chemistry, are acknowledged for contributions to the characterization of **22**.

Supporting Information Available: Complete analytical and spectroscopic characterization for **17**, **18**, and **19** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980513C