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Inverse electron-demand Diels–Alder chemistry in the synthesis of a regioselectively protected analogue of the staurosporine aglycone†

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Abstract—Regioselective Weinreb amidation of the C1 ester of dimethyl pyridazino[4,5-*b*]indole-1,4-dicarboxylate followed by an intramolecular inverse electron-demand Diels–Alder reaction and palladium-catalyzed coupling produced regioselectively protected N^6-methylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole (N^6-methylstaurosporinone). © 2001 Elsevier Science Ltd. All rights reserved.

1*H*-Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles represent a large family of natural alkaloids possessing remarkable biological activities.[1] Perhaps the best known member of the family, staurosporine (**1**), isolated from *Streptomyces staurosporeu*,[2] was found to have antibacterial,[3] antihypertensive[3] and antiedema properties,[3] and further testing revealed that it is an extremely potent inhibitor of protein kinase C.[4] Numerous synthetic studies of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole skeleton[5] as well as the completed synthesis of staurosporine[6] and related natural[7] and unnatural[8] products have been reported. Distinction of the indole-nitrogens (N12 and N13) with high regioselectivity, however, remains a synthetic challenge.

We initiated our efforts toward the synthesis of the indolo[2,3-*a*]carbazole skeleton utilizing an inverse electron-demand Diels–Alder strategy that would allow for selective protection of one of the indole nitrogens of the aglycone. Since this aglycone is common to other biologically active indolo[2,3-*a*]carbazole alkaloids, (Fig. 1), distinction of the indole nitrogens in the aglycone would have application to other targets as well.

The envisioned sequence of reactions centered on an intramolecular cycloaddition of the pyridazino[4,5-*b*]-indole **5** to form the 3-arylindolocarbazole **4** following the regioselective tethering of the alkynylamine (Scheme 1). The C4 ester group of **4** could then be converted to aniline **3** by hydrolysis and a Curtius rearrangement. Final ring closure to **2** would then be achieved by an intramolecular palladium-catalyzed aryl amination. The facile synthesis of pyridazino[4,5-*b*]-indole **6a**[9] from the cycloaddition of indole (**7**) with

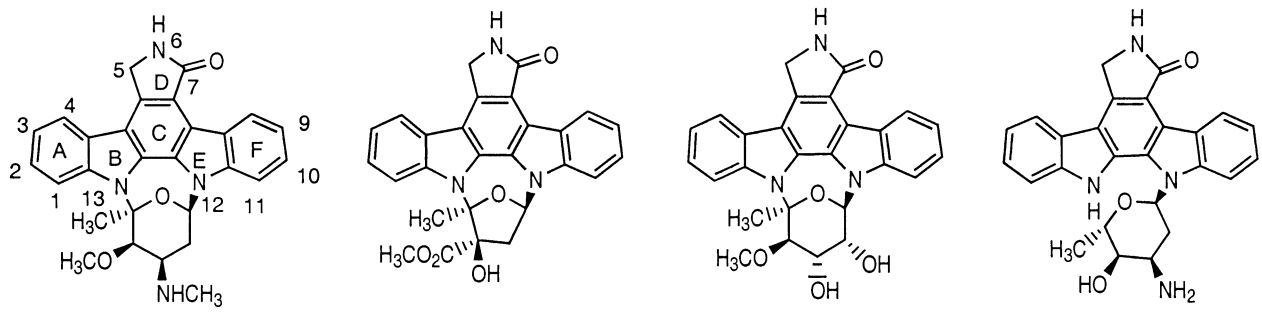

Figure 1. Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids.

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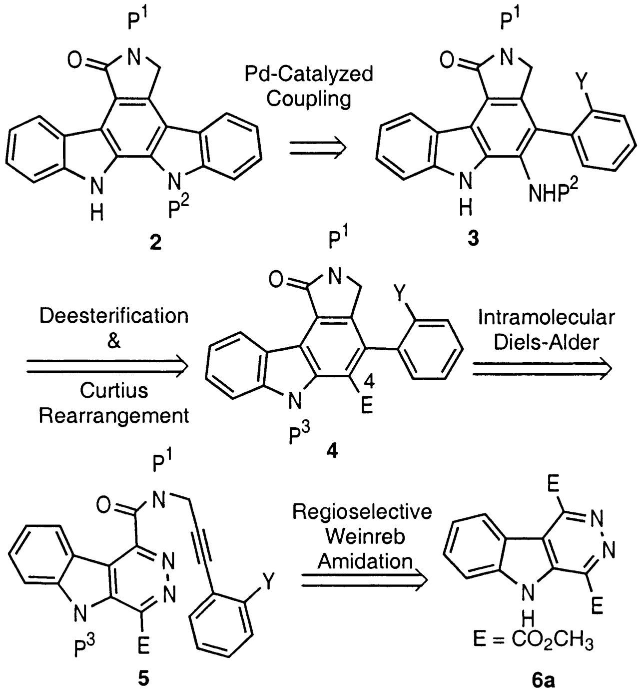
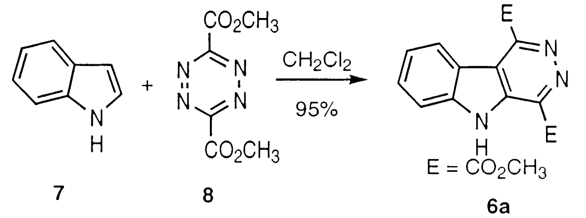


Scheme 1. Retrosynthetic analysis.

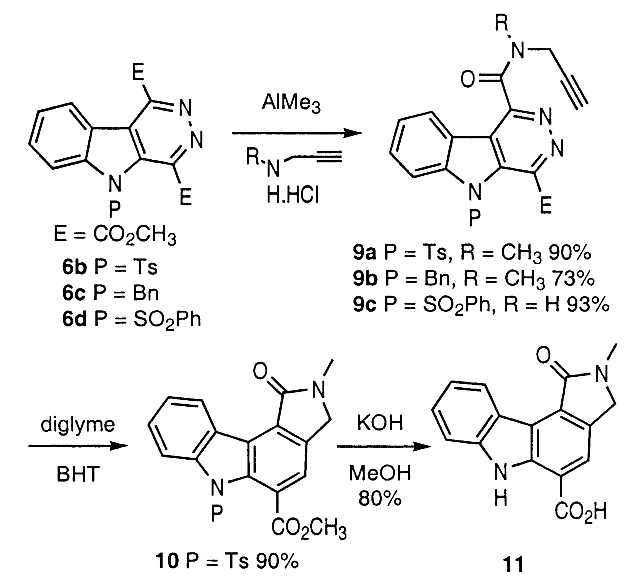
dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**8**)[10] provided an electron-deficient system for further cycloaddition chemistry (Scheme 2). Previously attempted intermolecular inverse electron-demand Diels–Alder reactions of pyridazinoindole **6a** have been unsuccessful,[9] though Diels–Alder reactions of the related 1,4-bis(trifluoromethyl)pyridazino[4,5-*b*]indole with enamines have been reported.[11] Thus, we turned our attention to intramolecular Diels–Alder reactions.

In model studies, introduction of an acetylenic dienophile onto the pyridazine ring at the C1 ester group was achieved regioselectively via Weinreb amidation[12] (Scheme 3). Weinreb amidation of **6b** and **6c** with *N*-methylpropargylamine hydrochloride salt occurred exclusively on the C1 ester to give the monoamides **9a** and **9b**, respectively. The cycloaddition of **9a** proceeded smoothly in refluxing diglyme in the presence of BHT (1 equiv.) to give carbazole **10a** in excellent yield (90%). In the absence of BHT, the reaction was not as clean and gave a yield of only 71%. The cycloaddition of **9b** was fruitless, giving back starting material, presumably due to the higher LUMO level of **9b** in comparison to **9a**. Weinreb amidation of **6d** with propargylamine hydrochloride also worked well, but no cycloaddition could be accomplished with secondary amide **9c**, returning only starting material. Hydrolysis of **10** to the acid **11** was accomplished under basic conditions (KOH, MeOH) in 80% yield, deprotecting the carbazole nitrogen as well under these conditions.

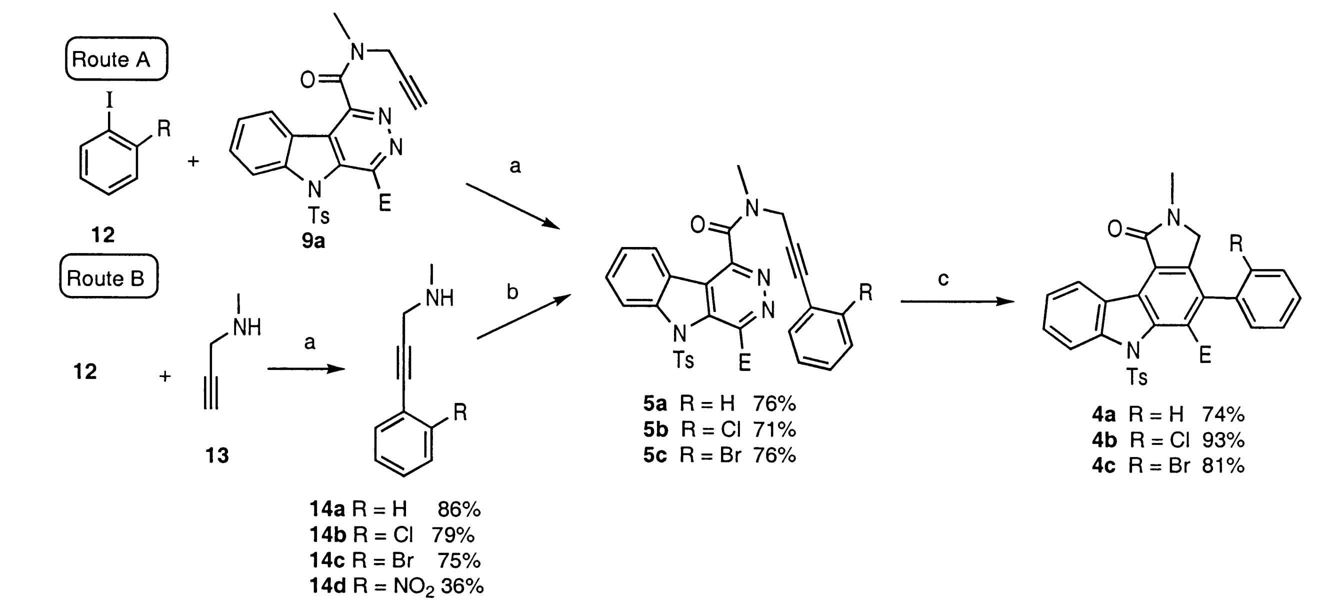
With the success of this model study, the next task was to incorporate the aryl ring onto the triple bond of the alkyne dienophile to complete the preparation of 4-arylpyrrolo[3,4-*c*]carbazoles **4**. In principle, this could be accomplished through Sonogashira coupling[13] of iodoarenes **12** with either amide **9a** (Scheme 4, Route A), or *N*-methylpropargylamine (**13**, Scheme 4, Route B), the latter route being preferred as a more convergent strategy. The former method led to unclean reactions, thus we turned our attention to Route B. Coupling of iodobenzene with *N*-methylpropargylamine (**13**) proceeded very cleanly, to give **14a** in 86% yield (Scheme 4). *o*-Chloro, *o*-bromo and *o*-nitro analogues **14b–d** were synthesized similarly with good yields for **14b** and **14c**, though only a modest yield for **14d**. Regioselective Weinreb amidation of the tosyl protected pyridazinoindole **6b** with the alkynes **14** gave the monoamides **5a–c** (mixtures of amide rotamers in ratios of ~3:2). The *o*-nitrophenyl derivative **14d**, however, failed to participate in the Weinreb amidation. Intramolecular inverse electron-demand Diels–Alder reactions of **5a–c** produced the pyrrolocarbazoles **4a–c** uneventfully in diglyme (150°C) in the presence of BHT (1 equiv.). The successful cycloadditions of **5a–c** with *ortho* halo-substituents produced the *ortho*-substituted 4-(*o*-halophenylpyrrolo[3,4-*c*]carbazoles necessary for the final coupling step to close the E-ring of staurosporinone. The methylene protons of the lactam ring of **4b** and **4c** are diastereotopic, appearing as doublets at δ 4.15 and 4.06 J_{AB} = 17.8 Hz (R = Cl) and at δ 4.17 and 4.03 J_{AB} = 17.8 Hz (R = Br) for the two cycloadducts in the ^{1}H NMR spectra indicating restricted rotation about the carbazole–phenyl C–C bond and resulting in axial chirality. Carbazoles analogous to **4**



Scheme 2. Synthesis of pyridazino[4,5-*b*]indole **2**.

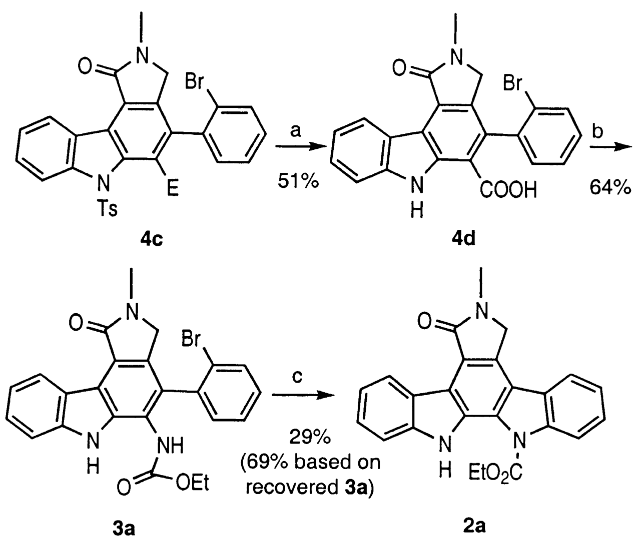


Scheme 3. Synthesis of pyrrolo[3,4-*c*]carbazole **8**.



Scheme 4. Synthesis of 4-phenylpyrrolo[3,4-*c*]carbazole-5-carboxylate. (a) $PdCl_2(PPh_3)_2$, CuI, $NHEt_2$; (b) (i) $AlMe_3$; (ii) **6b**; (c) BHT, diglyme.

have also attracted attention as staurosporine analogues,[14] and have been shown to be cytotoxic through PKC inhibition and to show thrombopoietic activity.[14a] Attempted demethylation of the ester of **4c** under the same conditions as **10** (KOH, MeOH) resulted only in loss of the tosyl group providing the deprotected carbazole with the ester still intact. However, treatment with $AlBr_3$/EtSH[15] produced carboxylic acid **4d** with the *N*-tosyl group also removed (Scheme 5). Presumably the highly hindered environment of the methyl ester in **4c** prevented its hydrolysis under the more common basic conditions. Curtius rearrangement[16] of acid **4d** was accomplished upon treatment with DPPA (64%), followed by intramolecular coupling[17] of the carbamate under Hartwig's conditions with an unoptimized yield of 29% to produce indolocarbazole **2a**[18] with differentiated nitrogens along with 58% of the starting carbamate.



Scheme 5. Synthesis of regioselectively protected staurosporinone **1a**. (a) $AlBr_3$, EtSH; (b) DPPA, Et_3N, THF; (c) $Pd(OAc)_2$, t-Bu_3P, NaOPh, toluene.

In summary, the intramolecular inverse electron-demand Diels–Alder reactions of pyridazino[4,5-*b*]indoles with acetylenic dienophiles introduced with exclusive regioselectivity yielded the arylcarbazole required for the final closure of the E-ring, which was accomplished by a palladium-catalyzed intramolecular aryl amination. The issue of regioselective introduction of the sugar moiety onto the indolocarbazole skeleton has been addressed by an orthogonal nitrogen protecting group strategy. Work is continuing to improve the yield of the final ring-closing arylamination.

Acknowledgements

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References

1. (a) Bergman, J. *Studies in Natural Products Chemistry*; Elsevier Science: New York, 1988; Vol. 1, pp. 3–30; (b) Gribble, G.; Berthel, S. *Studies in Natural Products Chemistry*; Elsevier Science: New York, 1993; Vol. 12, pp. 395–409; (c) Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265–290; (d) Pindur, U.; Kim, Y.-S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29–69.
2. (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Away, J.; Tsuchiya, H.; Takahashi, Y.; Matsuma, R. *J. Antibiot.* **1977**, *30*, 275–282; (b) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *J. Chem. Soc., Chem. Commun.* **1978**, 800–801.

3. Omura, S.; Iwai, Y.; Hirano, A. *Chem. Abstr*. **1978**, *89*, 178086.
4. (a) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun*. **1986**, *135*, 397–402; (b) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot*. **1995**, *48*, 535–548.
5. (a) Hughes, I.; Raphael, R. A. *Tetrahedron Lett*. **1983**, *24*, 1441–1444; (b) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469–476; (c) Magnus, P. D.; Exon, C.; Sear, N. L. *Tetrahedron* **1983**, *39*, 3725–3729; (d) Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795–2797; (e) Bergman, J.; Pelcman, B. *Tetrahedron Lett*. **1987**, *28*, 4441–4444; (f) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem*. **1987**, *52*, 1177–1185; (g) Bergman, J.; Pelcman, B. *J. Org. Chem*. **1989**, *54*, 824–828; (h) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Chem. Commun*. **1990**, 1667–1668; (i) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem*. **1992**, *57*, 2105–2114; (j) Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869–8880; (k) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett*. **1993**, *34*, 8361–8364; (l) Brüning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25–27; (m) Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *Hetereocycles* **1994**, *38*, 2267–2276; (n) Xie, G.; Lown, J. W. *Tetrahedron Lett*. **1994**, *35*, 5555–5558; (o) Sasaki, S.; Mizushima, T.; Hashimoto, T.; Maeda, M.; Sekimizu, K. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1771–1774; (p) Faul, M. M.; Sullivan, K. A.; Winneroski, L. L. *Synthesis* **1995**, 1511–1516; (q) Somei, M.; Hayashi, H.; Izumi, T.; Ohmoto, S. *Heterocycles* **1995**, *41*, 2161–2164; (r) Barry, J. F.; Wallace, T. W.; Walshe, N. D. A. *Tetrahedron* **1995**, *51*, 12797–12806; (s) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Morishima, H. *Tetrahedron* **1996**, *52*, 8099–8112; (t) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Ito, S.; Morishima, H. *Tetrahedron* **1997**, *53*, 5937–5950; (u) Eils, S.; Winterfeldt, E. *Synthesis* **1999**, 275–281; (v) Mahboobi, S.; Eibler, E.; Koller, M.; Kumar, S.; Popp, A.; Schollmeyer, D. *J. Org. Chem*. **1999**, *64*, 4697–4704.
6. (a) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc*. **1993**, *115*, 3782–3783; (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1995**, *117*, 552–553; (c) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, J. C.; Ballas, L. M. *J. Am. Chem. Soc*. **1996**, *118*, 2825–2842; (d) Wood, J. L.; Stolz, B. M.; Goodman, S. N. *J. Am. Chem. Soc*. **1996**, *118*, 10656–10657; (e) Wood, J. L.; Stolz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc*. **1997**, *119*, 9652–9661.
7. (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett*. **1985**, *26*, 4015–4018; (b) Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887–2897; (c) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem*. **1993**, *58*, 343–349; (d) Wood, J. L.; Stolz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc*. **1995**, *117*, 10413–10414; (e) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc*. **1996**, *118*, 5500–5501; (f) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem*. **1999**, *64*, 2465–2470; (g) Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc*. **1999**, *121*, 6501–6502; (h) Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem*. **2000**, *65*, 7541–7553.
8. (a) Shankar, B. B.; McCombie, S. W.; Kirkup, M. P.; Viet, A. Q.; Puar, M. S.; Ganguly, A. K. *Tetrahedron Lett*. **1993**, *34*, 5685–5688; (b) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirshenmeier, P.; Lin, S.-I.; Petrin, J.; Rosinski, K.; Shankar, B. B.; Wilson, O. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1537–1542; (c) Shankar, B. B.; McCombie, S. W. *Tetrahedron Lett*. **1993**, *35*, 3005–3008; (d) Yoshinari, T.; Matsumoto, M.; Arakawa, H.; Okada, H.; Noguchi, K.; Suda, H.; Okura, A.; Nishimura, S. *Cancer Res*. **1995**, *55*, 1310–1315; (e) Yamada, R.; Fukuda, K.; Kawanishi, M.; Ohmori, Y.; Nasu, M.; Seto, M.; Sasaki, Y.; Sunazuka, T.; Li, Z.; Fumato, N.; Iguchi, M.; Harigaya, Y.; Iwai, Y.; Omura, S. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1893–1896; (f) Jirousek, M. R.; Gillig, J. R.; Gonzalez, C. M.; Heath, W. F.; McDonald, III, J. H.; Neal, 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*, 2664–2671; (g) Hudkins, R. L.; Diebold, J. L. *Tetrahedron Lett*. **1997**, *38*, 915–918; (h) Merlic, C. A.; McInnes, D. M.; You, Y. *Tetrahedron Lett*. **1997**, *39*, 6787–6790; (i) Riley, D. A.; Simpkins, N. S.; Moffat, D. *Tetrahedron Lett*. **1999**, *40*, 3929–3932; (j) Mahboobi, S.; Burgemeister, T.; Dove, S.; Kuhr, S.; Popp, A. *J. Org. Chem*. **1999**, *64*, 8130–8137; (k) Ohkubo, M.; Nishimura, T.; Kawamoto, H.; Nakano, M.; Honma, T.; Yoshinari, T.; Arakawa, H.; Suda, H.; Morishima, H.; Nishimura, S. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 419–422.
9. (a) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem*. **1987**, *52*, 4610–4614; (b) Daly, K.; Nomak, R.; Snyder, J. K. *Tetrahedron Lett*. **1997**, *38*, 8611–8614; (c) Benson, S. C. Ph.D. Dissertation; Boston University: Boston, MA, 1992.
10. (a) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem*. **1984**, *49*, 4405–4409; (b) Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth*. **1991**, *70*, 79–92.
11. Haider, N.; Wanko, R. *Heterocycles* **1994**, *38*, 1805–1811.
12. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171–4174; (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun*. **1982**, *12*, 989–993; (c) Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. *J. Org. Chem*. **1994**, *59*, 1231–1233.
13. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467–4470; (b) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun*. **1977**, 291–292; (c) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun*. **1981**, *11*, 917–923; (d) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett*. **1981**, *22*, 315–318.
14. (a) Caballero, E.; Garcia, F.; Grávalos, D. G.; Medarde, M.; Sahagún, H.; Tomé, F. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2459–2462; (b) McCort, G.; Duclos, O.; Cadilhac, C.; Guilpain, E. *Tetrahedron Lett*. **1999**, *40*, 6211–6215; (c) Adeva, M.; Sahagún, H.; Caballero, E.; Peláez-Lamamié de Clairac, R.; Medarde, M.; Tomé, F. *J. Org. Chem*. **2000**, *65*, 3387–3394.
15. Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem*. **1981**, *46*, 1991–1993.
16. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc*. **1972**, *94*, 6203–6205; (b) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc*. **1994**, *116*, 1831–1838.

17. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.
18. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.85 (br s, NH), 9.46 (d, J=7.4 Hz, 1H), 8.11 (d, J=8.4 Hz, 1H), 7.62 (d, J=7.3 Hz, 1H), 7.53–7.44 (m, 3H), 7.39 (dd, J=8.4, 7.3 Hz, 1H), 7.31 (dd, J=7.3, 7.0 Hz, 1H), 4.57 (q, J=7.3 Hz, 2H), 4.53 (s, 2H), 3.25 (s, 3H), 1.60 (t, J=7.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.3, 153.2, 138.7, 137.4, 130.4, 127.3, 127.1, 126.41, 126.36, 126.32, 125.9, 123.9, 123.7, 122.3, 120.5, 119.7, 119.6, 117.3, 116.8, 110.5, 64.5, 51.9, 29.6, 14.4; EIHRMS (70 eV) m/z 397.1437 ([M+], 88%), calcd for $C_{24}H_{19}N_3O_3$ 397.1426.