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A New Entry to Polycyclic Indole Derivatives via Intramolecular Imino Diels−Alder Reaction: Observation of Unexpected Reaction

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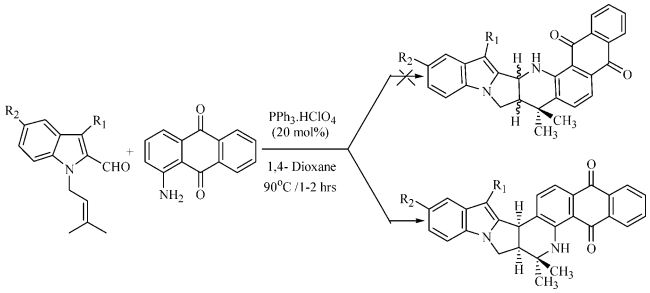

A new, efficient, and highly diastereoselective synthesis of polycyclic indole derivatives through intramolecular imino Diels−Alder reaction of aminoanthraquinone with *N*-prenylated indole-2-carboxaldehydes in the presence of 20 mol % of triphenylphosphonium perchlorate (TPPP) is reported with extremely high *cis* selectivity in good yield.

The indole system occurs in numerous natural products as well as in many therapeutic agents.[1] The preparation of polyfunctional indoles is therefore an important research field, and numerous methods have been developed.[2] As the core structure of [*a*]-annealed indole is present in a number of biologically active indole derivatives such as mitomycin and vincamine, the development of methods for the construction of [*a*]-annealed indole nuclei has been the subject of a number of reports.[3]

The pyrroloindole heterocyclic system is present in a growing class of alkaloid natural products, for example, physostigmine,[4] flustramines,[5] urochordamines,[6] mollenines,[7] himastatin,[8] and the numerous diketopiperazine derivatives.[9] Although a variety of methods have been developed to generate derivatives of this heterocycle and to modify its substitution pattern, new methods that stereoselectively provide indole derivatives are still of high interest in synthetic organic chemistry.[10]

In recent years the problem of multidrug resistance (MDR) toward numerous antitumor compounds has also become important. The presence of five- or six-membered heterocyclic ring(s) fused with the anthraquinone or acridine moiety is essential for the ability to overcome multidrug resistance.[11] The aminoalkyl-functionalized anthraquinone series of synthetic compounds has been the subject of much study in the quest for more active and less toxic analogs of the anthracycline antitumor antibiotics daunomycin and adriamycin.[12] Several aminoan-

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(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Sundberg, R. J. Pyrroles and Their Benzoderivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 4, pp 313−376. (c) Joule, J. A. Indole and its Derivatives. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme Verlag: Stuttgart, Germany, 2000; Category 2, Vol. 10, Chapters 10 and 13. (d) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207.

(2) For some recent methods, see: (a) Smith, A. B., III; Kurti, L.; Davulcu, A. H. *Org. Lett.* **2006**, *8*, 2167−2170. (b) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263−1266. (c) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C. H.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573−3575. (d) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551−1553. (e) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592−11593. (f) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355−1358. (g) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (h) Beller, M.; Breinde, C.; Riermeier, T. H.; Eichberger, M; Tranlhwein, H *Angew. Chem., Int. Ed.* **1998**, *37*, 3389−3391. (i) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426−2430. (j) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511. (k) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *3*, 1141−1144. (l) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504. (m) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662−5663. (n) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (o) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571−1578. (p) Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5*, 3213−3216. (q) Knepper, K.; Bräse, S. *Org. Lett.* **2003**, *5*, 2829−2832. (r) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317−1326.

(3) (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479−3486. (b) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111−1112. (c) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785−787. (d) Vigushin, D. M.; Brooke, G.; Willows, D.; Coobes, R. C.; Moody, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3661−3663. (e) Coleman, R. S.; Felpin, F. X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 7309−7316.

(4) (a) Takano, S.; Ogasawara, K. In *The Alkaloids. Chemistry and Pharmacology*; Brosi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 225−251. (b) Pharmacology, review: Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3−31.

(5) Carle, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586−1589.

(6) Tsukamoto, S.; Hirota, H.; Kato, H.; Fusetani, N. *Tetrahedron Lett.* **1993**, *34*, 4819−4822.

(7) Wang, H.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1998**, *61*, 804−807.

(8) Kamenecka, T. M.; Danishefsky, S. J. *Chem. Eur. J.* **2001**, *7*, 41-63.

(9) (a) Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380−386. (b) Takase, S.; Kawai, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1985**, *41*, 3037−3048. (c) Scott, P. M.; Merrien, M.-A.; Polonsky, J. *Experientia* **1976**, *32*, 140−141. (d) Scott, P. M.; Kennedy, P. C. *J. Agric. Food Chem.* **1976**, *24*, 865−868. (e) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329−2344. (f) Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod.* **1999**, *62*, 315−317.

(10) Reviews: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (c) Gribble, G. W. et al. *Curr. Org. Chem.* **2005**, *9*, 1493−1519. (d) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2003**, *20*, 216−242.

(11) (a) Stefańska, B.; Dzieduszycka, M.; Bontemps-Gracz, M. M.; Borowski, E.; Martelli, S.; Supino, R.; Pratesi, G.; De Cesare, M. A.; Zunino, F.; Kuśnierczyk, H.; Radzikowski, C. *J. Med. Chem.* **1999**, *42*, 3494. (b) Bontemps-Gracz, M. M.; Kupiec, A.; Antonini, I.; Borowski, E. *Acta Biochim. Pol.* **2002**, *49*, 87. (c) Pors, K.; Paniwnyk, Z.; Ruparelia, K. C.; Teesdale-Spittle, P.; Hartley, J. A.; Kelland, L. R.; Patterson, L. H. *J. Med. Chem.* **2004**, *47*, 1856−59. (d) Pors, K.; Plump, J. A.; Brown, R.; Teesdals-Spittle, P.; Searcey, M.; Smith, P. J.; Patterson, L. H. *J. Med. Chem.* **2005**, *48*, 6690−95.

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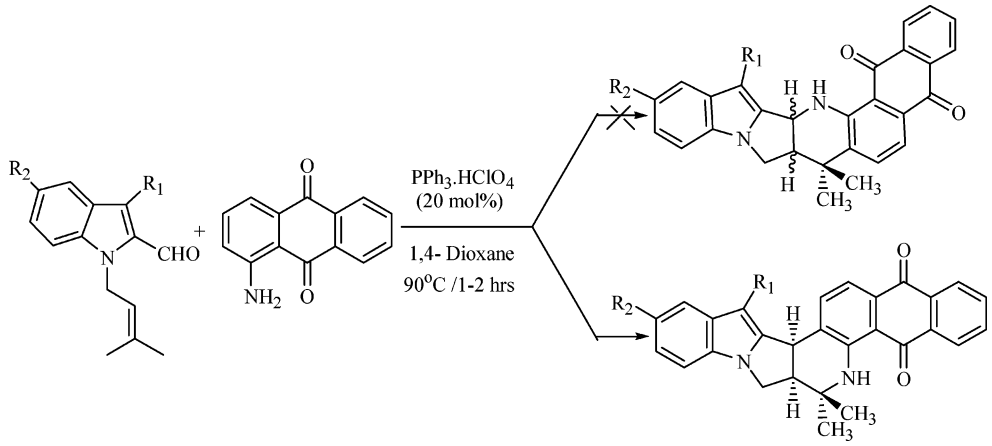
SCHEME 1



thraquinone derivatives are used as DNA intercalating agents.[13] In this connection, we present our recent results demonstrating that imines derived from *N*-prenylated indole-2-carboxaldehydes and 1-aminoanthraquinone are excellent substrates for an intramolecular imino Diels−Alder reaction catalyzed by triphenylphosphonium perchlorate (TPPP) to provide a highly functionalized products with excellent diastereoselectivity.

Hetero Diels−Alder reactions constitute a powerful method for the preparation of biologically interesting heterocycles and natural product synthesis.[14] For instance, the imino Diels−Alder reaction (IDA) provides a rapid means for the construction of functionalized rings containing nitrogen with control of regio-, diastereo-, and enantioselectivity.[15] The reactions of imines with electron-rich dienophiles have been reported to be catalyzed by Lewis acids such as $BF_3{\cdot}Et_2O$,[18] lanthanide triflates,[19] $AlCl_3$,[20] and $LiClO_4$.[21] However, some of these reagents suffer from disadvantages such as expense, long reaction time, and low yield. Moreover, many Lewis acids are either decomposed or deactivated as a result of the formation of water during imine formation. We have carried out our reactions with Lewis acid, $BF_3{\cdot}Et_2O$, and triphenylphosphonium perchlorate, and best results were obtained with triphenylphosphonium perchlorate as a catalyst. Triphenylphosphonium perchlorate is inexpensive and readily available and has been found to retain its activity even in the presence of amines, water, and other active functional groups such as NO_2 and COOH present in the substrates.

Our objective is to synthesize new polycyclic indole derivatives by the imino Diels−Alder reaction of 1-aminoanthraquinone with substituted *N*-prenylated indole-2-carboxaldehydes catalyzed by triphenylphosphonium perchlorate. The reactions were conducted in a one-pot procedure at 90 °C, and the reactions are normally completed within 1−2 h. The heptacyclic ring system was obtained by this process.

The TPPP-catalyzed reaction of 1-aminoanthraquinone **2** and *N*-prenylated indole carboxaldehyde **1** leads to the novel pyrrolizinoquinoline ring system **3a** in 80% yield (Scheme 1).

The single-crystal X-ray structure of the product **3a**[20] shows a structure different than the expected Diels−Alder product. Formation of this type of product is unusual in a Diels−Alder reaction, and especially, the intramolecular cycloaddition is highly regioselective.

The stereochemistry of the product **3a** was assigned on the basis of the coupling constants and NOE studies. Both six-membered piperidine and five-membered pyrrolidine rings are *cis* fused, as depicted by the coupling constant $J_{14b-7a} = 7.2$ Hz between H_{14b} (δ 4.75) and H_{7a} (δ 3.23) for **3a** (Figure 1).

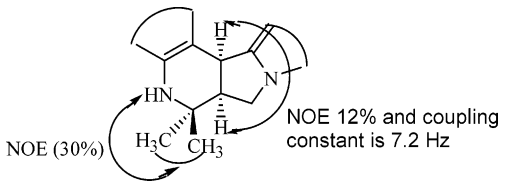


FIGURE 1. NOE of compound **3a**.

The compound **3a** was also characterized by NOE experiment by irradiating the hydrogen attached to nitrogen with two methyl groups and 30% of NOE was found, which confirms adjacent proximity of the two methyl groups with amino hydrogen. This clearly shows that the compound **3a** is the unexpected product.

Under similar conditions, several 2-formyl indoles **1b−f** were treated with the aminoanthraquinone **2** to illustrate the novelty of the present strategy, and results are summarized in Table 1. In all the cases the reactions are highly stereoselective, leading

(12) (a) Cairns, D.; Michalitsi, E.; Jenkins, T. C.; Mackay, S. P. *Bioorg. Med. Chem.* **2002**, *10*, 803−807. (b) Agbandje, M.; Jenkins, T. C.; Mckenna, R.; Reszka, A. P.; Neidle, S. *J. Med. Chem.* **1992**, *35*, 1418−1429. (c) Murdock, K. C.; Child, R. G.; Fabio, P. F.; Angier, R. B.; Wallace, R. E.; Durr, F. E.; Citarella, R. V. *J. Med. Chem.* **1979**, *22*, 1024−1030. (d) Zee-Cheng, R. K.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 291−294.

(13) Dzieduszycka, M.; Bontemps-Gracz, M. M.; Stefanska, B.; Martelli, S.; Piwkowska, A.; Arciemiuk, M.; Borowski, E. *Biorg. Med. Chem.* **2006**, *14*, 2880−2886.

(14) Haug, H.-S.; Chiou, J.-F.; Fong, Y.; Hou, C.−C.; Lu, Y.-C.; Wang, J.-Y.; Shih, J.-W.; Pan, Y.-R.; Lin, J.-J. *J. Med. Chem.* **2003**, *46*, 3300−3307.

(15) (a) Waldmann, H. *Synlett* **1995**, 133−141. (b) Barluenga, J.; Joglar, J.; Gonzalez, F. J.; Fustero, S. *Synlett* **1990**, *129*, 138. (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, *15*, 27. (c) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun.* **2002**, 444−445. (d) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16−22. (e) Waldmann, H. *Synthesis* **1994**, 535−551. (f) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259−88. (g) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (h) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120. (i) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−48.

(16) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869−2939. (b) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579−582.

(17) a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195−1202. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749−1760.

(18) Fadel, F.; Titouani, S. L.; Soufiaoui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905−5908.

(19) Yadav, J. S.; Reddy, B. V. S.; Venkateswara Rao, C.; Srinivas, R. *Synlett* **2002**, 993−995.

SCHEME 2. Expected Mechanism of the Product

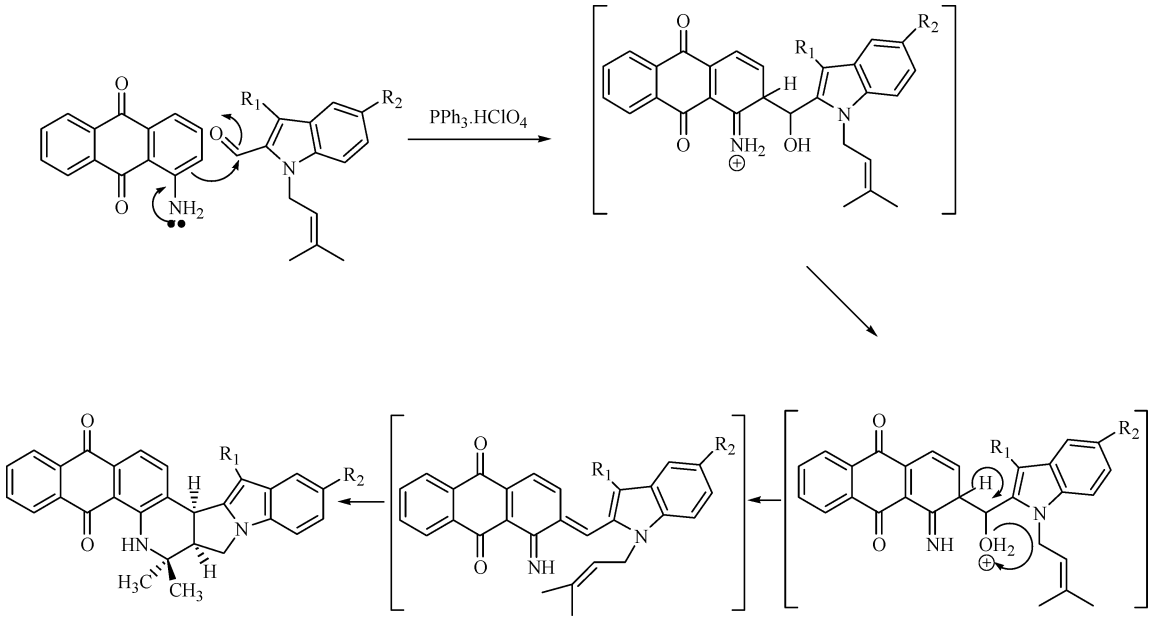


TABLE 1. TPPP-Catalyzed Synthesis of Polycyclic Indole Derivatives.

entry	R_1	R_2	product	time (min)	yield (%)[a]
1	Cl	H	**3a**	70	80
2	Cl	Cl	**3b**	90	75
3	Cl	Br	**3c**	82	78
4	Cl	CH_3	**3d**	100	70
5	Cl	OCH_3	**3e**	120	66
6	CH_3	H	**3f**	60	85

[a] Without the catalyst, no reaction was observed; the temperature of 90 °C is necessary.

to the exclusive formation of *cis* isomer. The single-crystal X-ray analysis of compound **3b** and **3c** was also achieved in order to confirm their molecular structure. The two methyl groups are observed at different chemical shift values around δ 1.52 (3H, s) and δ 1.45 (3H, s) because the six-membered ring exists in chair form, and thereby axial and equatorial methyl groups were observed at different chemical shift values. An N−H peak was observed at δ 9.83−9.84 as a sharp singlet. The expected mechanism of the reaction is shown in Scheme 2. NMR experiments also supported the proposed mechanism (see Supporting Information).

Initial Schiff base formation is not observed; rather there is electrophilic addition of aminoanthraquinone with a 2-formyl indole derivative, followed by dehydration, generating imino diene. The iminodiene further undergoes non-concerted cycloaddition[21] that leads to the imino Diels−Alder adduct.

One of the most important reactions for the anthracyclinone synthesis using anthraquinone as starting materials is the reaction of an aldehyde with anthraquinones, the Marschalk reaction.[22] This reaction is used for the introduction of various side chains on the anthraquinone skeleton. In our case, the initial step is an unexpected variation of the Marschalk reaction, and once the tethered azadiene system is assembled, then the imino Diels−Alder reaction was observed.

We have described a novel, highly efficient, and highly diastereoselective method for the synthesis of polycyclic indole derivatives through intramolecular imino Diels−Alder reaction. The method is simple and straightforward starting from easily accessible starting materials.

Experimental Section

14-Chloro-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo-[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (3a). To a stirred solution of 1-aminoanthraquinone **2** (0.6 g, 2.5 mmol) and 3-chloro-1-(3-methylbut-2-ene)-1*H*-indole-2-carboxaldehyde **1a** (0.93 g, 3.75 mmol) in dry 1,4-dioxane was added TPPP (0.18 g, 20 mol %), and the reaction mixture was heated to 90 °C for the appropriate time. The reaction was monitored by TLC. After completion of the reaction, as indicated by the TLC, the excess solvent was distilled off, and the crude reaction mixture was poured over water and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was chromatographed over neutral silica gel (prepared by eluting hexane/NEt_3 solution up to pH 7, 100−200 mesh size) and eluted with hexane/ethyl acetate to afford 0.972 g (80%) of **3a** as a pink solid. Analytical data for **3a**: mp 238 °C; IR (KBr) 3248, 3052, 2962, 2987, 1666, 1624, 1574, 1259, 1228, 1021, 987 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$) δ 9.85 (1H, s, N*H*), 8.26 (1H, d, J = 7.6 Hz, ArC*H*), 8.20 (1H, d, J = 7.6 Hz, ArC*H*), 8.03 (1H, d, J = 7.7 Hz, ArC*H*), 7.69−7.76 (2H, m, ArC*H*), 7.55−7.59 (2H, m, ArC*H*), 7.12−7.16 (3H, m, ArC*H*), 4.75 (1H, d, J = 7.2 Hz, C*H*), 4.05−4.24 (2H, m, CH_2), 3.24 (1H, q, J = 8.5 Hz, C*H*), 1.52 (3H, s), 1.46 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ 185.3 , 183.1, 147.3, 140.8, 136.6, 134.8, 133.9, 133.1, 133.1, 133.0, 131.5, 129.0, 128.3, 126.7, 126.6, 126.5, 122.3,

(20) The CCDC deposition number for compound **3a** is 621081. Formula: $C_{28}H_{21}ClN_2O_2$. Unit cell parameters: a = 9.2070(6), b = 11.4137(8), c = 11.9039(8), α = 62.6740(10), β = 88.6850(10), γ = 81.2650(10); space group *P*-1. The CCDC deposition number for compound **3b** is 621082. Formula: $C_{56}H_{40}Cl_4N_4O_4$. Unit cell parameters: a = 11.9652(14), b = 23.078(3), c = 17.208(2), β = 102.416(2), space group *P*2(1)/*n*. The CCDC deposition number for compound **3c** is 621083. Formula: $C_{28}H_{20}BrClN_2O_2$. Unit cell parameters: a = 21.701(7), b = 13.626(5), c = 7.846(3), β = 98.523(6), space group *P*2(1)/*c*.

(21) (a) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633−9636. (b) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451−2460.

(22) Krohn, K. *Tetrahedron* **1990**, *46*, 291−318.

119.9, 118.4, 116.5, 113.3, 109.6 (aromatic *C*), 96.9, 51.9, 49.7, 45.4, 36.9, 29.0, 27.5 (aliphatic *C*); LC-MS $m/z = 451$ ($M - H^+$), negative mode. Anal. Calcd for $C_{28}H_{21}ClN_2O_2$: C, 74.25; H, 4.67; N, 6.18. Found: C, 74.30; H, 4.72; N, 6.41.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, including files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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