VOLUME 72, NUMBER 10 JOC Articles MAY 11, 2007

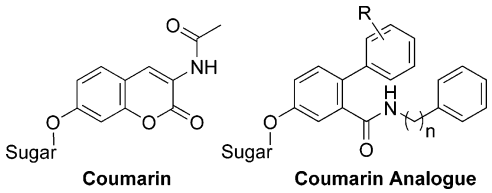
A Library of Noviosylated Coumarin Analogues

Yung-Tzung Huang and Brian S. J. Blagg*

Department of Medicinal Chemistry and The Center for Chemical Methodologies and Library Development, The University of Kansas, 1251 Wescoe Hall Drive, Malott Hall 4070, Lawrence, Kansas 66045-7563

bblagg@ku.edu

Received October 7, 2006



The DNA gyrase inhibitor, novobiocin, was recently shown to inhibit Hsp90 via a previously unrecognized C-terminal ATP-binding site. Previous structure−activity relationship studies identified key moieties that appear important for Hsp90 inhibitory activity. In an effort to provide a more efficacious lead compound, a parallel library of noviosylated coumarin analogues was prepared.

Introduction

Novobiocin is a natural product isolated from soil samples containing *Streptomyces spheroids*[1] and has clinical use for the treatment of bacterial infection[2−5] and more recently some forms of cancer.[6−9] The mechanism of action by which novobiocin exerts its antimicrobial activity has been described by its ability to inhibit bacterial DNA gyrase.[10−13] DNA gyrase mediates the topology of double stranded DNA similar to the process utilized by the 90 kDa heat shock proteins (Hsp90) to fold nascent polypeptides into biologically active three-dimensional structures.[14] Both proteins require ATP as a requisite source of energy for the reorientation of topological substrates and they both bind ATP in a similar manner. In contrast to most ATP-utilizing proteins that bind nucleotide substrates in an extended conformation, DNA gyrase[15−17] and Hsp90[18] bind ATP in an unusual bent conformation. On the basis of similarities of binding and previously recognized antitumor activity, Neckers and co-

* To whom correspondence should be addressed. Phone: 785-864-2288. Fax, 785-864-5326.

(1) Hengeller, C.; Licciardelo, G.; Tudino, V.; Marcelli, E.; Virgilio, A. *Nature* **1965**, *205*, 418−419.
(2) Maxwell, A. *Biochem. Soc. Trans.* **1999**, *27*, 48.
(3) Hooper, D. C.; Wolfson, J. S.; McHugh, G. L.; Winters, M. B.; Swartz, M. N. *Antimicrob. Agents Chemother.* **1982**, *22*, 662.
(4) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Iwai, N.; Hiyama, Y.; Suzuki, K.; Ito, H.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J. *J. Med. Chem.* **2004**, *47*, 3693.
(5) Albernamm, C.; Soriano, A.; Jiang, J.; Vollmer, H.; Biggins, J. B.; Barton, W. A.; Lesniak, J.; Nikolov, D. B.; Thorson, J. S. *Org. Lett.* **2003**, *5*, 933.
(6) Gobernado, M.; Canton, E.; Santos, M. *Eur. J. Clin. Microbiol.* **1984**, *3*, 371.
(7) Schwartz, G. N.; Teicher, B. A.; Eder, J. P., Jr.; Korbut, T.; Holden, S. A.; Ara, G.; Herman, T. S. *Cancer Chemother. Pharmacol.* **1993**, *32*, 455.
(8) Nordenberg, J.; Albukrek, D.; Hadar, T.; Fux, A.; Wasserman, L.; Novogrodsky, A.; Sidi, Y. *Br. J. Cancer* **1992**, *65*, 183.
(9) Hombrouck, C.; Capmau, M.; Moreau, N. *Cell Mol. Biol.* **1999**, *45*, 347.
(10) Lewis, R. J.; Tsai, F. T.; Wigley, D. B. *BioEssays* **1996**, *18*, 661.
(11) Reece, R. J.; Maxwell, A. *Crit. Rev. Biochem. Mol. Biol.* **1991**, *26*, 335.
(12) Laurin, P.; Ferroud, D.; Schio, L.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2875.
(13) Ali, J. A.; Jackson, A. P.; Howells, A. J.; Maxwell, A. *Biochemistry* **1993**, *32*, 2717.
(14) Blagg, B. S. J.; Kerr, T. D. *Med. Res. Rev.* **2006**, *26*, 310−338.
(15) Jackson, A. P.; Maxwell, A.; Wigley, D. B. *J. Mol. Biol.* **1991**, *217*, 15.
(16) Tsai, F. T. F.; Singh, O. M. P.; Skarzynski, T.; Wonacott, A. J.; Weston, S.; Tucker, A.; Pauptit, R. A.; Breeze, A. L.; Poyser, J. P.; O'Brien, R.; Ladbury, J. E.; Wigley, D. B. *Proteins* **1997**, *28*, 41.

10.1021/jo062083t CCC: $37.00
Published on Web 03/01/2007

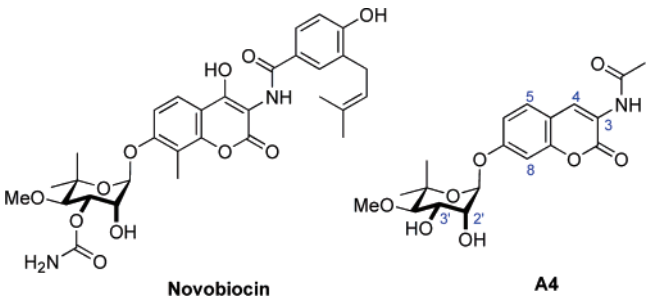


FIGURE 1. Hsp90 C-terminal inhibitors, novobiocin and A4.

workers proposed that novobiocin may be exerting its antitumor activity through inhibition of the Hsp90-mediated protein folding process.[19,20] Results from their studies proved that novobiocin did inhibit Hsp90, but at a much higher concentration than that needed to inhibit DNA gyrase (0.9 μM). Furthermore, their studies concluded that novobiocin did not bind to the analogous ATP-binding pocket located at the N-terminus of Hsp90, but instead bound to a previously unidentified C-terminal nucleotide binding pocket. In Hsp90 assays, novobiocin was found to manifest an IC_{50} value of ~700 μM, suggesting the need for improved analogues that exhibit increased efficacy.

In an effort to identify more potent inhibitors of Hsp90, a small library of novobiocin analogues was prepared and initial structure−activity relationships (SAR) revealed.[21] The most potent compound identified from this library was **A4**, which is structurally related to novobiocin, but lacks the 4-hydroxyl, the benzamide side chain, and the 3′-carbamate. Those studies clearly demonstrated that the 3′-carbamate was detrimental to anti-Hsp90 activity, suggesting an important role for the 2′,3′-diol of the noviose appendage. A summary of the observed SAR trends elucidated by this initial investigation is presented in Figure 2.

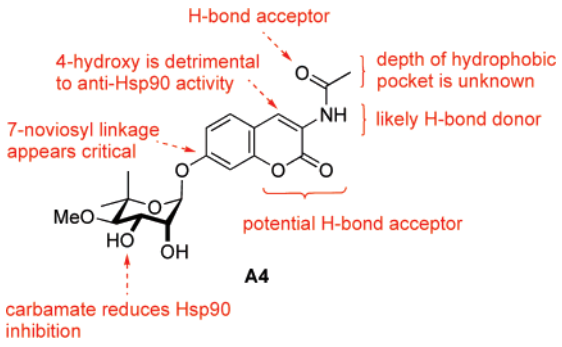


FIGURE 2. Previously observed SAR between **A4** and Hsp90.

On the basis of these observations and previously elucidated SAR's for novobiocin and DNA gyrase, a parallel library of noviosylated coumarin analogues was envisioned to provide a succinct method for continued exploration of SAR. The library

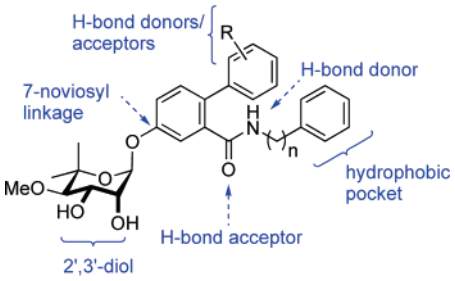


FIGURE 3. Rationale for noviosylated coumarin analogues.

was designed so that both the 4-hydroxyl and 3′-carbamate were omitted. However, additional hydrophobic and hydrogen bonding interactions could be provided by incorporation of additional functionalities as shown in Figure 3. Specifically, the 2-aryl was designed for incorporation of additional H-bond donors/acceptors, whereas the benzamide allowed for inclusion of various aromatics that were expected to occupy the hydrophobic cavity to which the prenylated benzamide side chain of novobiocin resides. Consistent with data obtained from prior studies, the 7-noviosyl linkage was maintained as well as the requisite 2′,3′-diol. In this paper we report the parallel synthesis of a library containing 56 noviosylated coumarin anlogues that exhibit these attributes.

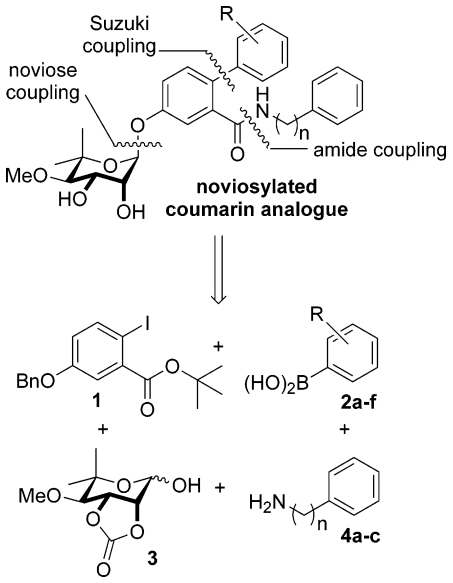
Results and Discussion

Retrosynthetically, the scaffold chosen for elucidation of structure−activity relationships was envisioned for construction from four components: an *o*-iodobenzoic ester (**1**),[22] a variety of commercially available boronic acids (**2a**−**f**), noviose (**3**),[23] and a series of amines (**4a**−**c**, Scheme 1). Previous work from our laboratory demonstrated that the trichloroacetimidate of noviose carbonate couples readily with coumarin phenols to give the desired α-anomer in high yield.[24] However, the β-anomers have not been prepared nor have their activities been evaluated. Therefore, we elected to synthesize both the α- and β-anomers in an effort to further diversify this library. The boronic acids were chosen to contain both electronic and steric moieties that could aid in elucidation of additional SAR and reveal crucial interactions with the surrounding pocket to which the benzamide side chain of novobiocin binds Hsp90 and gyrase.

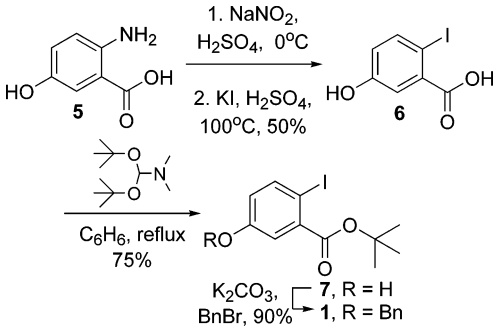
The Suzuki precursor, *tert*-butyl 4-benzyloxy-2-iodobenzoate (**1**), was prepared from 2-amino-5-hydroxybenzoic acid, **5** (Scheme 2).[25] Treatment of the 2-amino group with sodium nitrate under acidic conditions resulted in formation of the corresponding diazonium salt, which underwent nucleophilic aromatic substitution with potassium iodide to give the iodinated product, **6**. Conversion of the acid to the *tert*-butyl ester (**7**) was accomplished upon reflux with *N*,*N*-dimethylformamide di-*tert*-butyl acetal.[26] The phenol was then protected as the benzyl

(17) Holdgate, G. A.; Tunnicliffe, A.; Ward, W. H. J.; Weston, S. A.; Rosenbrock, G.; Barth, P. T.; Taylor, I. W. F.; Pauptit, R. A.; Timms, D. *Biochemistry* **1997**, *36*, 9663.
(18) Roe, S. M.; Prodromou, C.; O'Brien, R.; Ladbury, J. E.; Piper, P. W.; Pearl, L. H. *J. Med. Chem.* **1999**, *42*, 260.
(19) Marcu, M. G.; Schulte, T. W; Neckers, L. *J. Natl. Cancer Inst.* **2000**, *92*, 242.
(20) Marcu, M. G.; Chadli, A.; Bouhouche, I.; Catelli, B.; Neckers, L. M. *J. Biol. Chem.* **2000**, *276*, 37181.
(21) Yu, X. M.; Shen, G.; Neckers, L.; Blake, H.; Holzbeierlein, J.; Cronk, B.; Blagg, B. S. J. *J. Am. Chem. Soc.* **2005**, *127*, 12778−12779.
(22) Mulbarier, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4393−4394.
(23) Yu, X. M.; Shen, G.; Blagg, B. S. J. *J. Org. Chem.* **2004**, *69*, 7375−7378.
(24) Shen, G.; Yu, X. M.; Blagg, B. S. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5903−5906.
(25) (a) Moss, R. A.; Alwis, K. W.; Shin, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 2651−2655. (b) Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2047−2049. (c) Patterson, S.; Lorenz, C.; Slawin, A. M. Z.; Westwood, N. J. *QSAR Comb. Sci.* **2004**, *23*, 883−890.
(26) Widmer, U. *Synthesis* **1983**, 135−136.

SCHEME 1. Retrosynthetic Analysis of Coumarin Analogue Scaffold



SCHEME 2. Preparation of *tert*-Butyl 4-Benzyloxy-2-iodobenzoate



ether under standard conditions[27] to provide the Suzuki precursor **1**, for use in construction of the library.

Substrates for the Suzuki reaction were selected based on previously reported SAR. It was clear from the structure of novobiocin that there was a hydrophobic pocket into which the benzamide side chain projected.[21] Furthermore, there appeared to be interactions between the amide itself and the binding pocket, suggesting the potential for key hydrogen-bonding interactions. Therefore, we carefully selected 10 boronic acids (**2a**−**f**) for coupling to aryl iodide **1** (Figure 4). These molecules contained variously substituted H-bond donors/acceptors as well as hydrophobic moieties that would allow for exploration of the Hsp90 C-terminal binding pocket as described previously in Figures 2 and 3.

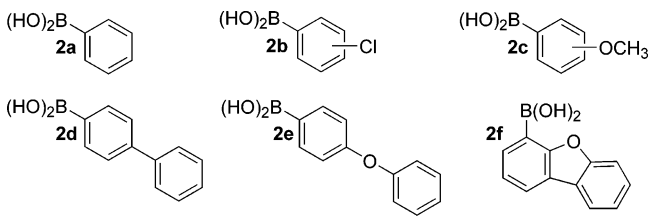
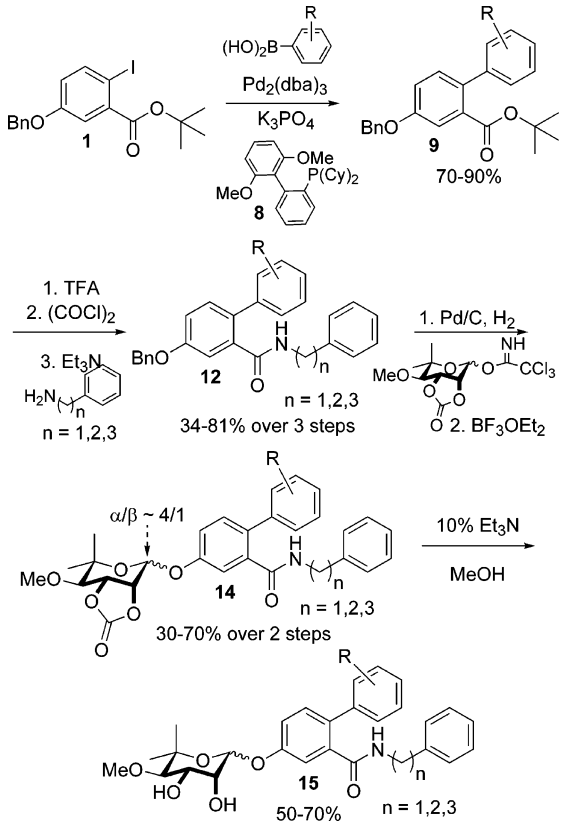


FIGURE 4. Boronic acid/esters used for elucidation of SAR.

Upon selection of the boronic acid/ester library, our attention turned toward assembly of the novobiocin-like library. The boronic acids were coupled to the *o*-iodo benzoate (**1**) via the use of Buchwald's ligand,[28] **8**, which proved essential to this reaction (Scheme 3). Although other ligands were probed, none were capable of producing the diaryl compounds in yields greater than 10%. With the desired compounds in hand (**9**), the *tert*-butyl esters were removed upon exposure to trifluoroacetic acid to furnish the corresponding acids. The resulting acids were subjected to a wide array of coupling conditions, but the presence of the *o*-aryl substituent significantly encumbered the reactivity of this moiety, which resulted in little or no coupled products. Consequently, we chose to convert the acid into the acid chloride and then treat those products directly with the requisite amines to form the corresponding amides, **12**. This latter reaction worked well for all three amino substrates investigated, including benzylamine, phenethylamine, and phenpropylamine substrates. Upon construction of the amides, the benzyl ethers were removed by hydrogenolysis to afford the free phenols, which were then noviosylated using our standard protocol[24] to give a mixture of anomers, **14**. The cyclic carbonates were then solvolyzed with triethylamine in methanol to give the requisite diols, **15**, which were purified via silica chromatography.

SCHEME 3. Preparation of the Noviosylated Coumarin Analogue Library



In total, 56 members of the library were prepared including an equal number of α- and *β*-anomers as shown in Figures 5 and 6, respectively. The compounds obtained were individually characterized and their identity confirmed by normal spectral methods. The compounds reported herein represent the first set of coumarin analogues prepared for elucidation of DNA gyrase

(27) Kim, S.; Wu, J. Y.; Zhang, Z.; Tang, W.; Doss, G. A.; Dean, B. J.; DiNinno, F.; Hammond, M. L. *Org. Lett.* **2005**, *7*, 411−414.

(28) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

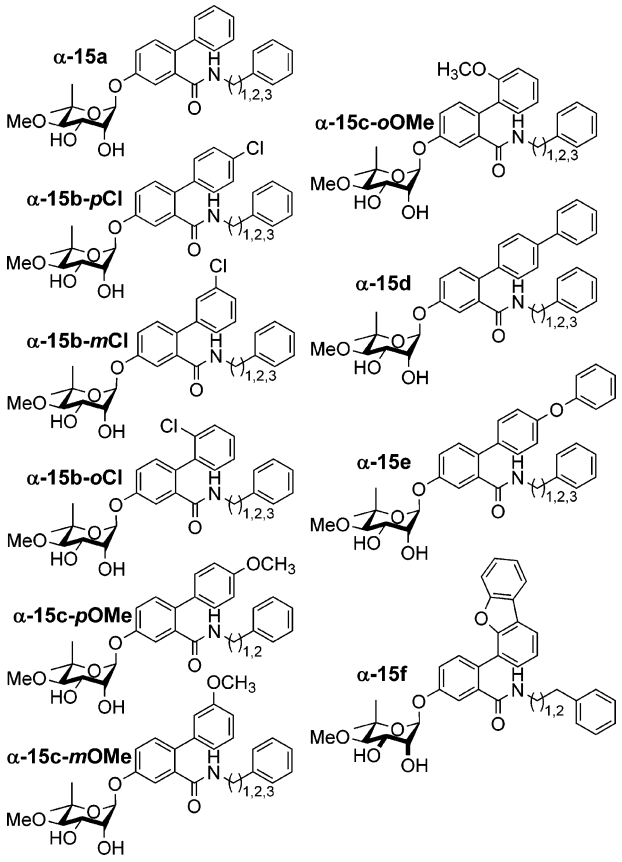


FIGURE 5. α-Anomeric members of the library prepared.

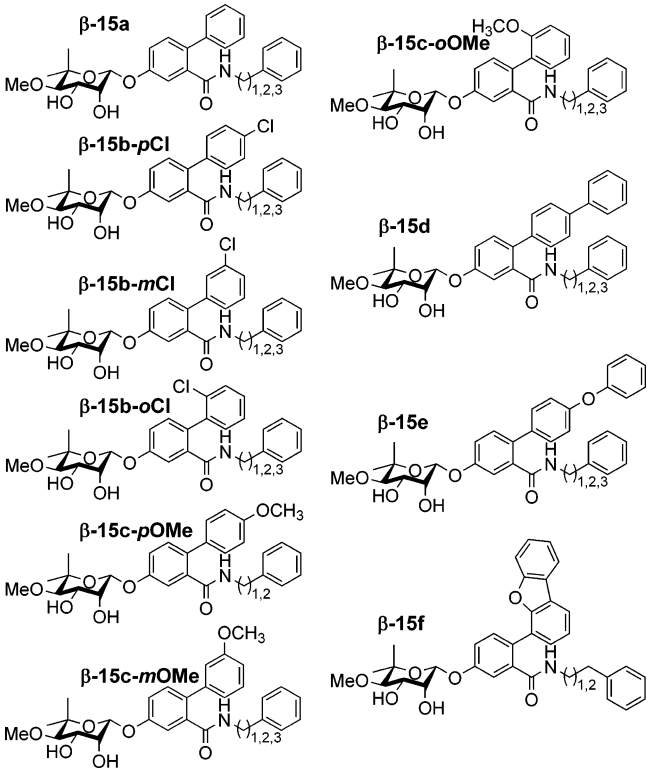


FIGURE 6. β-Anomers of the library prepared.

and Hsp90 structure−activity relationships. Biological studies with these compounds are currently under investigation and the results from such studies will be disclosed in due course along with optimized derivatives.

Experimental Procedures

***tert*-Butyl 5-(Benzyloxy)-2-iodobenzoate (1).** *tert*-Butyl 5-hydroxy-2-iodobenzoate **7** (0.6507 g, 2.0 mmol) was dissolved in anhydrous DMF (25 mL) before K_2CO_3 (0.46 g, 3.3 mmol) and benzyl bromide (0.3 mL, 2.6 mmol) were added to the solution. The resulting mixture was stirred for 14 h at room temperature. The reaction was quenched by the addition of H_2O (30 mL) and the aqueous phase extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified via chromatography (SiO_2, 8:1, hexanes:EtOAc) to afford **1** (0.7512 g, 90%) as a light yellow oil: ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.80 (d, J = 8.7 Hz, 1H), 7.47−7.30 (m, 6H), 6.78 (dd, J = 8.7, 3.1 Hz, 1H), 5.07 (s, 2H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 165.9, 158.7, 141.7, 138.2, 136.2, 128.8 (2C), 128.3, 127.6 (2C), 119.2, 117.5, 82.8, 82.3, 70.3, 28.2 (3C); IR (neat) 3088, 3065, 3032, 3001, 2978, 2930, 2874, 1728, 1589, 1562, 1454, 1393, 1300, 1254, 1165, 1026, 845, 779, 696, 642 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}IO_3N$ [M + NH_4]$^+$ 428.0723, found 428.0745.

***tert*-Butyl 5-(Benzyloxy)-2-(dibenzo[*b*,*d*]furan-4-yl)benzoate (9f).** *tert*-Butyl 5-(benzyloxy)-2-iodobenzoate **1** (0.3509 g, 0.86 mmol, 1.0 equiv), 4-dibenzofuranboronic acid **2f** (0.2731 g, 1.29 mmol, 1.5 equiv), $Pd_2(dba)_3$ (0.0164 g, 0.02 mmol, 4.0 mol %), K_3PO_4 (0.5623 g, 2.57 mmol, 3.0 equiv), and 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-byphenyl **8** (0.029 g, 0.07 mmol, 8.0 mol %) were dissolved in toluene (30 mL). The resulting solution was stirred for 15 min at room temperature and then heated at reflux for 14 h. The product was filtered through a pad of silica gel and eluted with EtOAc. The eluent was concentrated and the product purified via chromatography (SiO_2, 20:1, hexane/EtOAc) to afford **9f** (0.3512 g, 0.78 mmol, 91%) as a colorless solid: ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.96−7.83 (m, 2H), 7.67−7.58 (m 1H), 7.51−7.22 (m, 11H), 7.20−7.12 (m, 1H), 5.13 (s, 2H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 167.1, 158.6, 156.1, 153.9, 136.7, 134.3, 132.7, 129.3, 128.8 (2C), 128.3, 127.8 (2C), 127.4, 127.2, 126.8, 124.4, 123.8, 123.0, 122.8, 120.8, 119.4, 118.4, 116.1, 112.1, 81.1, 70.4, 27.5 (3C); IR (neat) 3398, 3063, 3036, 2978, 2932, 2874, 1713, 1604, 1566, 1508, 1450, 1369, 1296, 1169, 1080, 1026, 910, 845, 752 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{26}O_4Na_1$ [M + Na]$^+$ 473.1729, found 473.1717.

4-(Benzyloxy)-2′-chlorobiphenyl-2-carboxic acid (10b-*o*Cl). *tert*-Butyl ester **9b-*o*Cl** (0.3946 g, 1.0 mmol) and trifluoroacetic acid (TFA, 5 mL) were dissolved in CH_2Cl_2 (30 mL) and stirred for 6 h at room temperature. The solvent was removed and the product purified via chromatography (SiO_2, 1:1 to 2:1, hexanes:EtOAc) to afford **10b-*o*Cl** (0.2691 g, 0.8 mmol, 80%) as a colorless solid: ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.73 (d, J = 2.4 Hz), 7.52−7.36 (m 6H), 7.33−7.19 (m, 5H), 5.17 (s, 2H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 171.9, 158.4, 140.2, 136.6, 133.9, 133.3, 132.8, 130.6, 130.4, 129.2, 128.9 (2C), 128.6, 128.4, 127.8 (2C), 126.7, 119.8, 116.5, 70.5; IR (neat) 3063, 3009, 2964, 2918, 2872, 2860, 2818, 1693, 1682, 1603, 1504, 1418, 1277, 1227, 1026, 999, 824, 733, 696 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{16}Cl_1O_3$ [M + H]$^+$ 339.0788, found 339.0795.

General Procedure for Amide Formation. Carboxylic acid **10d** (0.1964 g, 0.52 mmol, 1.0 equiv), oxalyl chloride (0.18 mL, 2.1 mmol, 4.0 equiv), and one drop of DMF were dissolved in CH_2Cl_2 (15 mL), and the solution was stirred for 5 h at room temperature. The solvent was removed and the acid chloride product **11d** was used in the next step without further purification. The freshly made acid chloride **11d** (0.0719 g, 0.18 mmol, 1.0 equiv), 3-phenyl-1-propylamine (0.11 mL, 0.78 mmol, 4.0 equiv), and Et_3N (0.26 mL, 1.8 mmol, 10.0 equiv) were dissolved in CH_2Cl_2 (12 mL) and stirred for 14 h at room temperature. After the solvent was removed, the

product was purified via chromatography (SiO_2, 5:1, hexanes:EtOAc) to afford **12d** ($n = 3$) (0.0712 g, 0.14 mmol, 79%) as a colorless solid: ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.67−7.62 (m, 2H), 7.57−7.53 (m, 2H), 7.52−7.33 (m, 12H), 7.21−7.10 (m, 4H), 7.03−6.99 (m, 2H), 5.33 (t, $J = 5.8$ Hz, 1H), 5.16 (s, 2H), 3.27−3.20 (m, 2H), 2.37 (t, $J = 7.8$ Hz, 2H), 1.60−1.50 (m 2H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 169.4, 158.5, 141.3, 140.5 (2C), 139.1, 137.1, 136.7, 131.8, 131.7, 129.4 (2C), 129.0 (2C), 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.3, 127.7 (2C), 127.7, 127.5 (2C), 127.2 (2C), 126.1, 117.6, 114.5, 70.4, 39.6, 33.1, 30.7; IR (neat) 3279, 3082, 3061, 3028, 2962, 2924, 2895, 2856, 1632, 1607, 1539, 1479, 1454, 1313, 1049, 1003, 690 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{31}N_1O_2Na_1$ $[M + Na]^+$ 520.2253, found 520.2225.

General Procedure for Removal of Benzyl Protecting Group. The benzyl protected phenol **12c-*o*OMe** ($n = 2$) (0.0477 g, 0.11 mmol, 1.0 equiv) and 10% palladium on carbon (0.011 g, 20% g/g) were stirred in EtOAc (12 mL). The slurry was stirred under hydrogen gas (1 atm) for 14 h before the mixture was filtered through a pad of silica gel and eluted with EtOAc. The eluent was concentrated and the product purified via chromatography (SiO_2, 1:1, hexanes:EtOAc) to afford **13c-*o*OMe** ($n = 2$) (0.0378 g, 0.11 mmol, 99%) as a colorless solid: ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 8.81 (s, 1H), 7.75 (d, $J = 2.6$ Hz, 1H), 7.41−7.34 (m, 1H), 7.30−7.12 (m, 5H), 7.08−6.90 (m, 5H), 5.74 (t, $J = 5.5$ Hz, 1H), 3.74 (s, 3H), 3.48−3.40 (m, 2H), 2.50 (t, $J = 6.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 170.1, 157.0, 156.7, 138.5, 136.2, 132.6, 131.1, 129.4, 129.2, 128.8 (2C), 128.7 (2C), 126.8, 126.7, 121.3, 118.4, 116.4, 110.8, 55.5, 41.2, 35.2; IR (neat[1]) 3409, 3269, 3244, 3232, 3217, 3086, 3063, 3026, 2928, 2874, 2854, 2835, 1639, 1601, 1568, 1531, 1483, 1454, 1308, 1263, 1238, 1028, 752, 700 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}N_1O_3$ $[M + H]^+$ 348.1600, found 348.1598.

General Procedure of the Noviose Coupling Reaction. Noviose carbonate (0.1428 g, 0.65 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL) before Cs_2CO_3 (0.0431 g, 0.13 mmol, 0.2 equiv) and trichloroacetonitrile (0.14 mL, 1.37 mmol, 2.0 equiv) were added to the solution. The resulting mixture was stirred for 14 h at room temperature. The slurry was filtered through a cotton-packed pipet and the solvent removed. The product was used in the next step without further purification. The freshly prepared noviose carbonate trichloroacetimidate (∼0.090 g, ∼0.25 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added to a solution of **13c-*p*OMe** ($n = 2$) (0.0861 g, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) and the mixture was stirred for 10 min before BF_3-OEt_2 (0.010 mL, 0.08 mmol, 0.3 equiv) was added. The resulting mixture was stirred for 14 h at room temperature. The reaction was quenched by the addition of Et_3N (250 μL) and stirred for 5 min. After the solvent was removed, the product was purified via chromatography (SiO_2, 1:20, acetone:CH_2Cl_2) to afford a mixture of α- and *β*-**14c-*p*OMe** ($n = 2$), which was used without further purification.

General Procedure for Solvolysis the Cyclic Carbonate. The noviosylated coumarin mimic **14a** ($n = 1$) (∼0.05 g, ∼0.1 mmol) was dissolved in methanolic Et_3N (10 mL, 10% solution) and stirred for 14 h at room temperature. The solvent was removed and the product purified via chromatography (SiO_2, 1:4, acetone:CH_2Cl_2) to afford α- and *β*-**15a** ($n = 1$) as colorless solids. α-**15a** ($n = 1$): ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.40−7.33 (m 6H), 7.29−7.13 (m, 5H), 6.90−6.85 (m, 2H), 5.56 (d, $J = 2.0$ Hz, 1H), 4.33 (d, $J = 5.4$ Hz, 2H), 4.25−4.18 (m, 1H), 4.18−4.15 (m, 1H), 3.62 (s, 3H), 3.39 (m, 2H), 2.97 (d, $J = 4.4$ Hz, 1H), 1.82 (br s, 1H), 1.39 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 169.3, 156.3, 140.0, 137.4, 136.6, 133.2, 131.8, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.0 (2C), 127.7, 127.6, 117.8, 116.7, 98.1, 84.5, 78.6, 71.4, 68.7, 62.1, 44.5, 29.2, 23.1; IR (neat) 3418, 3323, 3107, 3061, 3030, 2982, 2932, 2854, 2931, 1643, 1634, 1607, 1480, 1304, 1223, 1130, 1040, 993, 808, 734, 700 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{32}N_1O_6$ $[M + H]^+$ 478.2230, found 478.2232. *β*-**15a** ($n = 1$): ^{1}H NMR ($CDCl_3$/400 MHz, ppm) δ 7.46−7.14 (m, 11H), 6.92−6.87 (m, 2H), 5.52 (t, $J = 4.7$ Hz, 1H), 5.41 (br s, 1H), 4.34 (d, $J = 5.4$ Hz, 2H), 4.22 (s, 1H), 3.87−3.80 (m, 1H), 3.65 (s, 3H), 3.32 (d, $J = 9.4$ Hz, 1H), 2.77 (s, 1H), 2.71 (d, $J = 7.6$ Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$/400 MHz, ppm) δ 168.8, 156.3, 139.9, 137.5, 136.7, 134.1, 131.9, 129.0 (2C), 129.9 (2C), 128.8 (2C), 127.9 (2C), 127.8, 127.6, 118.5, 116.4, 94.2, 84.4, 76.3, 71.5, 71.3, 62.2, 44.4, 28.8, 18.8; IR (neat) 3348, 3107, 3063, 3030, 2980, 2928, 2903, 2853, 2833, 1645, 1599, 1520, 1479, 1383, 1227, 1107, 1030, 883, 769, 698 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{32}N_1O_6$ $[M + H]^+$ 478.2230, found 478.2228.

Acknowledgment. The authors gratefully acknowledge the Department of Defense Prostate Cancer Research Program (PC050269) and the NIH Center of Excellence in Combinatorial Methods and Library Development (5 P50 GM069663) for financial support of this project.

Supporting Information Available: General experimental conditions and spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062083T