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Combined Directed Remote Metalation−Transition Metal Catalyzed Cross Coupling Strategies: The Total Synthesis of the Aglycones of the Gilvocarcins V, M, and E and Arnottin I

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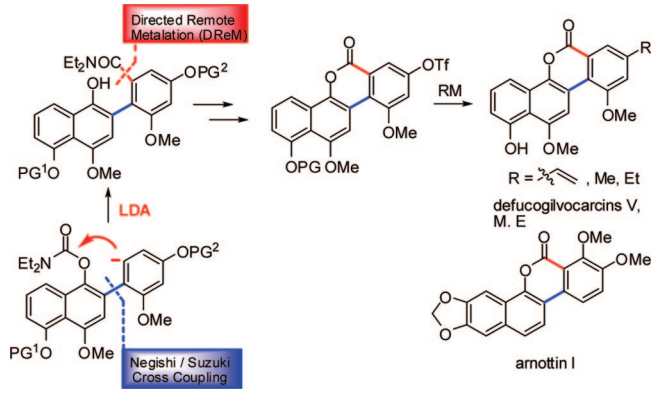

A key directed remote metalation (DreM)−carbamoyl migration strategy was applied in an efficient synthesis of the naturally occurring 6H-naphtho[1,2-*b*]benzopyran-6-one defucogilvocarcin V (**1a**, Scheme 11). The required biarylcarbamate **33d** was best prepared by a high yielding Suzuki coupling reaction of **31a** with the differentially protected trioxygenated naphthalene coupling partner **32d** which was synthesized using a selective acylation of a juglone derivative. In the late stages of the synthesis, the triflate **39** served as the common intermediate to install the required C-8 vinyl group of **1a** (Stille coupling) as well as the required substituents for the preparation of defucogilvocarcins M (**1b**) and E (**1c**). A variety of protecting group strategies were investigated and provided insight into which groups are preferred for the DreM−carbamoyl migration process. The strategic lessons learned from this total synthesis were applied in the successful total synthesis of the structurally similar natural product arnottin I (**2**).

Introduction

We report on the total synthesis[1] of the aglycones of the gilvocarcins **1, 1a** (R′ = H, R = vinyl), **1b** (R′ = H, R = Me), and **1c** (R′ = H, R = Et) and arnottin I (**2**) (Scheme 1) by a strategy that originates with sequential directed *ortho* metalation (D*o*M) and Suzuki−Miyaura cross coupling reactions and is terminated by a directed remote metalation (DreM)−lactonization step (Scheme 2, **3** → **4**). The work is a rational extension of the discovery[2] and application[3] of the DreM tactic for the construction of dibenzopyranone **4** derivatives and natural products,[4] isolated mainly from plant and microbial sources[5] and exhibiting cytotoxic[6] and antiestrogen activity,[7] and related to the more complex ellagic acids and chartreusin that, owing to their additional important biological activities (antiviral,[8] antitumor,[9] antitopoisomerase,[10] anitestrogen[11]), have also elicited synthetic interest.[12]

The naphtho[*b*,*d*]benzopyran-6-ones (Scheme 1, **1A**−**F**), benzannulated analogues to the dibenzopyranones (**4**), constitute

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(1) For a preliminary report of our total syntheses of defucogilvocarcins V, M and E see: James, C. A.; Snieckus, V. *Tetrahedron Lett.* **1997**, *38*, 8149. Nomenclature of the aglycones used throughout: Defucogilvocarcin V: **1a**, R' = H, R = vinyl, Defucogilvocarcin M: **1b**, R′ = H, R = Me, and Defucogilvocarcin E: **1c**, R′ = H, R = Et. Defucogilvocarcin V is itself a natural product, see ref 13e.

(2) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.

(3) (a) Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293. (b) Kalinin, A.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992. (c) Mohri, S.-I.; Stefinovic, Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072. For a brief review, see: (d) Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; p 106.

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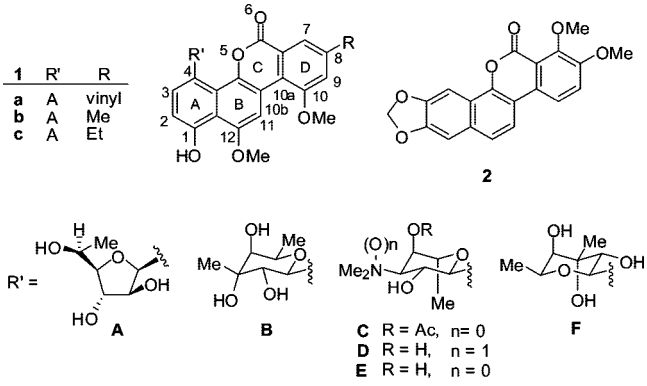
SCHEME 1



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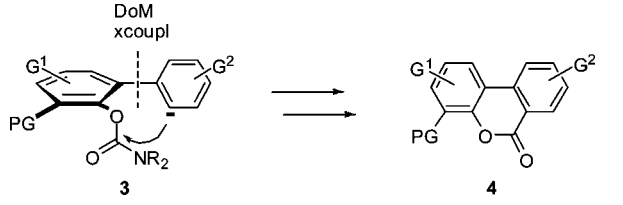


a relatively small family of antibiotic natural products that were isolated from various strains of *Streptomyces*[13] exhibiting major structural variation of the C-4 C-glycoside as well as minor dissimilarity at the C-8 position: gilvocarcin V (**1a**, R = vinyl), gilvocarcin M (**1b**, R = Me), and gilvocarcin **E** (**1c**, R = Et).[14] This class of natural products exhibits diverse bioactivity which includes bactericidal,[15] antitumor,[16] and photochemotherapeutic properties.[17,18]

In comparison to the gilvocarcins, arnottin I (Scheme 1, **2**), a sugarless naptho[*b*,*d*]benzopyranone with a different oxygenation pattern, was isolated in 1977 by Ishikawa and co-workers as a minor constituent from the bark of *Xanthoxylum arnottianum*[19] together with arnottin II (a spirolactone oxidatively related to **2**). The structural elucidation of arnottin I was not achieved[20] until 1993 due, in part, to the fact that the producing plant yielded only small quantities of the material. The coisolation of the benzophenanthridine alkaloid chelerythrine[21] was a biogenetic hint for the relationship of these three natural products and their dissimilarity to the gilvocarcins, which are

(4) For a review on dibenzopyranone synthesis, see: (a) Darbarwar, M.; Sundaramurthy, V. *Synthesis* **1982**, 337. For recent work, see Hurtley reaction: (b) Pandey, J.; Jha, A. K.; Hajela, K. *Bioorg. Med. Chem.* **2004**, *12*, 2239. Diels-Alder: (c) Minami, T.; Matsumoto, Y.; Nakamura, S.; Koyanagi, S.; Yamaguchi, M. *J. Org. Chem.* **1992**, *57*, 167. (d) Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, 477. Addition of phenols to quinones: (e) Muller, P. V.; Venakis, T.; Eugster, C. H. *Helv. Chim. Acta* **1979**, *62*, 2833. Photoactivated $S_{RN}1$: (f) Petrillo, G.; Novi, M.; Dell'Erba, C.; Tavani, C. *Tetrahedron* **1991**, *47*, 9297. (g) Beuglemans, R.; Bois-Choussy, M.; Chastanet, J.; Le Gleuher, M.; Zhu, J. *Tetrahedron* **1993**, *36*, 2723. Baeyer-Villiger oxidation of fluorenone: (h) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. *Synthesis* **1991**, 739. Hypervalent iodine-mediated cyclization of 1-phenylbenzoic acid: (i) Togo, H.; Muraki, T.; Yokoyam, M. *Tetrahedron Lett.* **1995**, *36*, 7089. Enediyne cyclization: (j) Suzuki, I.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Heterocylces* **2001**, *54* (2), 571. (k) Suzuki, I.; Wakayama, M.; Shigenaga, A.; Nemoto, H.; Shibuya, M. *Tetrahedron Lett.* **2000**, *41*, 10019. Dienone-phenol rearrangements: (l) Hart, D. J.; Kim, A.; Krishnamurthy, R.; Merriman, G. H.; Waltos, A.-M. *Tetrahedron Lett.* **1992**, *48*, 8179. Sonogashira coupling—Benzannulation: (m) Kawasaki, T.; Yamamto, Y. *J. Org. Chem.* **2002**, *67*, 5138. Suzuki coupling—cyclization: (n) Alo, B. I.; Kandil, P. A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763. (o) Kemperman, G. J.; Ter Horst, B.; Van de Goor, D.; Roeters, T.; Bergweff, J.; Van der Eem, R.; Basten, J. *Eur. J. Org. Chem.* **2006**, *71*, 3169. Intramolecular Pd(II) catalysed coupling: (p) Abe, H.; Nishioka, K.; Takeda, S.; Arai, M.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2005**, *46*, 3197[3 + 3] cyclization-Suzuki cross coupling: (q) Nguyen, V. T. H.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 1013. Oxidative radical cyclization: (r) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991. Intermolecular C—H Activation: (s) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. For an interesting Pd catalyzed CO insertion into a boroxarophenanthrene, see: (t) Zhou, Q. J.; Worm, K.; Dolle, R. E. *J. Org. Chem.* **2004**, *69*, 5147. Hauser-initiated tandem annulations: (u) Ray, S.; Patra, A.; Mal, D. *Tetrahedron* **2008**, *64*, 3253.

(5) A conspicuous exception is the isolation of an unnamed dibenzopyranone from the deposits of the organs of the Canadian beaver, see: (a) Lederer, E. *Bull. Soc. Chim. Biol.* **1942**, *24*, 1115. For its synthesis, see: (b) Ghosal, S.; Lal, J.; Singh, S. K.; Kumar, Y.; Soti, F. *J. Chem. Res. (S)* **1989**, 350. For the recent isolation of a structurally related naphthoquinone see: (c) Tanhmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. *Tetrahedron Lett.* **2006**, *47*, 3067. For the isolation of the highly oxygenated dibenzopyranone amurensisin, see: (d) Wang, J.-N.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Phytochemistry* **2000**, *53*, 1097. For the recent isolation of the Graphisolactones, see: (e) Tanahashi, T.; Takenaka, Y.; Nagakura, N.; Hamada, N. *Phytochemistry* **2003**, *62*, 71.

(6) (a) Pero, R. W.; Owens, R. G.; Dale, S. W.; Harvan, D. *Biochim. Biophys. Acta* **1971**, *230*, 170. For a recent report of a dibenzopyranone derivative as a nonsteroidal-specific endothielial cell proliferation inhibitor, see: (b) Schmidt, J. M.; Tremblay, G. B.; Pagé, M.; Mercure, J.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. *J. Med. Chem.* **2003**, *46*, 1289.

(7) Sun, W.; Cama, L. D.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1468.

(8) Anti-HIV activity: (a) Ogata, T.; Kato, A. *Jpn. Kokai Tokyo Koho. Chem. Abstr.* **1992**, *118*, 45735. Recently ellagic acid has been shown to have anti hepatitis B activity: (b) Shin, M. S.; Kang, E. H.; Lee, Y. I. *Antiviral Res.* **2005**, *67*, 163.

(9) (a) Kashiwada, Y.; Nonaka, G.; Nishioka, I.; Chang, J.-J.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 1033. (b) Miyamoto, K.; Murayama, T.; Yoshida, T.; Hatano, T.; Okuda, T. *ACS Symp. Ser.* **1997**, *662*, 245.

(10) Miyamoto, K.; Nomura, M.; Murayama, T.; Furukawa, T.; Hatano, T.; Yoshida, T.; Koshiura, R.; Okuda, T. *Biol. Pharm. Bull.* **1993**, *16*, 379.

(11) (a) Pandey, J.; Jha, A. K.; Hajela, K. *Bioorg. Med. Chem.* **2004**, *12*, 2239. (b) Larrosa, M.; González-Sarrías, A.; García-Conesa, M. T.; Tomás-Barberán, F. A.; Espín, J. C. *J. Agric. Food. Chem.* **2006**, *54*, 1611.

(12) (a) Itoh, T.; Chika, J.-I.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J.-I. *J. Org. Chem.* **1996**, *61*, 3700. (b) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798. (c) Hauser, F. M.; Combs, D. W. *J. Org. Chem.* **1980**, *45*, 4071.

(13) Gilvocarcin V, M and E: (a) Nakano, H.; Matsuda, Y.; Ito, K.; Ohkubo, S.; Morimoto, M.; Tomita, F. *J. Antibiot.* **1981**, *34*, 266. (b) Balitz, D. M.; O'Herron, F. A.; Bush, J.; Vyas, D. M.; Nettleton, D. E.; Grulich, R. E.; Bradner, W. T.; Doyle, T. W. *J. Antibiot.* **1981**, *34*, 1544. (c) Hatano, K.; Hagashide, E.; Kameda, Y.; Horii, S.; Mizuno, K. *Agric. Biol. Chem.* **1980**, *44*, 1157. (d) Wei, T. T.; Byrne, K. M.; Warnick-Pickle, D.; Greenstein, M. *J. Antibiot.* **1982**, *35*, 545. Defucogilvocarcin V: (e) Misra, R.; Tritch III, H. R.; Pandey, R. C. *J. Antibiot.* **1985**, *38*, 1280. Virenomycin M, V: (f) Streilitz, F.; Flon, H.; Asheshov, I. N. *J. Bacteriol.* **1955**, *69*, 280Ravidomycins: (g) Sehgal, S. N.; Vezina, C. *Eur. Pat. Appl. 10 964; Chem. Abstr.* **1985**, *102*, 130–570s. (h) Narita, T.; Matsumoto, M.; Mogi, K.; Kukita, K.-I.; Kawahara, R.; Nakashima, T. *J. Antibiot.* **1989**, *42*, 347. Albacarcin M, V: (i) Matson, J. A.; Myllymaki, R. W.; Doyle, T. W.; Bush, J. A. *Chem. Abstr.* **1985**, *102*, 4456a U. S. Patent 4,461,831.

(14) Structural Elucidation: (a) Findlay, J. A.; Liu, J.-S.; Radics, L. *Can. J. Chem.* **1983**, *61*, 323. (b) Takahashi, K.; Yoshida, M.; Tomita, F.; Shirahata, K. *J. Antibiot.* **1981**, *34*, 271. X-ray crystal structure of gilvocarcin M: (c) Hirayama, N.; Takahashi, K.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1338. For isolation of compounds related to gilvocarcin M but bearing a C-12 glycoside: (d) Kojiri, K.; Arakawa, H.; Satoh, F.; Kawamura, K.; Okura, A.; Suda, H.; Okanashi, M. *J. Antibiot.* **1991**, *44*, 1054. (e) Nakajima, S.; Kojiri, K.; Suda, H.; Okanishi, H. *J. Antibiot.* **1991**, *44*, 1061.

(15) Tomita, F.; Takahashi, K.-I.; Tamaoki, T. *J. Antibiot.* **1982**, *35*, 1038.

(16) (a) Tomita, F.; Takahashi, K.-I.; Tamaoki, T. *J. Antibiot.* **1982**, *35*, 1038. (b) Morimoto, M.; Okubo, S.; Tomita, F.; Marumo, H. *J. Antibiot.* **1981**, *34*, 701. (c) Bockstahler, L. E.; Elespuru, R. K.; Hitchins, V. M.; Carney, P. G.; Olvey, K. M.; Lytle, C. D. *Photochem. Photobiol.* **1990**, *51*, 477.

(17) (a) Elespuru, R. K.; Gonda, S. K. *Science* **1984**, *223*, 69. (b) Greenstein, M.; Monji, T.; Yeung, R.; Maiese, W. M.; White, R. J. *Antimicrob. Agents Chemother.* **1986**, *29*, 861. For recent discussion of the differentiation of the mechanism of action of the gilvocarcins relative to other DNA intercalators see: (c) Matsumoto, A.; Hanawalt, P. C. *Cancer Res.* **2000**, *60*, 3921. RAJIV17For the elucidation of the complete gene cluster of gilvocarcin V see: (d) Fischer, C.; Lipata, F.; Rohr, J. *J. Am. Chem. Soc.* **2003**, *125*, 7818. For further studies on the biosynthesis of gilvocarcin V: (e) Liu, T.; Fischer, C.; Beninga, C.; Rohr, J. *J. Am. Chem. Soc.* **2004**, *126*, 12262. (f) Liu, T.; Kharel, M. K.; Fischer, C.; McCormick, A.; Rohr, J. *ChemBioChem* **2006**, *7*, 1070.

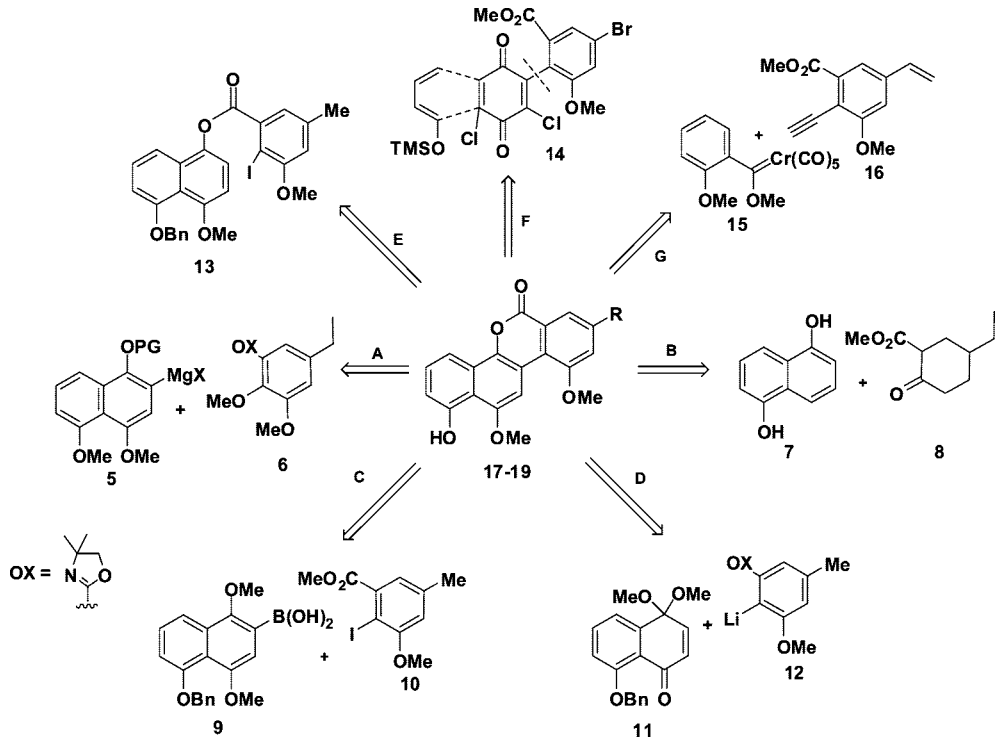
(18) For studies on the mechanism of action see: (a) McGee, L. R.; Misra, R. *J. Am. Chem. Soc.* **1990**, *112*, 2386, and references cited therein. (b) Matsumoto, A.; Hanawalt, P. C. *Cancer Res.* **2000**, *60*, 3921.

(19) Ishii, H.; Ishikawa, T.; Haginiwa, J. *Yakugaku Zasshi* **1977**, *97*, 890 *Chem. Abstr.* **1977**, *87*, 197250g.

(20) Ishii, H.; Ishikawa, T.; Murota, M.; Aoki, Y.; Harayama, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1019.

(21) Ishii, H.; Ishikawa, T.; Takeda, S.; Suzuki, M.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 2002.

SCHEME 3



polyketide derived. In fact, Ishikawa has suggested[22] that arnottin I was a potential biosynthetic intermediate of chelerythrine. Although the biological activity of the arnottins has not been established, compounds related to chelerythrine have shown significant antileukemic properties.[23,24]

The considerable synthetic effort[25,26] toward the construction of the gilvocarcin ring system has generally focused on the formation of the C10a−C10b biaryl bond followed by lactonization to generate the tetracyclic ring system (Scheme 3). Thus, Findlay[26a] and Danishefsky[26b] used the Meyers[27] nucleophilic aromatic substitution tactic of *ortho*-methoxyl aryloxazolines with aryl Grignards in independent syntheses of defucogilvocarcin V (path A). In a convergent approach to defucogilvocarcin M, McGee[26c] used the Pechmann condensation[28] to generate the key bond (path B). Jung[26d] and co-workers made use of the versatile Suzuki coupling process (path C) whereas the strategy of Hart[26e] involved the 1,4-addition of a lithiated oxazoline to a naphthoquinone derivative (path D). The diazonium Meerwein coupling[29] in conjunction with the Stille coupling strategy allowed McKenzie[26f−h] to prepare a series of derivatives varying the substituents at C-8 (Path F). Parker[26i] used a Fischer carbene−alkyne reaction as the key *de novo* ring B generation step (path G) in a convergent but inefficient synthesis of defucogilvocarcin V methyl ether. A palladium catalyzed biaryl bond construct was used by Martin[26j] as the key step in the synthesis of defucogilvocarcins M and E and also by Suzuki in an elegant syntheses of gilvocarcins M[30] and V[31] (path E).

In contrast to the rich synthetic activity in the gilvocarcin area, only three syntheses of Arnottin I have been reported: Ishii[32] used a strategy involving the oxidative cleavage of a benzofuran derivative for lactone generation and Harayama[33] developed a route similar to those of Martin and Suzuki (Scheme 3, path C) Recently, Cheng[34] developed a concise synthesis of Arnottin I based on the nickel-catalyzed ring-opening of 1,4-epoxynaphthalenes with aryliodides.

We set these natural products as targets in order to test the viability of our evolving methodologies in DoM, DreM, and cross coupling. Furthermore, we concentrated on the construc-

(22) Ishii, H.; Ishikawa, T.; Murota, M.; Aoki, Y.; Harayama, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1019.

(23) Ishii, H.; Chen, I.-S.; Ishikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 671.

(24) Stermitz, F. R.; Larson, K. A.; Kim, D. K. *J. Med. Chem.* **1973**, *16*, 939.

(25) For a review, see: (a) Hua, D. H.; Saha, S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 341. For an elegant three component synthesis of the gilvocarcin framework: (b) Takemura, I.; Imura, K.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2004**, *6*, 2503. For methods involving early-stage incorporation of the C-glycoside: (c) Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2005**, *3*, 4432. (d) Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 7335.

(26) For literature concerning structural determination and an organized collection of the synthetic work, see: (a) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427. (b) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003. (c) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695. (d) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517. Defucogilvocarcin M: (e) Hart, D. J.; Merriman, G. H. *Tetrahedron Lett.* **1989**, *30*, 5093. (f) McKenzie, T. C.; Hassen, W.; McDonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435. (g) McKenzie, T. C.; Hassen, W. *Tetrahedron Lett.* **1987**, *28*, 2563. (h) MacDonald, S. J. F.; McKenzie, T. C.; Hassen, W. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1528. (i) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, *56*, 1666. (j) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313. Defucogilvocarcin E: (k) Hua, D. H.; Saha, S.; Roche, D.; Maeng, J. C.; Iguchi, S.; Baldwin, C. *J. Org. Chem.* **1992**, *57*, 399.

(27) (a) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. (b) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

(28) Sethna, S.; Phadka, R. *Org. React.* **1953**, *7*, 1.

(29) Rondestvedt, C. S., Jr. *Org. React.* **1976**, *24*, 225.

(30) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568.

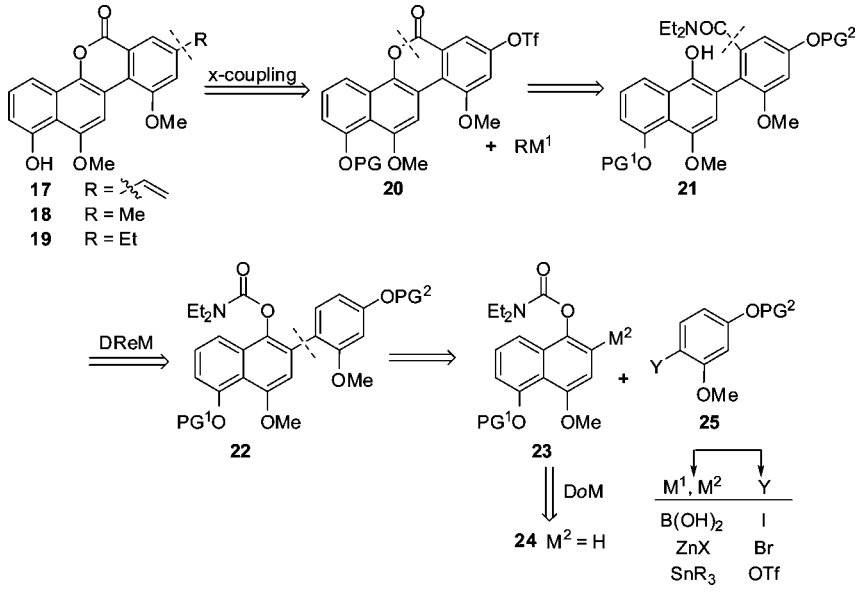
(31) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

(32) Ishii, H.; Ishikawa, T.; Murota, M.; Aoki, Y.; Harayama, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1019.

(33) (a) Harayama, T.; Yasuda, H.; Akiyama, T.; Takeuchi, Y.; Abe, H. *Chem. Pharm. Bull.* **2000**, *48*, 861. (b) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61.

(34) Madan, S.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 8312.

SCHEME 4

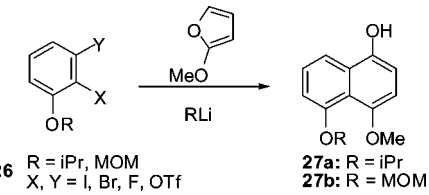


tion of the gilvocarcin aglycones in view of the extensive available work on glycosylation of gilvocarcins[35,25d] and related structures as well as the demonstration for lack of requirement of the sugar moiety for antitumor activity.[36] While successful, these journeys taught additional lessons in protection−deprotection strategies which are consistent with common wisdom.[37]

Results and Discussion

Defucogilvocarcins V, M, and E. Retrosynthetic Analysis. The envisaged approach to defucogilvocarcins **V** (**1a**), M (**1b**), and E (**1c**) (Scheme 4) incorporates a C8 alkyl group scission to the penultimate intermediate triflate **20** which would serve efficiently for transition metal catalyzed coupling processes (e.g., Kumada-Corriu, Suzuki−Miyaura, Negishi, Stille)[38] to the three aglycones and, potentially, to analogues for bioscreening purposes. Lactone opening reveals the phenol amide **21** which is expected to be derived from **22** by a key Directed remote Metalation (DreM)−carbamoyl migration[2] step followed by standard lactonization. Biaryl carbamate **22** is disconnected to naphthyl carbamate **24** and arene **25** *via* a transition metal catalyzed cross coupling retron. Initial concerns of choice of PG^1, PG^2 to withstand cross coupling and DreM conditions and regioselective synthesis of a differentially protected trioxygenated naphthalene[26d,j] requirement for **24** were evident. However, the advantages in the choice of, and ability to interconvert M^1, M^2−Y combinations in the cross coupling partners **23** and **25**, the power of the O-carbamate[39] favoring regioselective DoM in **24,** and, most significantly, DreM protocol facilitating piggybacking the amide into the alternate ring, **22** → **21** (Scheme 4), hence allowing the use of less hindered cross coupling partners compared to those required by a direct method, encouraged pursuit of the retrosynthetic plan.

SCHEME 5



Construction of the A/B Ring Precursor. The initial task was the preparation of the highly oxygenated naphthalene derivative **24** as the A/B ring fragment. In previous syntheses of naptho[*b*,*d*]benzopyranones, the construction of trioxygenated naphthalenes involved the differentiation of juglone (5-hydroxy-1,4-naphthaquinone) derivatives by reductive lactonization, protection - reprotection sequences or selective alkylation or acylation methods[40] which, although proceeding from readily available starting materials and incorporating high yielding key steps, were protracted.[41] To devise a short and convenient method, initial efforts focused on the application of the cycloaddition of alkoxyarynes to 2-methoxyfuran developed by Suzuki and co-workers[42] and subsequently evolved into an instructive foray into alternate aryne precursors (Scheme 5) as well as useful lessons in DoM chemistry of some deceptively simple substrates.[43] Consideration of phenol protection as its isopropyl ether was based on its known stability under the DReM conditions[2] and its mild and selective cleavage in the presence of arylmethyl ethers,[44] and similarly, the MOM derivative **27b** was available analogously.

(35) Ravidomycin: (a) Suzuki, K. *Pure Appl. Chem.* **2000**, *72*, 1783. (b) Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063. (c) Parker, K. A.; Su, D.-S. *J. Carbohyd. Chem.* **2005**, *24*, 187. Gilvocarcins: see ref 41. For general methods of C-arylglycosidation, see: (d) Yamamoto, Y.; Saigoku, T.; Nishiyama, H.; Ohgai, T.; Itoh, K. *Org. Biomol. Chem.* **2005**, *3*, 1768. (e) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263. (f) Somsák, L. *Chem. Rev.* **2001**, *101*, 81. (g) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589. (h) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700. (i) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (k) Postema, M. H. *Tetrahedron* **1992**, *48*, 8545. (l) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201.

(36) (a) Tse-Dinh, T. C.; McGee, L. R. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 808. (b) See ref 11e. (c) See however ref 16f.

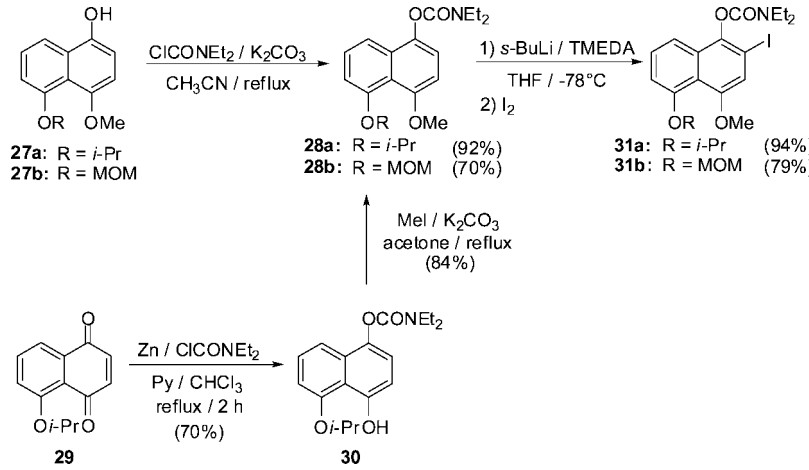
(37) See Kocienski, *Protective Groups*, 3rd ed.; Thieme Verlag: Stuttgart 2003, p 2: "Protection is not a principle but an expedient" attributed to Disraeli, B., March 17, 1845.

(38) For excellent coverage of all reactions, see: (a) Diederich, F., de Meijere, A., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Vols 1 and 2; Wiley-VCH: Weinheim, 2004. For a review on the DoM−cross coupling strategy, see: (b) Anctil, E. J.-G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol *1*, pp 761−813. (c) For applications of cross coupling reactions to total synthesis Nicolau, K. C.; Bulger, P. G.; Sartah, *Angew. Chem. Int. Ed* **2005**, *44*, 4442.

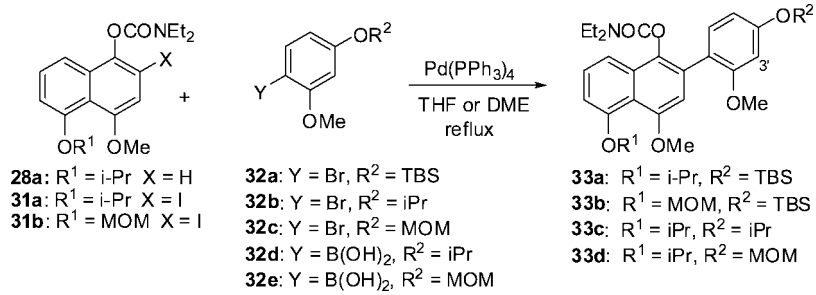
(39) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.

(40) See refs 22a,b,d,e,j for examples of this strategy.

SCHEME 6



SCHEME 7



Although reasonably efficient routes to the desired oxygenated naphthols **27a** and **27b** had been established via the aryne methodology, the expense and difficult preparation of 2-methoxyfuran encouraged return to juglone-related approaches. Thus (Scheme 6), using a modification of the procedure for the selective acetylation of juglone derivatives by Giles,[45] treatment of isopropoxy juglone[46] **29** with $ClCONEt_2$ in the presence of pyridine and Zn dust afforded the selectively carbamoylated naphthol **30** which was then smoothly methylated to furnish the required A/B ring precursor **28a** (3 steps, 45% overall yield from commercial juglone). Although both isopropoxy (**28a**) and OMOM (**28b**) derivatives were available in modest yields via the aryne chemistry ultimately, due to its relative brevity and ability to work on scale-up, the selective carbamoylation intermediate **30** was used as the advanced intermediate. Subjection of **28a** and **28b** to the standard carbamate metalation conditions followed by iodine quench afforded the required cross coupling partners **31a** and **31b** in respectable yields.

Formation of A/B−C Ring Biaryl Bond by Cross Coupling. With the A/B ring moiety **31a** in hand and the necessary D ring coupling fragments **32a−c**, available *via* a reported regioselective tosylation technology of 4-bromoresorcinol,[47] initial studies focused on Negishi cross coupling conditions to establish the biaryl bond (Scheme 7). The choice of the TBS protection was chosen based on ease of cleavage in the presence of aryl methyl and isopropyl ethers. Lithiation of **28a** (s-BuLi/THF/−78 °C/20 min) followed by addition of a solution of $ZnCl_2$ and direct treatment with bromide **32a** in the presence of $Pd(PPh_3)_4$ at reflux afforded the key biaryl **33a** in 45% yield (Table 1, entry 1). Subsequently, a two step, inverted partner, protocol was found to be more efficient. Negishi coupling of the iodide **31a** with the arylzinc reagent derived from metal−halogen exchange and $ZnCl_2$ transmetalation of **32a** provided the desired biaryl in excellent yield (Table 1, entry 2). A similar protocol applied to the 5-OMOM carbamate **31b** led to the corresponding biaryl **33b** in comparable yield (Table 1, entry 3). As will become evident, the C4′-TBS series **33a−b** was inappropriate for the conclusion of the total synthesis of the gilvocarcins and was superseded by the corresponding C4′-i-Pr **33c** and C4′-MOM **33d** derivatives. The preparation of these biaryls by the Negishi protocol using both possible combinations, met initial difficulties. Thus, DoM — Zn transmetalation of **28a** followed by coupling with **32b** failed (Table 1, entry 4) and inversion of partners and coupling of **31a** with the arylzinc derived from **32b** afforded **33c** in only 21% yield (Table 1, entry 5). Turning to the Suzuki-Miyaura reaction, application of standard conditions to the coupling of **31a** with the arylboronic acid **32e** derived by metal−halogen exchange — boronation of **32b** led to similarly poor results (Table 1, entry 6) However, changing the base from Na_2CO_3 to $Ba(OH)_2$,[48] led to substantial improvement affording the isopropoxy biaryl **33c** (Table 1, entry

(41) For example, Findlay's route (see ref 26a) furnishes an arylbromide precursor to a Suzuki coupling in 3 steps but is not selectively protected and requires a protection-deprotection sequence late in the synthesis. The synthesis by Jung provides a differentially protected arylboronic acid Suzuki precursor in 5 steps and ca 67% yield; however, the boronic acid is used in crude form and the overall yield is not known (see ref 26d).

(42) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735.

(43) Full details of the routes pursued, their rationale and lessons learned are given in the Supporting Information (Section 1).

(44) (a) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593. (b) Banwell, M. G.; Flynn, B. L.; Stewart, S. G. *J. Org. Chem.* **1998**, *63*, 9139.

(45) Chorn, T. A.; Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1339.

(46) Laatsch, H. *Liebigs Ann. Chem.* **1985**, 251.

(47) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293.

TABLE 1. Cross Coupling Reactions for the Preparation of 33a−d

Entry	ArX	R^1	X	ArY	Y	R^2	Conditions	Yld,[a] %
1	**28a**	*i*-Pr	ZnCl	**32a**	Br	TBS	$Pd(PPh_3)_4$/THF/reflux/12 h	45
2	**31a**	*i*-Pr	I	**32a**	ZnCl	TBS	$Pd(PPh_3)_4$/THF/reflux/12 h	90
3	**31b**	MOM	I	**32a**	ZnCl	TBS	$Pd(PPh_3)_4$/THF/reflux/12 h	90
4	**28a**	*i*-Pr	ZnCl	**32b**	Br	iPr	$Pd(PPh_3)_4$/THF/reflux/12 h	0
5	**31a**	*i*-Pr	I	**32b**	ZnCl	iPr	$Pd(PPh_3)_4$/THF/reflux/48 h	21
6	**31a**	*i*-Pr	I	**32d**	$B(OH)_2$	iPr	aq Na_2CO_3/DME/reflux/12 h	28
7	**31a**	*i*-Pr	I	**32d**	$B(OH)_2$	iPr	aq $Ba(OH)_2$/DME/reflux/12 h	92
8	**31a**	*i*-Pr	I	**32e**	$B(OH)_2$	MOM	aq $Ba(OH)_2$/DME/reflux/1 h	99

[a] Yields of isolated products.

SCHEME 8

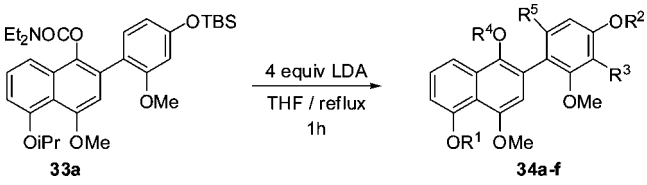


TABLE 2. DreM Reactions of *O*-Carbamate 33a

34	R^1	R^2	R^3	R^4	R^5	Yld,[a] %
a	*i*-Pr	TBS	H	H	H	4
b	*i*-Pr	H	TBS	$CONEt_2$	H	27
c	H	H	TBS	H	H	16
d	*i*-Pr	TBS	H	H	$CONEt_2$	4
e	*i*-Pr	H	TBS	H	$CONEt_2$	21
f	H	H	TBS	H	$CONEt_2$	13

[a] Yields of isolated products.

7) as well as the MOM derivative **33d** in excellent yield (Table 1, entry 8). The boronic acid **32e** was prepared analogously to the preparation of **32d** (see Supporting Information).

Directed Remote Metalation (DreM) Reaction. Completion of the Tetracyclic Ring System: C-Ring Construction. Subjection of biarylcarbamate **33a** to the standard LDA induced DreM−carbamoyl migration conditions[2] led to initially discouraging results (Scheme 8, Table 2). Of the compounds isolated, several are derived from the desired carbamoyl migration process (**34d-f**); however, the desired product **34d** was obtained in only 4% yield. The formation of compound **34a** in very low yield resulting from carbamate cleavage was expected based on previous results.[2] On the other hand, the characterization of **34b**, **34e**, and **34f** (total 61% yield), indicative of competitive C-3′ metalation followed by 4′-O →3′-C TBS migration,[49] suggested the need for a more robust protecting group. Cleavage of the C-1 protective group as evidenced by product **34c** was also competitive, presumably resulting from LDA induced E_2 reaction (*vide infra*).

As a possible circumvention of the lability of the 4′-TBS protective group to DreM conditions, the corresponding O-*i*-Pr derivative **33c** was tested under the standard LDA conditions (Scheme 9).[50] Again, a complex reaction mixture resulted; although cleavage of the C-4′ isopropoxy group was not observed and the desired product **34i** was obtained in 41% yield, the C-5 isopropoxy proved labile accounting for 39% of the reaction mixture in the form of products **34h** and **34j**.[51] The site of isopropyl group cleavage in **34j** was established by cyclization to the lactone **36** and subsequent NOE experiements.[52] In a separate experiment, treatment of **33c** with LDA and direct conversion into the tetracyclic lactone bis-isopropyl ether **35** (Scheme 9) and cleavage of the isopropoxy group with BCl_3 gave lactone **36** which was identical by ^1H NMR to the material obtained from **34j**. Susequent NOE diference experiments confirmed these results.[52] Unfortunately, attempts under a variety of conditions, including excess BCl_3 treatment, to obtain the 4′,5-bisphenol by double deprotection failed, thus thwarting the test of selective 4′-triflation in order to proceed for final alkyl or vinyl group introduction by cross coupling tactics for the completion of the total syntheses.

Contemplation of the failures with feeble (**33a**) and robust (**33c**) protective groups led to examination of the 4-OMOM derivative **33d** (Scheme 10) as a potential expedient and practical solution.[37] Subjection of **33d** to the standard conditions for the DreM protocol afforded the desired hydroxyl amide **37** in a disappointing but, at this stage encouraging, 28% yield. Optimization was achieved after considerable experimentation of the migration conditions. Thus, introduction of LDA in two portions (1.3 equiv and then 1.3 equiv after 1 h, followed by treatment of the reaction mixture with 1:1 HOAc:H_2O afforded **38** in 70% yield. The introduction of the base in two portions may serve to keep the concentration of LDA low during the reaction, suppressing the base induced cleavage of the isopropoxy and carbamoyl groups.[53]

C-8 Substituent Introduction. Completion of the Total Syntheses of defucogilvocarcins V (1a), M (1b), and E (1c). In pursuit of the end game (Scheme 11), the phenol **38** was converted, after several failures owing to solubility problems, into the corresponding triflate **39** employing NEt_3 as a cosolvent (5 equiv) at −78 °C followed by a low temperature quench with $NaHCO_3$. Modified Stille conditions[54] using tri-n-butyl vinylstannane furnished 1-isopropoxydefucogilvocarcin

(48) (a) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

(49) For precedents see: (a) Billideau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515. (b) Sinhababu, A. K.; Kawase, M.; Borchhardt, R. T. *Tetrahedron Lett.* **1987**, *28*, 4139.

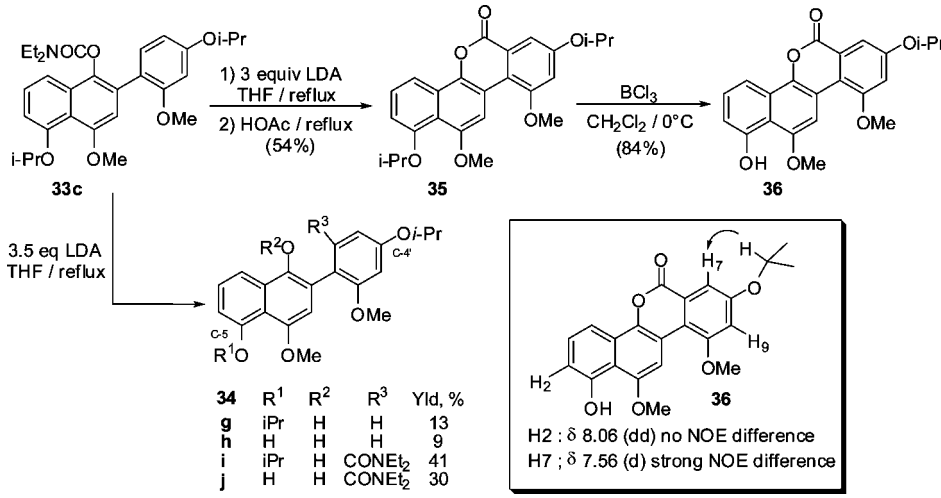
(50) This work was encouraged by the previously demonstrated stability of isopropyl ethers under LDA mediated carbamate DreM rearrangements (ref 1) as well as model studies (ref 51, p 77.)

(51) Selective 5-*i*-Pr cleavage suggests bridging 5-Oi-Pr-4-OMe coordination with LDA and E_2 -type elimination with excess of the reagent, a result which may be rationalized by the Complex Induced Proximity Effect (CIPE): Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225. This rationalization may also be invoked for the reaction of **34i** to give **34j** (90%) under the standard DReM conditions. For a related case, see ref 1.

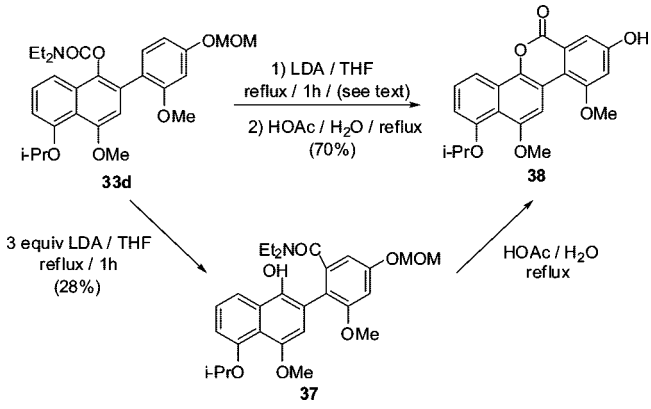
(52) James, C. A. Ph.D thesis, University of Waterloo, 1998.

(53) That the improved yield of **33d** → **38** (combined process) vs **33d** → **37** → **38** (stepwise) results from the portion-wise introduction of LDA is supported by the relative amounts of C-5 phenolic products observed for the former reaction compared to the corresponding reactions of **33a** and **33c**. However, this suggestion is speculative since an experiment with the same substrate using the two different sets of DReM conditions, and to a common product was not carried out. Furthermore, a detailed analysis of DReM reaction products of **33d** was not performed due to the relatively less straightforward (cf. Scheme 8 and 9) purification of the reaction mixtures and the instability of some fractions on silica gel.

SCHEME 9



SCHEME 10



V **40a** in satisfactory yield. Treatment of **39** under Negishi−Quesnelle coupling conditions with MeZnCl[55] afforded the corresponding methyl derivative **40b** in 59% yield while Suzuki conditions[56] with BEt_3 afforded 1-isopropoxydefucogilvocarcin E **40c** in 75% yield and concluded a demonstration of the richness of modern cross coupling chemistry. Finally, as established above for related systems, BCl_3 induced isopropyl ether deprotection proceeded smoothly to afford defucogilvocarcin V **1a** in 95% yield which was shown to be identical with the natural product by comparison of physical and spectroscopic data (see Supporting Information). Similar deprotection of **40b** and **40c** afforded defucogilvocarcin M (**1b**) and defucogilvocarcin E (**1c**) in 83 and 86% yields, respectively.

Arnottin I. With the protection−deprotection gambit of the defucogilvocarcins *en arrière*, arnottin I (**2**) was initially recognized as a less daunting target molecule the retrosynthetic plan for which would follow similar lines (Scheme 12). However, the presence of the methylenedioxy functionality was cause for concern in view of its known sensitivity to strong base conditions.[57]

The construction of the A/B ring precursors **46a,b** (Scheme 13) was initiated from readily available bromosesamol[58] (**43a**) which was smoothly converted into the triflate **43b** and tosylate **43c** derivatives in high yields. Treatment of **43b** and **43c** with *n*-BuLi at −78 and −100 °C respectively in the presence of a large excess of furan afforded the cycloadduct **44a** in good to excellent yields whose ring-opening−aromatization was effected with BCl_3 under low temperature conditions to furnish the naphthol **45a** which, in turn, was acylated to provide the key O-carbamate **46a**. Subsequently, the DoM−$ZnCl_2$ transmetalation−cross coupling sequence of **46a** with arylbromide **48a** or its inverted partner reaction, **47a**, available in modest yield by metalation−iodination of **46a**, with the zinc reagent derived from arylbromide **48a** afforded biaryl **49a** in acceptable yield (see Table 3).

Attempts to effect DreM−carbamoyl migration reactions using LDA, LiTMP, and the Martin *in situ* LiTMP/TMSCl[59] conditions on **49a** were categorically unsuccessful,[52] (Scheme 14) leading to mixtures of starting material, decomposition products, and formation of the catechol **49c** in 22−43% yields as the somewhat predicted product from strong base derived cleavage of the methylenedioxy group.[57]

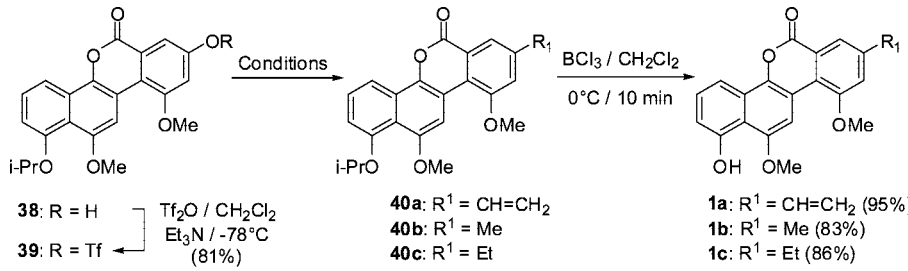
To circumvent this impasse, the diisopropoxy biaryl **49b** was prepared for a DreM study based on the consideration that the position of the protection would mitigate LDA mediated elimination as had been observed in the gilvocarcin series (**33a** Scheme 8, **33c** Scheme 9). Initial Negishi coupling (Scheme 13) afforded the desired biaryl **49b** in poor yield. Success was achieved again drawing on the lessons learned in the synthesis of the defucogilvocarcins (Table 1, entry 7). Thus, Suzuki−Miyaura coupling of **48b** and **47b** using $Ba(OH)_2$ as base afforded the diisopropoxy biphenyl DReM precursor **49b** in nearly quantitative yield.

After considerable experimentation to effect the carbamoyl migration, the lessons learned in the synthesis of gilvocarcin **33d** → **38** (Scheme 10) bore fruit in that portion-wise addition of LDA to a solution of **49b** at rt provided a migration product in 68% yield. Although the operation of a DMG effect of the 2-OMe was expected to produce **50a**, ^{1}H NMR failed to clearly

(54) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(55) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349.
(56) (a) Harada, T.; Yoshida, T.; Inoue, A.; Takeuchi, M.; Oku, A. *Synlett* **1995**, 283. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

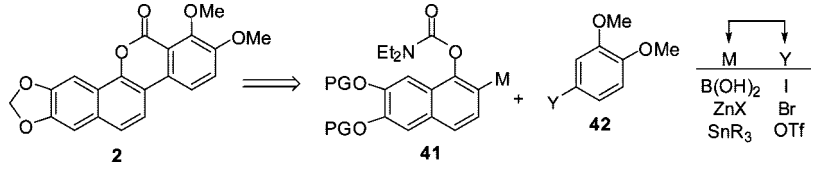
(57) (a) *Protective Groups in Organic Synthesis*, 3rd ed; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley and Sons, Inc.: New York, 1999. For sensitivity during addition of RMgX reagents: (b) Pizzonero, M,; Keller, L.; Dumas, F.; Ourevitch, M.; Morgant, G.; De-Bire Spasojevic, A.; Bogdanov, G.; Ghermani, N. E.; D'Angelo, J. *J. Org. Chem.* **2004**, *69* (13), 4336. Alkoxides and NaCN: (c) Imakura, Y.; Okimoto, K.; Konishi, T.; Hisazumi, M.; Yamazaki, J.; Kobayashi, S.; Yamashita, S. *Chem. Pharm. Bull.* **1992**, *40* (7), 1691.
(58) Alexander, B. H.; Oda, T. A.; Brown, R. T.; Gertler, S. I. *J. Org. Chem.* **1958**, *23*, 1969.
(59) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

SCHEME 11



Conditions	R^1	40	Yld, %
$C_2H_3SnBu_3$ / Pd_2dba_3 NMP / LiCl / (2-furyl)$_3$P	vinyl	**a**	69
MeZnCl / $NiCl_2$(dppp) THF / reflux	Me	**b**	59
BEt_3 / $PdCl_2$(dppf) K_3PO_4 / THF / relfux	Et	**c**	75

SCHEME 12



SCHEME 13

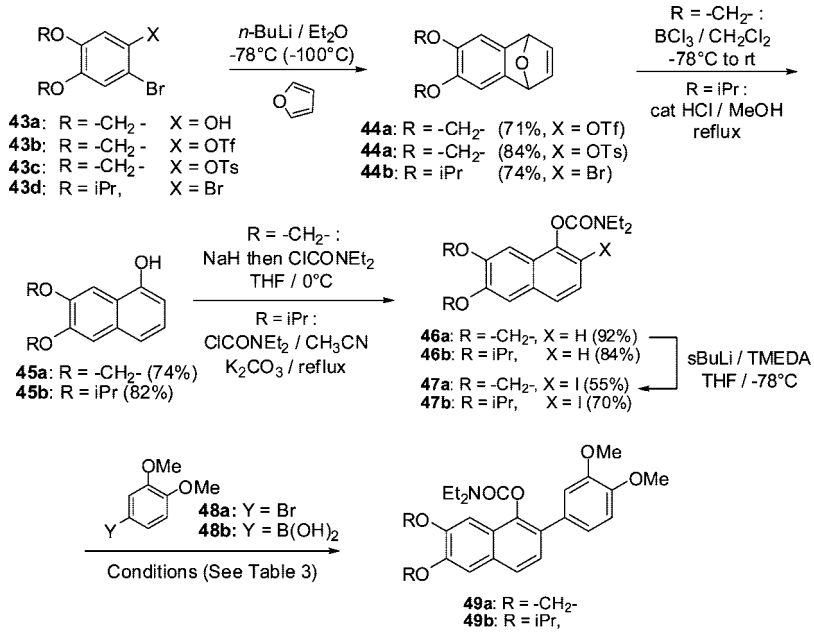


TABLE 3. Cross Coupling Reactions for the Preparation of 49a,b

49	R	X	Y	Yld, %
a	-CH_2-	ZnCl	Br[a]	60
a	-CH_2-	I	ZnCl	68
b	*i*-Pr	ZnCl	Br	32
b	*i*-Pr	I	$B(OH)_2$[b]	>95

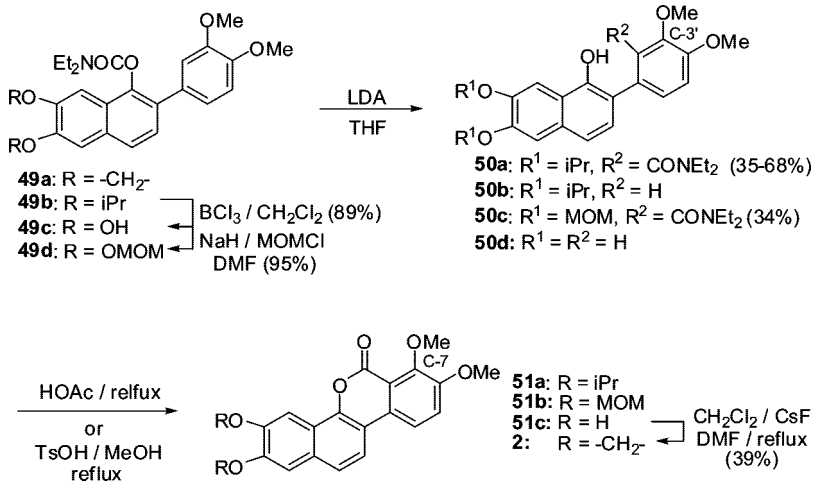
[a] $Pd(PPh_3)_4$/THF/reflux. [b] $Ba(OH)_2$/DME/reflux.

establish the regiochemistry of the product and therefore the crude material was cyclized to the lactone **51a** (62% yield over two steps) for structural verification. Isopropyl ether cleavage with BCl_3 of either **50a** or **51a** under a variety of conditions[52] led to complex mixtures whose products were difficult to characterize due to their insolubility. NMR analysis suggested loss of the isopropyl protective group in addition to competitive 3′-demethylation, resulting from initial coordination of reagent to the amide or lactone carbonyl.[60]

The use of the successful MOM protection strategy devised and used in the gilvocarcin series (Scheme 10) for Arnottin I was initially discounted due to previous DreM results observed for substrate **33b**.[61] In the hope of altering cyclization conditions that may allow isolation of **51b** (Scheme 14), this protection mode was now placed to the test on the available **49b**. BCl_3

(60) (a) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1329–1337. (b) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899.

SCHEME 14



mediated isopropyl ether cleavage proceeded smoothly to give the corresponding catechol which, upon treatment with MOMCl furnished the requisite **49d** in high yield. Exploration of a variety of conditions using LDA as base afforded the hydroxyl- amide **50c** in optimal 34% yield. Attempts at simultaneous cyclization−MOM cleavage resulted, as feared, in the formation of mixtures of intractable products which, when subjected to conditions of methylenedioxy formation (CH_2Br_2/CuO/K_2CO_3/DMF/reflux),[62] led, in irreproducible manner, to a hint of the formation of arnottin I (**2**). However, treatment of **49d** with excess LDA followed by cyclization with TsOH in MeOH led to the desired catechol **51c** which fortunately precipitated from the reaction mixture, allowing its isolation in 44% yield. Of the available methods for catechol methylenation,[62,63] the reliable conditions of Clark[64] were adapted to the insoluble **51c** to furnish arnottin I (**2**) in 39% yield. Synthetic arnottin I was shown to be identical with the natural product by physical and spectral data comparison (see Experimental Section).

Conclusions

Although thought and experiment is being expended in protective group-free strategies,[65] practice of organic synthesis continues to require circuitous protection regimens that cause annoyance, two additional steps (or more) and, at times, completely incapacitate a total synthesis project at a very inappropriate stage. Synthesis thence continues with strong dependency *and* expediency on protective measures chosen from the armory of approximately one thousand protective groups.[63] In the present synthetic programs to the defucogilvocarcins and arnottin I, the key objective was to assess the application of key metalation and cross coupling methods evolving in our laboratories. Secondary but rational thought at the outset and as the work progressed taught us the protection−deprotection requirements for aryl oxygen functionality. In the events, nuances in reactivity and drastic contrasts in physical properties of intermediates led to unpredictable impasses and the need for several renewed ascents as may be predicted with certainty in total synthesis endeavors.

Nevertheless, defucogilvocarcin V (**1,** Scheme 11) was conquered in 9 steps and 16% overall yield starting from commercially available juglone. Aryl - furan cycloaddition (see Supporting Information) and the more reliable reductive acylation of isopropoxy juglone routes were established for the construction of the differentially protected trioxygenated naphthalenes **28a** and **31a** (Scheme 6). Thence, convergence to the key C4′-triflate **39** was achieved by application of modern cross coupling strategies (Suzuki-Miyaura, Negishi, Stille) which allowed the efficient additional syntheses of defucogilvocarcin M (**1b**, Scheme 11) and defucogilvocarcin E (**1c**, Scheme 11) in 9 steps and 15% overall yields. These routes may be adaptable to the preparation of non-natural analogues with an eye toward biological screening. As one possibility, appendage of OMe, CO_2R, Ph, or alkene substituents to the vinyl group of defucogilvocarcin V (**1a**, Scheme 1) may sufficiently alter the chromophore for potentially enhanced interaction with DNA under UV irradiation.[17]

The total synthesis of arnottin I (**2**, Scheme 14) was achieved in a less satisfactory 11 steps and 2% overall yield. The DreM−carbamoyl migration protocol (Scheme 14) was shown to be an effective, convergent strategy for the construction of the naphtho[1,2-*b*]benzo[*d*]pyran-6-one framework of these natural products which led to its generalization for the preparation of heterocyclic counterparts.[66] Considerable useful knowledge was gained in use of isopropyl and silyl aryl ethers as protective groups under LDA conditions and the instability of the methylenedioxy group to such conditions was confirmed.

Experimental Section

For General Methods and Standard Procedures see the Supporting Information.

***N*,*N*-Diethyl *O*-(4-Hydroxy-5-isopropoxy)naphthyl-1-carbamate (30).** A mixture of 5-isopropoxyjuglone (**29**)[46] (0.289 g, 1.34

(61) DreM reactions of **33b** were as complex as those of **33a**, yielding several C5-phenolic products. The subsequent successful use of a C4′- MOM PG in **33c** provided the impetus for its deployment for the protection of **49c** (Scheme 14). See also ref 53.

(62) Bick, I. R. C.; Russell, R. A. *Aust. J. Chem.* **1969**, *22*, 1563.

(63) *Protective Groups in Organic Synthesis*, 4th ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley and Sons, Inc.: New York, 2007; p 424.

(64) Clark, J. H.; Holland, H. L.; Miller, J. L. *Tetrahedron Lett.* **1976**, *17*, 3361.

(65) (a) Jackson, R. F. W.; Rilatt, I.; Murray, P. J. *Org. Biomol. Chem.* **2004**, *2*, 110. (b) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (c) Jeanmart, S.; Taylor, R. K. *Tetrahedron Lett.* **2005**, *46*, 9043. (d) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738. (e) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404.

(66) James, C. A.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, DOI: 10.1021/jo900146d.

mmol), $ClCONEt_2$ (0.5 mL, 3.95 mmol), pyridine (0.32 mL, 3.96 mmol), and Zn dust (0.917 g, 14.03 mmol) in $CHCl_3$ (7.0 mL) was heated at reflux until disappearance of starting material (TLC, 2 h). The reaction mixture was cooled, diluted with H_2O followed by 10% aq HCl, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (×2), and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexane/EtOAc) and then by recrystallization (EtOH/H_2O), affording the title compound as light-brown plates (0.294 g, 70%). Mp 66−67 °C (EtOH/H_2O). IR (KBr) ν (max) 3374, 3064, 2977, 2934, 1715, 1635, 1393, 1514, 1462, 1404, 1350, 1316, 1267, 1235, 1211, 1154, 1109, 1033 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.69 (s, 1H), (dd J = 8.4, 1.3 Hz, 1H), 7.32 (t J = 7.4, Hz, 1H), 7.12 (d J = 8.4 Hz, 1H), 6.82 (d J = 7.6, 1.0 Hz, 1H), 6.79 (d J = 8.4 Hz, 1H), 4.85 (sept J = 6.1 Hz, 1H), 3.57 (q, br, J = 7.0 Hz, 2H), 3.42 (q, br, J = 7.0 Hz, 2H), 1.49 (d J = 6.1 Hz, 6H), 1.35 (t, br, J = 7.0 Hz, 3H), (t, br, J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.6 (e), 154.3 (e), 152.3 (e), 139.3 (e), 130.2 (e), 126.2 (o), 120.1 (o), 116.3 (e), 115.0 (o), 109.1 (o), 107.0 (o), 72.89 (o), 42.25 (e), 41.89 (e), 21.96 (o), 14.42 (o), 12.61 (o), MS (EI (70 eV)) *m/e*: (rel intensity) 317 (M^+, 25), 260 (0.5), 204 (1.3), 175 (12), 147 (1.6), 100 (100), 72 (27); Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41 found: C, 68.26; H, 7.36; N, 4.33.

***N,N*-Diethyl-5-isopropoxy-4-methoxy-1-naphthyl-*O*-carbamate (28a). Procedure 1: From Naphthol 27a.** According to General Procedure A, a mixture of naphthol **27a** (see Supporting Information) (2.86 g, 12.32 mmol), K_2CO_3 (2.92 g, 18.5 mmol), $ClCONEt_2$ (2.34 mL, 18.47 mmol) in CH_3CN (100 mL) was heated at reflux for 12 h. Standard workup followed by column chromatography (7:3 hexane/Et_2O), and recrystallization (hexane/Et_2O) afforded the title compound as colorless plates (3.68 g, 90%). Mp 84−85 °C (hexane/Et_2O); IR (KBr) ν (max) 3070, 2950, 1722, 1586, 1513, 1323, 1249, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd J = 8.4, 1.1 Hz, 1H), 7.36 (dd J = 8.4, 7.6 Hz, 1H), 7.10 (d J = 8.4 Hz, 1H), 6.90 (dd J = 7.6, 1.1 Hz, 1H), 6.80 (d J = 8.4 Hz, 1H), 4.55 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.61 (q J = 7.0 Hz, 2H), 3.40 (q J = 7.0 Hz, 2H), 1.42 (d J = 6.0 Hz, 6H), 1.36 (t J = 7.0 Hz, 3H), 1.23 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.2 (e), 154.7 (e), 141.1 (e), 131.2 (e), 126.8 (o), 120.4 (e), 118.4 (o), 114.8 (o), 113.8 (o), 106.2 (o), 73.30 (o), 56.93 (o), 42.39 (e), 42.02 (e), 22.13 (o), 14.56 (o), 13.52 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 331 (M^+, 46), 289 (2), 231 (4), 189 (20), 100 (100), 72 (58); Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23; found: C, 69.00; H, 7.71; N, 4.22.

Procedure 2: From Hydroxycarbamate 30. A mixture of **30** (1.37 g, 4.35 mmol), K_2CO_3 (3.39 g, 24.53 mmol), and MeI (1.60 mL, 25.7 mmol) in acetone (50 mL) was heated at reflux for 12 h. The reaction mixture was cooled to rt and standard workup followed by column chromatography (silica plug, 2:1 hexane/EtOAc), and recrystallization (hexane/Et_2O) afforded the title compound as colorless plates (1.21 g, 84%). Mp 86−87 °C (hexane/Et_2O). Mixture mp with a sample prepared by Procedure 1: 85−86 °C. Spectral properties were found to be identical with those for material prepared by procedure 1.

***N,N*-Diethyl *O*-(2-Iodo-5-isopropoxy-4-methoxy)-1-naphthylcarbamate (31a).** According to General Procedure B, a solution of *N,N*-diethyl *O*-(4-methoxy-5-isopropoxy)-1-naphthylcarbamate (**28a**) (0.278 g, 0.839 mmol) and TMEDA (0.15 mL, 0.99 mmol) in THF (10 mL) at −78 °C was treated with a solution of s-BuLi (0.79 mL, 1.28 mol/L). The reaction mixture was stirred for 20 min, a solution of I_2 in THF (5 mL) was added and the resulting solution was allowed to warm to rt (6 h). Standard workup followed by column chromatography (4:1 hexane/EtOAc) afforded the title compound (0.383 g, 94%) as a viscous oil. IR (neat) ν (max) 2976, 2983, 1724, 1609, 1575, 1502, 1457, 1424 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.07 (s, 1H), 6.94 (t J = 4.4 Hz, 1H), 4.51 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.63 (m, 2H), 3.42 (m, 2H), 1.42 (t J = 7.1 Hz, 3H), 1.36 (d J = 6.0 Hz, 6H), 1.25 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.2 (e), 154.9 (e), 152.9 (e), 142.2 (e), 131.2 (e), 127.6 (o), 119.8 (e), 114.9 (o), 114.8 (o), 113.6 (o), 88.16 (e), 73.1 (e), 56.7 (o), 42.4 (e), 42.1 (e), 21.9 (o), 14.5 (o), 13.3 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 457 (M^+; 14), 315 (13), 357 (0.1) 100 (100), 72 (63); HRMS (EI (70 eV)) *m/e* calcd for $C_{19}H_{24}NO_4I$: 457.0750, found 457.0731.

2-Methoxy-4-methoxymethoxybromobenzene (32c). To a suspension of NaH (0.833 g, 60% dispersion in mineral oil, 20.83 mmol), in DMF (20 mL) at 0 °C was added a solution of 4-bromo-3-methoxyphenol[47] (2.38 g, 11.78 mmol) in DMF (15 mL). The resulting mixture was allowed to stir at 0 °C until the evolution of H_2 ceased (30 min); MOMCl (1.50 mL, 19.75 mmol) was then added, and the reaction mixture was allowed to warm to rt over 2 h. The resulting suspension was poured slowly into 150 mL of ice water and the whole was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed (H_2O (5 × 100 mL), brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by distillation giving a colorless liquid (2.64 g, 91%). Bp 100−105 °C/0.2 mmHg; IR (neat) ν (max) 2935, 2831, 1587, 1471, 1409, 1288, 1215, 1192, 1155, 1079 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (d J = 8.6 Hz, 1H), 6.46 (d J = 2.6 Hz, 1H), 6.39 (dd J = 8.6, 2.4 Hz, 1H), 4.99 (s, 2H), 3.70 (s, 3 h), 3.31 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.8 (e) 156.5 (e), 133.2 (o), 108.9 (o), 103.7 (e), 101.6 (o), 94.6 (e), 56.1 (o), 56.0 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 248 (100), 246 (100), 218 (41), 216 (41), 175 (18), 173 (18); HRMS (EI (70 eV)) *m/e* calcd for $C_9H_{11}BrO_3$: 245.9891, found 245.9882.

2-Methoxy-4-methoxymethoxyphenylboronic acid (32e). To a solution of 4-methoxymethoxy-2-methoxybromobenzene (**32c**) (2.13 g, 8.60 mmol) in THF (50 mL) at −78 °C was added a solution of *n*-BuLi (1.64 mL, 1.75 mol/L) and the resulting solution was allowed to stir for 10 min. A solution of $B(OMe)_3$ (3.00 mL, 26.42 mmol) was added in one portion and the mixture was allowed to warm slowly to rt. The reaction mixture was quenched with satd NH_4Cl solution and the THF ws removed in vacuo. The residue was diluted with H_2O and acidified to ca. pH 5−6 with 10% HCl. The acidic aqueous solution was then extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by recrystallization (hexane/Et_2O) giving the title compound as colorless plates (1.31 g, 72%). mp 79−81 °C (hexane/Et_2O); IR (KBr) ν (max) 3320 (br), 1604, 1572, 1540, 1504, 1455, 1419, 1341, 1306, 1260, 1190, 1149, 1118, 1076 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 (d J = 8.2 Hz, 1H), 6.70 (dd J = 8.2, 2.0 Hz, 1H), 6.60 (d J = 2.0 Hz, 1H), 5.86 (s (br), 2H), 5.21 (s, 2H), 3.90 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.8 (e), 161.1 (e), 138.6 (o), 137.9 (o), 108.0 (o), 99.1 (o), 94.1(e), 56.0 (o), 55.4 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 212 (M^+, 11), 182 (5.3), 168 (3.2), 138 (2.7), 69 (5.3), 45 (100); Anal. Calcd for $C_9H_{13}BO_5$: C, 50.99; H, 6.18; found: C, 50.90; H, 6.27.

***N,N*-Diethyl *O*-[4-Methoxy-5-isopropoxy-2-(2-methoxy-5-methoxymethoxyphenyl)]-1-naphthylcarbamate (33d).** According to General Procedure G, a mixture of naphthyl iodide **31a** (1.00 g, 2.1970 mmol), arylboronic acid **32e** (0.677 g, 3.1920 mmol), $Ba(OH)_2$•$8H_2O$ (1.73 g, 5.48 mmol), and $Pd(PPh_3)_4$ (0.140 g, 0.121 mmol) in DME (100 mL) and H_2O (10 mL) was refluxed for 3 h. Standard workup followed by column chromatography (2:1 hexane/EtOAc) afforded the title compound as a gum (1.05 g, 99%). IR (neat) ν (max) 2961, 1715, 1581, 1509, 1460, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd J = 8.4,1.3 Hz, 1H), 7.35 (dd J = 8.4, 7.5 Hz, 1H), 7.24 (dd J = 7.5, 1.3 Hz, 1H), 6.93 (dd J = 7.5, 1.3 Hz, 1H), 6.76 (s, 1H), 6.68 (m, 2H), 5.21 (s, 2H), 4.53 (sept J = 6.0 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 2.05 (m, 4H), 1.39 (d J = 6.0 Hz, 6H), 1.03 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.8 (e), 157.5 (e), 154.6 (e), 153.6 (e), 153.5 (e), 138.1 (e), 127.7 (e), 126.3 (o), 120.4 (e), 119.4 (e), 115.1 (o), 113.2 (o), 109.3 (o), 106.8 (o), 99.9 (o), 94.1 (e), 72.7 (o), 56.3 (o), 55.4 (o), 55.1 (o), 41.5 (e), 41.2 (e), 21.6 (o), 13.6 (o), 12.7 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 497 (M^+, 36) 455 (6.2), 397 (32), 331

(10), 271 (8.4), 227 (8.0), 168 (62), 100 (100), 72 (44); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{35}NO_7$: 497.2415, found: 497.2412.

***N,N*-Diethyl 3-Methoxy-5-methoxymethoxy-2-(4-methoxy-5-isopropoxy-1-hydroxynaphthyl)benzamide (37).** According to General Procedure C1, a solution of carbamate **33d** (0.520 g, 0.956 mmol) in THF (8 mL) was added at 0 °C to a solution of LDA (3.24 mmol) in THF (5 mL). The cooling bath was removed, and the mixture was heated to reflux until disappearance of starting material (TLC) (1 h). Standard workup followed by column chromatography (3:2 hexane/EtOAc) afforded the title compound (0.145 mg 28%) as a glass. IR (neat) ν (max) 3238, 2974, 2935, 1600, 1482, 1455, 1411, 1377, 1325, 1274, 1217, 1187, 1153, 1127, 1078 cm^{-1}; NMR indicated a 3:1 mixture of rotamers. Absorptions for the major rotamer is given followed by the corresponding peaks for the minor rotamer: ^1H NMR (250 MHz, $CDCl_3$) δ 8.06 (d J = 8.3 Hz, 1H) 7.99 (d J = 8.3 Hz, 1H), 7.32 (t J = 8.0 Hz, 1H) corresponding rotamer peak partially obscured, 6.94 (d J = 7.6 Hz, 1H) 6.98 (d J = 7.6 Hz, 1H), 6.71 (d J = 2.2 Hz, 1H) 6.83 unresolved d 1H, 6.60 (d J = 2.3 Hz, 1H) 6.69 unresolved d 1H, 6.56 (s 1H) 6.87 (s, 1H), 6.00 (s, br, 1H, exch) 7.57 (s, br, 1H, exch), 5.24 (d J = 6.8 Hz, 1H) corresponding rotamer peak partially obscured, 5.17 (d J = 6.8 Hz, 1H) 5.19 (d, J = 6.6 Hz), 4.56, (sept J = 6.0 Hz, 1H) 4.45 (sept J = 6.0 Hz), 3.83 (s, 3H) 3.89 (s), 3.66 (s, 3H) 3.85 (s), 3.50 (s, 3H) rotamer peak obscured, 3.42 (m, 1H) 3.56 (m), 3.20 (m, 1H) 2.83 (m), 3.01 (m, 2H) 2.55 (m), 1.40 (d J = 6.0 Hz, 1H) 1.34 (d J = 6.0 Hz), 0.98 (t J = 7.0 Hz, 3H) 1.24 (t J = 7.0 Hz), 0.62 (t J = 7.0 Hz, 3H) 0.69 (t J = 7.0 Hz, H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.5 (e) 169.3 (e), 158.7 (e) 158.4 (e), 158.1 (e) 156.1 (e), 153.9 (e) 154.4 (e), 149.8 (e) 149.9 (e), 144.1 (e) 142.5 (e), 138.6 (e) 140.6 (e), 131.0 (e) 128.9 (e), 125.2 (o) 125.5 (o), 120.1 (e) 120.0 (e), 118.4 (e) 117.1 (e), 117.4 (e) 116.5 (e), 117.2 (o) 116.6 (o), 113.1 (o) 115.5 (o), 111.9 (o) 109.7 (o), 104.5 (o) 107.9 (o), 101.0 (o) 100.6 (o), 94.4 (e) corresponding rotamer peak obscured, 72.4 (o) 73.9 (o), 57.8 (o) 56.0 (o), 55.9 (o) 56.4 (o), 55.6 (o) 56.2 (o), 42.9 (e) 41.8 (e), 38.7 (e) 38.0 (e), 21.9 (o) 21.9 (o), 13.6 (o) 14.0 (o), 11.5 (o) 11.8 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 497 (5) M^+, 481 (10), 424 (100), 408 (45), 394 (8), 382 (97), 368 (30), 352 (10), 338 (31), 323 (13), 294 (14), 279 (12); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{35}NO_7$: 497.2415, found 497.2409.

8-Hydroxy-1-isopropoxy-10,12-dimethoxy-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (38). According to General Procedure C2, a solution of carbamate **33d** (1.18 g, 2.38 mmol) in THF (15 mL) was added to a solution of LDA (3.05 mmol) in THF (30 mL) and the mixture heated at reflux for 2 h. At this point, a solution of LDA (3.05 mmol) in THF (5 mL) was added. Heating was continued until the disappearance of starting material (TLC) (1 h). Standard workup afforded the crude hydroxyamide which was dissolved in HOAc (10 mL) and the resulting solution was heated at reflux for 10 min. After cooling, an equal volume of H_2O was added and heating was continued for 1 h. The reaction mixture was cooled to rt, the solvents were removed *in vacuo,* and the residue was dissolved in acetone. Silica gel (10 g) was added and the acetone was removed in vacuo. The residue was dry loaded directly onto a flash column. Purification by column chromatography (2:1 hexane/EtOAc → EtOAc) afforded the title compound as a yellow powder (0.641 g, 70% which could not be recrystallized due to its insolubility, mp > 260 °C (dec). IR (KBr) ν (max) 3393, 2956, 1693, 1601, 1487, 1452 cm^{-1}; ^1H NMR (250 MHz, pyridine-d_5) δ 8.56 (s, 1H) 8.29 (d J = 8.5 Hz, 1H), 8.01 (d J = 2.2 Hz, 1H), 7.50 (m, 1H overlapping with solvent), 7.20 (d J = 2.2 Hz, 1H), 7.09 (d J = 7.7 Hz, 1H), 5.50 (s, br, 1H), 4.61 (sept J = 6.0 Hz, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 1.40 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.3 (e), 160.5 (e), 159.7 (e), 155.5 (e), 153.5 (e), 139.8 (e), 127.6 (e), 127.6 (o), 125.0 (e), 119.1 (e), 116.73 (e), 114.9 (o), 114.7 (e), 113.0 (o), 107.9 (o), 107.3 (o), 105.4 (o), 72.4 (o), 57.0 (o), 56.2 (o), 22.2 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 380 (M^+, 74), 338 (100), 323 (29), 295 (25), 252 (7.2), 236 (4.0); HRMS (EI (70 eV)) *m/e* calcd for $C_{22}H_{20}O_6$: 380.1260, found 380.1257.

1-Isopropoxy-10,12-dimethoxy-8-trifluoro-methanesulfonyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (39). To a suspension of phenol **38** (0.699 g, 1.84 mmol) in CH_2Cl_2 (35 mL) at rt was added Et_3N (1.50 mL, 10.76 mmol) The resulting homogeneous yellow solution was cooled to −78 °C, treated with Tf_2O (0.40 mL, 2.37 mmol) by dropwise addition, and the whole was allowed to stir for 1 h, quenched with sat $NaHCO_3$ and the cooling bath was removed. Standard workup followed by column chromatography (7:2:1 hexane/CH_2Cl_2/EtOAc) afforded **39** (0.759 g, 81%) as bright-yellow needles, mp 219−221 °C (hexane/CH_2Cl_2); IR (CH_2Cl_2) ν (max) 3058, 2982, 1728, 1592, 1462, 1424 1386, 1134 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.20 (dd J = 8.5, 0.8 Hz, 1H), 7.99 (d J = 2.5 Hz, 1H), 7.51 (dd J = 8.2, 8.0 Hz, 1H), 7.17 (d J = 2.5 Hz, 1H), 7.08 (d, br, J = 7.5 Hz, 1H), 4.62 (sept, J = 6.0 Hz, 1H), 4.13 (s, 3H), 3.99 (s, 3H), 1.45 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 159.6 (e), 158.7 (e), 154.7 (e), 153.2 (e), 148.6 (e), 141.2 (e), 127.4 (e), 126.6 (e), 124.9 (e), 124.3 (e), 119.8 (e), 118.7 (e, q J = 321 Hz), 103.6 (o), 72.9 (o), 56.7 (o), 56.5 (o), 22.0 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 512 (41), 476 (49), 337 (100), 309 (9), 294 (26), 279 (14) Anal. Calcd for $C_{23}H_{19}SO_8F_3$: C, 53.91; H, 3.74; found: C,54.14; H, 3.88.

1-Isopropoxy-10,12-dimethoxy-8-vinyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (40a). A solution of triflate **39** (0.102 g, 0.199 mmol), vinyltributyltin (79.8 mg, 0.239 mmol), LiCl (45.0 mg, 1.06 mmol), tri-(2-furyl)phosphine (4.90 mg, 0.201 mmol), and Pd_2dba_3 (9.8 mg, 0.0107 mmol) in anhydrous NMP was stirred at rt under Ar for 1 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed (H_2O, brine) and dried (Na_2SO_4). The solvents were removed under reduced pressure (high vacuum for remaining NMP), and the residue was purified by column chromatography (5:2 hexane/EtOAc) and recrystallization (CH_2Cl_2/hexane), affording the title compound (53.4 mg, 69%) as a fine yellow powder. Mp 211−213 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2) ν (max) 3154, 2984, 1722, 1587, 1422, 1384 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.19 (dd J = 8.4, 1.0 Hz, 1H), 8.07 (d J = 1.5 Hz, 1H), 7.47 (dd J = 7.8, 8.4 Hz, 1H), 7.26 (d overlaps solvent, 1H), 7.05 (dd J = 7.8, 0.8 Hz, 1H), 6.74 (dd J = 10.9, 17.5 Hz, 1H), 5.90 (d J = 17.5 Hz, 1H), 5.04 (d J = 10.9 Hz, 1H), 4.58 (sept J = 6.1 Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 1.43 (d J = 6.1 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 161.2 (e), 157.2 (e), 154.6 (e), 152.7 (e), 140.8 (e), 138.3 (e), 135.3 (o), 127.0 (o), 126.7 (e), 123.6 (e), 123.2 (e), 120.3 (o), 119.5 (e), 116.1 (e), 115.5 (o), 114.6 (o), 113.7 (o), 113.2 (e), 104.3 (o), 73.1 (o), 56.4 (o), 56.0 (o), 22.1 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 390 (M^+, 34), 348 (100), 333 (44), 305 (37), 267 (14); Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.70; found: C, 73.90; H, 5.70.

1-Isopropoxy-10,12-dimethoxy-8-methyl-6H-naphtho[1,2-*b*]benzo[*d*]-pyran-6-one (40b). To a solution of MeLi (0.96 mL, 2.20 mol/L in Et_2O) in THF (10 mL) at −78 °C was added dropwise *via* canula a solution of flame-dried $ZnCl_2$ (0.345 g, 2.53 mmol) in THF (10 mL) over 15 min. The solution was maintained at −78 °C for 30 min and then allowed to warm to rt over a period of 1 h. This solution was then added *via* canula to a separate flame-dried flask which was charged with triflate **39** (0.370 g, 0.722 mmol) and $NiCl_2$(dppp) (43.0 mg, 0.0793 mmol). The resulting solution was stirred at rt for 2 h. Standard workup followed by column chromatography (3:1 hexane/EtOAc) afforded the title compound (0.161 g, 59%) as fine yellow needles. Mp 232−233 °C (hexane/CH_2Cl_2). IR (CH_2Cl_2) ν (max) 3018, 2990, 1722, 1588, 1422, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.23, (s, 1H), 8.18 (dd J = 7.7, 0.8 Hz, 1H), 7.85 (s, 1H), 7.47 (app t J = 8.1 Hz, 1H), 7.03 (m, 2H), 4.58 (sept J = 6.0 Hz, H), 3.98 (s, 3H), 3.96 (s, 3H), 2.42 (s, 3H), 1.43 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.4 (e), 157.0 (e), 154.5 (e), 152.6 (e), 140.5 (e), 139.6 (o), 126.9 (e), 126.8 (o), 122.5 (e), 121.8 (o), 119.3 (o), 117.9 (e), 115.5 (e),

114.4 (e), 113.4 (o), 73.1 (o), 56.6 (o), 56.0 (o), 21.5 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 378 (M^+, 40), 336 (100), 321 (41), 293, (26),250 (9); Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86; found: C, 72.58; H, 5.64.

1-Isopropoxy-10,12-dimethoxy-8-ethyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (40c). A suspension of K_3PO_4 (0.224 g, 1.05 mmol), $PdCl_2$(dppf) (20.0 mg, 0.0301 mmol) and BEt_3 (0.95 mL, 1.0 mol/L in hexane) in THF (5 mL) under Ar was stirred at rt for 10 min and a suspension of triflate **39** (0.231 g, 0.450 mmol) in THF (4 × 5 mL) was added. The reaction mixture was heated at reflux until disappearance of starting material (TLC) (1 h). The reaction mixture was cooled to rt, treated with 5% NaOH (1.4 mL) and 30% H_2O_2 (0.5 mL), and the whole was stirred at rt for 1.5 h. The mixture was then poured into 10% HCl (20 mL) containing ice and the whole was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (7:1:0.5 → 7:2:1 hexane/CH_2Cl_2/EtOAc) and recrystallization to afford the title compound (0.132 g, 75%) as fine yellow needles. Mp 215−216 °C (hexane/CH_2Cl_2). IR (KBr) ν (max) 3055, 2975, 1719, 1610, 1586, 1484, 1448, 1382 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.18 (dd J = 8.4, 0.9 Hz, 1H), 7.85 (d J = 0.6 Hz, 1H), 7.46 (dd J = 8.4, 7.8 Hz, 1H), 7.02 (m, 2H), 4.57 (sept J = 6.0 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.69 (q J = 7.6 Hz, 4H), 1.43 (d J = 6.0 Hz, 6H), 1.28 (t J = 7.6 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.4 (e), 157.1 (e), 154.5 (e), 152.6 (e), 145.7 (e), 140.5 (e), 126.8 (e), 126.8 (o), 126.7 (e), 123.0 (e), 122.0 (e), 121.2 (o), 119.3 (e), 116.8 (o), 115.4 (o), 114.3 (o), 113.4 (e), 104.7 (e), 73.0 (o), 56.5 (o), 56.0(o), 28.8 (e), 22.1 (o), 14.9 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 392 (M^+, 54), 350 (100), 335 (41), 307 (34), 249 (9); Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16; found: C, 73.37; H, 6.06.

1-Hydroxy-10,12-dimethoxy-8-vinyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (defucogilvocarcin V) (1a). To a solution of isopropyl ether **40a** (33.1 mg, 0.0849 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise BCl_3 (0.40 mL, 1.0 mol/L in CH_2Cl_2). The solution was stirred for 15 min and quenched with H_2O. Standard workup followed by column chromatography (4:1 CH_2Cl_2/hexane) afforded **1a** as a yellow solid (28.4 mg, 95%). Mp 259−264 °C (dec), lit mp[26a] 263−265 °C (dec). ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, 1H, exch), 8.29 (s, 1H), 8.13 (d J = 1.7 Hz, 1H), 8.06 (d J = 8.5, 1.0 Hz, 1H), 7.49 (app t J= 8.0 Hz, 1H), 7.32 (d J = 1.7 Hz, 1H), 7.01 (dd J = 7.7, 1.0 Hz, 1H), 6.92 (dd J = 17.6, 10.9 Hz, 1H), 5.94 (d J = 17.6 Hz, 1H), 5.45 (d J = 10.9 Hz, 1H), 4.10 (s, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 348 (M^+, 100), 333 (19), 319 (4.4), 262 (7.0), 305 (19), 234 (2.9), 205 (3.1), 174 (10), 149 (14); HRMS (EI (70 eV)) *m/e* calcd for $C_{21}H_{16}O_5$: 348.0998, found 348.0992. Spectral data were found to be identical to those reported for the authentic material.[26a]

1-Hydroxy-10,12-dimethoxy-8-methyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one, (Defucogilvocarcin M) (1b). To a solution of isopropyl ether **40b** (0.113 g, 0.298 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise over 10 min BCl_3 (1.50 mL, 1.0 mol/L in CH_2Cl_2). The solution was stirred for 10 min and then treated with H_2O. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 CH_2Cl_2/EtOAc) and recrystallization to give **1b** (83.4 mg, 83%) as a fine yellow powder, mp 271−274 °C (dec), (CH_2Cl_2/hexane), lit[67] mp 273−274 °C (dec). ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.23 (s, 1H), 8.04 (dd J = 8.4, 0.9 Hz, 1H), 7.89 (s, 1H), 7.48 (app t J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.99 (dd J = 7.7, 0.9 Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 2.48 (s, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 336 (M^+, 100), 321 (37), 293 (36), 250 (12); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{16}O_5$: 336.0998, found 336.0991. Spectral data were found to be identical to those reported for the authentic material.[67]

1-Hydroxy-10,12-dimethoxy-8-ethyl-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (Defucogilvocarcin E) (1c). To a solution of isopropyl ether **40c** (56.0 mg, 0.143 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise BCl_3 (0.72 mL, 1.0 mol/L in CH_2Cl_2) over 5 min. The solution was stirred for 10 min and then treated with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 CH_2Cl_2/EtOAc) and then recrystallization (CH_2Cl_2/hexane) to afford **1c** as a fine yellow powder (43.2 mg, 86%). Mp 255−256 °C (CH_2Cl_2/hexane) lit[26c] mp 242−244 °C ^1H NMR (250 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.29 (s, 1H), 8.06 (dd J = 8.4, 1.0 Hz, 1H), 7.95 (d J = 1.6 Hz, 1H), 7.49 (app t J = 8.1 Hz, 1H), 7.14 (d J = 1.6 Hz, 1H), 6.99 (dd J = 7.7, 1.0 Hz, 1H), 4.09 (s, 3H), 4.07 (s, 3H), 2.79 (q J = 7.6 Hz, 2H), 1.34 (t J = 7.6 Hz, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 350 (M^+, 100), 335 (25), 307 (30), 292 (5), 249 (9); HRMS (EI (70 eV)) *m/e* calcd for $C_{21}H_{18}O_5$: 350.1154, found 350.1159. Spectral data were found to be identical to those reported for authentic material.[26c]

4,5-Dibromo-1,2-diisopropoxybenzene (43d). To a solution of 1,2-diisopropoxybenzene[68] (5.02 g, 26.4 mmol) and NaOAc (4.60 g, 55.5 mmol) in $CHCl_3$ (75 mL) at rt was added a solution of Br_2 (2.80 mL, 54.16 mmol) in $CHCl_3$ (18 mL) dropwise over 1 h. After complete addition the reaction mixture was allowed to stir for 1 h and was diluted with enough H_2O to dissolve the inorganic salts and the layers separated. The aq phase was further extracted with $CHCl_3$ (2 × 50 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation affording the title compound as a light yellow oil (7.41 g, 80%). bp 104−120 °C/0.2 mmHg. IR (neat) ν (max) 3070, 2976, 1578, 1552, 1478, 1384, 1355, 1290, 1138 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (s, 2H), 4.42 (sept J = 6.1 Hz, 1H), 1.30 (d J = 6.1 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.0 (e), 122.1 (o), 115.3 (e), 72.7 (o), 21.9 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 354 (37), 352 (65), 350 (39), 312 (9.8), 310 (17), 308 (9.8), 270 (72), 268 (100), 266 (71), 241 (8.7), 239 (17), 237 (17); HRMS (EI (70 eV)) *m/e* calcd for $C_{12}H_{16}Br_2O_2$: 351.9497, found 351.9485.

1,4-Dihydro-6,7-diisopropoxy-1,4-epoxynaphthalene (44b). To a solution of furan (72.0 mL, 0.963 mol) and *n*-BuLi (47.0 mL, 1.65 mol/L) in Et_2O (350 mL) at −74 °C (internal) was added a solution of dibromide **43d** (20.06 g, 57.02 mmol) in Et_2O (100 mL) dropwise *via* a dropping funnel over a period of 1.5 h. During the addition the temperature was not allowed to rise above −70 °C (internal). After complete addition, the reaction mixture was quenched with sat NH_4Cl at −70 °C and was allowed to warm to rt. Standard workup followed by purification by column chromatography (8:1 hexane/EtOAc) and then recrystallization (hexane) afforded the title compound (11.00 g, 74%) as colorless plates. Mp 52−52.5 °C (hexane); IR (KBr) ν (max) 2930, 1737, 1605, 1466, 1418, 1049 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.99 (d J = 0.6 Hz, 2H), 6.95 (s, 2H), 5.62 (d J = 0.5 Hz, 2H), 4.37 (sept J = 6.0 Hz, 1H), 1.28 (d J = 6.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.8 (e), 142.9 (o), 142.3 (e), 113.1 (o), 82.3 (o), 72.7 (o), 72.6 (o), 22.2 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 260 (M^+, 91), 218 (18), 176 (55) 148 (100); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; found: C, 73.68; H, 7.60.

6,7-Diisopropoxy-1-naphthol (45b). A solution of epoxynaphthalene **44b** (0.253 g, 0.973 mmol) and HCl (1 drop, 12 mol/L) in MeOH (10 mL) was heated at reflux until the disappearance of starting material as monitored by TLC (45 min). The reaction was cooled and concentrated on the rotovap and the residue dissolved in CH_2Cl_2 (20 mL). The organic layer was washed (H_2O, brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified

(67) Merriman, G. H. Ph.D. Thesis, Ohio State University, Columbus, OH, 1990; *Diss. Abstr. Int. B.*, **1991**, *51*, 5875, Order # 9111767.

(68) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102* (9), 3056.

by recrystallization (hexane/Et_2O) affording the title compound as colorless plates (0.208 g, 82%). Mp 121−122 °C (hexane/Et_2O). IR (KBr) ν (max) 3402, 3085, 2978, 1629, 1593, 1515, 1470, 1387, 1329, 1282, 1177, 1068 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.21 (d J = 8.2 Hz, 1H), 7.09 (dd J = 8.2, 7.4 Hz, 1H), 6.65 (dd J = 7.4, 0.9 Hz, 1H), 6.37 (s, 1H), 4.65 (sept J = 6.1 Hz, 1H), 1.38 (app t J = 6.1 Hz, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.7 (e), 149.2 (e), 148.3 (e), 131.0 (e), 124.2 (o), 120.2 (e), 118.7 (o), 111.8 (o), 107.4 (o), 106.2 (o), 71.9 (o), 21.9 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 260 (23), 218 (6.9), 176 (100), 147 (37); HRMS (EI (70 eV)) *m/e* calcd for $C_{16}H_{20}O_3$: 260.1412, found 260.1405.

***N*,*N*-Diethyl *O*-(6,7-Diisopropoxy)-1-naphthylcarbamate (46b).** According to general procedure A, a mixture of naphthol **45b** (5.04 g, 19.38 mmol) K_2CO_3 (5.40 g, 39.07 mmol) and $ClCONEt_2$ (3.70 mL, 29.07 mmol) in CH_3CN (100 mL) was heated at reflux for 12 h. Standard workup followed by recrystallization (hexane/Et_2O) afforded the title compound as colorless needles (6.96 g, 84%). Mp 113.5−114.5 °C (hexane/Et_2O). IR (KBr) ν (max) 3056, 2980, 2974, 1715, 1603, 1501, 1470, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (d J = 8.1 Hz, 1H), 7.29 (dd J = 8.1, 7.6 Hz, 1H), 7.23 (s, 1H), 7.20 (s, 1H), 7.13 (dd J = 7.6, 1.2 Hz, 1H), 4.59, (m, 2H), 3.41−3.59 (m, 4H), 1.40 (d J = 6.1, Hz, 6H), 1.39 (d J = 6.1, Hz, 6H), 1.20−1.32 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.1 (e), 149.4 (e), 149.3 (e), 146.3 (e), 130.9 (o), 123.6 (o), 123.5 (o), 123.3 (e), 116.2 (o), 112.3 (o), 105.5 (o), 71.8 (o), 71.7 (o), 42.3 (e), 42.0 (e), 21.9 (o), 14.4 (o), 13.4 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 359 (M^+, 29), 280 (0.26), 260 (0.40), 217 (1.0), 175 (7.0), 147 (11), 100 (100), 72 (45), 44 (11); Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90; found: C, 70.26; H, 8.27; N, 3.87.

***N*,*N*-Diethyl *O*-(2-Iodo-6,7-diisopropoxy)-1-naphthylcarbamate (47b).** According to general procedure B, carbamate **46b** (0.692 g, 1.93 mmol) was treated sequentially with TMEDA (0.28 mL, 1.864 mmol), a solution of *s*-BuLi (1.40 mL, 1.41 mol/L) and I_2 (0.552 g, 2.18 mmol). Standard workup followed by column chromatography (6:1 hexane/EtOAc) afforded a the title compound as a light-blue solid (0.654 g, 70%). Mp 102−103 °C (hexane/Et_2O). IR (KBr) ν (max) 2977, 2933, 1723, 1622, 1587, 1496, 1462, 1411 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (d J = 8.6 Hz, 1H), 7.25 (d J = 8.6 Hz, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 4.49−4.61 (m, 2H), 3.57−3.66 (m, br, 2H), 3.43 (q J = 7.1 Hz, 2H), 1.38 (t J = 6.3 Hz, 15H), 1.24 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.4 (e), 149.8 (e), 149.6 (e), 146.8 (e), 132.5 (o), 130.4 (o), 125.3 (o), 124.4 (e), 111.8 (o), 105.5 (o), 86.6 (e), 71.7 (o), 71.6 (o), 42.3 (e), 42.1 (e), 21.8 (o), 21.7 (o), 14.5 (o), 13.3 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 485 (M^+, 15), 358 (5.9), 301 (3.6), 273 (2.6), 174 (4.0), 100 (100), 72 (20); Anal. Calcd for $C_{21}H_{28}NO_4I$: C, 51.97; H, 5.81; N, 2.89; found: C, 52.00; H, 5.87; N, 2.84.

***N*,*N*-Diethyl *O*-[6,7-Diisopropoxy-2-(3,4-dimethoxyphenyl)]-1-naphthyl-carbamate (49b).** According to general procedure F, a solution of naphthylcarbamate **46b** (1.81 g, 5.04 mmol) in THF (20 mL) was sequentially treated with TMEDA (0.845 mL, 5.61 mmol), a solution of *s*-BuLi (4.70 mL, 1.18 mol/L), $ZnCl_2$ (5.60 mL, 1.0 mol/L), a solution of 4-bromoveratrole (**48a**) (2.29 g, 10.55 mmol) in THF (10 mL) and $Pd(PPh_3)_4$ (130 mg, 0.112 mmol). The reaction was heated at reflux for 12 h and standard workup followed by column chromatography afforded the title compound as a colorless oil (0.790 g, 32%). IR (neat) ν (max) 2978, 2935, 1712, 1606, 1500, 1469 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.55 (d J = 8.4 Hz, 1H), 7.31 (d J = 8.4 Hz, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 7.04 (m, 2H), 6.92 (d J = 8.0 Hz, 1H), 4.59 (2 overlapping sept J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.40 (q J = 7.0 Hz, 2H), 3.30 (q J = 7.0 Hz, 2H), 1.40 (d J = 6.0 Hz, 12H), 1.17 (t J = 7.0 Hz, 3H), 1.08 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.9 (e), 149.9 (e), 149.3 (e), 148.5 (e), 148.1 (e), 142.8 (e), 131.2 (e), 130.2 (e), 129.7 (e), 126.3 (o), 124.2 (e), 123.9 (o), 121.6 (o), 112.7 (o), 112.6 (o), 111.1 (o), 106.3 (o), 72.0 (o), 71.9 (o), 56.0 (o), 55.8 (o), 42.1 (e), 41.9 (e), 22.0 (o), 22.0 (o), 14.2 (o), 13.3 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 495 (M^+, 26), 453 (1.0), 280 (11), 100 (100), 72 (38); HRMS (EI (70 eV)) *m/e* calcd for $C_{29}H_{37}NO_6$: 495.2622, found 495.2611.

***N*,*N*-Diethyl *O*-[6,7-Dihydroxy-2-(3,4-methoxyphenyl)]-1-naphthylcarbamate (49c).** To a solution of diisopropyl ether **49b** (0.197 g, 0.397 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BCl_3 (2.40 mL, 1.0 mol/L in CH_2Cl_2). The reaction was allowed to stir for 1 h and was then quenched with H_2O (20 mL). The layers were separated, and the aq phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by recrystallization (hexane/CH_2Cl_2) affording *N*,*N*-Diethyl *O*-[6,7-dihydroxy-2-(3,4-dimethoxy-phenyl)]-1-naphthyl-carbamate as colorless plates (0.145 g, 89%). mp 183−184 °C (hexane/CH_2Cl_2); IR (KBr) ν (max) 3550−2550 (br), 3052, 2951, 1690, 1638, 1603, 1579, 1514, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.61 (s, 1H, exch), 8.53 (s, 1H, exch), 7.52 (d J = 8.4 Hz, 1H), 7.24 (m, 3H), 7.09 (d J = 1.3 Hz, 1H), 6.95−7.03 (m, 2H), 3.82 (s, 6H), 3.46 (q J = 7.0 Hz, 2H), 3.29 (q J = 7.0 Hz, 2H), 1.15 (t J = 7.0 Hz, 3H), 1.05 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.6 (e), 149.9 (e), 149.6 (e), 147.8 (e), 147.3 (e), 143.7 (e), 132.5 (e), 130.8 (e), 129.8 (e), 126.3 (o), 125.1 (e), 124.3 (o), 122.4 (o), 114.1 (o), 112.7 (o), 110.5 (o), 105.1 (o), 56.2 (o), 42.5 (e), 14.6 (o), 13.6 (o); MS (EI (70 eV)) *m/e*: (rel intensity); 411 (M^+, 85), 397 (2.0), 340 (1.6), 296 (1.9), 281 (3.6), 237 (1.5), 215 (2.1), 100 (100), 72 (34); Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.41 found: C, 66.96; H, 6.21, N, 3.38.

***N*,*N*-Diethyl *O*-[6,7-Dimethoxymethoxy-2-(3,4-methoxyphenyl)]-1-naphthylcarbamate (49d).** To a suspension of NaH (1.20 g, 30.00 mmol) containing MOMCl (1.60 mL, 21.07 mmol) in dry DMF (50 mL) at 0 °C was added a solution of *N*,*N*-Diethyl *O*-[6,7-dihydroxy-2-(3,4-dimethoxy-phenyl)]-1-naphthyl-carbamate (**49c**) in DMF (5 mL) dropwise. After the evolution of hydrogen had ceased, the mixture was allowed to warm to rt over 2 h. The reaction was then quenched by pouring *slowly* into 100 mL of H_2O containing ice. The resulting mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with H_2O (5 × 100 mL), brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane/EtOAc) giving the title compound as a colorless glass (1.51 g, 95%). IR (neat) ν (max) 2948, 2833, 1716, 1607, 1584, 1470, 1415 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60 (d J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.36 (d J = 8.5 Hz, 1H), 7.05−7.09 (m, 2H), 6.92 (d J = 8.1 Hz, 1H), 5.38 (s, 2H), 5.35 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.55 (s, 3H), 3.53 (s, 3H), 3.49 (q J = 6.6 Hz, 2H), 3.30 (q J = 6.6 Hz, 2H), 1.21 (t J = 6.6 Hz, 3H), 1.09 (t J = 6.6 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.7 (e), 148.4 (e), 148.1 (e), 147.3 (e), 142.9 (e), 131.3 (e), 130.2 (e), 130.0 (e), 126.8 (o), 124.3 (e), 124.2 (o), 121.5 (o), 112.4 (o), 111.5 (o), 111.0 (o), 106.0 (o), 95.5 (e), 95.2 (e), 56.1 (o), 56.0 (o), 55.8 (o), 55.7 (o), 42.1 (e), 41.9 (e), 14.1 (o), 13.1 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 499 (M^+, 95), 467 (5.6), 455 (4.6), 437 (3.1), 399 (3.7), 350 (8.0), 336 (9.3), 323 (8.6), 292 (12), 265 (3.7), 165 (2.5), 100 (100), 72 (47); HRMS (EI (70 eV)) *m/e* calcd for $C_{27}H_{33}NO_8$: 499.2206, found 499.2191.

***N*,*N*-Diethyl 5,6-Dimethoxy-2-(1-hydroxy-6,7-bis(methoxymethoxy)-2-naphthyl)benzamide (50c). Procedure 1.** According to general procedure C1, a solution of carbamate **49dc** (0.463 g, 0.928 mmol) in THF (5 mL) was added to a solution of LDA (5.60 mmol) in THF (10 mL) at 0 °C and the solution allowed to stir at rt for 6 h. Standard workup followed by column chromatography (3:2 hexane/EtOAc) afforded the title compound as a foam (0.114 g, 25%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H, exch), 8.02 (s, 1H), 7.44 (s, 1H), 7.27 (d J = 8.3 Hz, 1H), 7.05 (d J = 8.3 Hz, 1H), 7.00 (d J = 8.6 Hz, 1H), 6.95 (d J = 8.6 Hz, 1H), 5.39 (s, 2H), 5.37 (s, 2H), 3.91 (s 6H), 3.56 (s, 3H), 3.55 (s, 3H), 3.40 (m, 1H), 3.21 (m, 1H), 3.04 (q J = 7.2 Hz, 2H), 0.91−0.84 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.6 (e), 151.6 (e), 148.9 (e),

147.6 (e), 146.6 (e), 143.7 (e), 131.3 (e), 130.7 (e), 129.1 (e), 127.5 (o), 127.3 (o), 123.0 (o), 118.8 (o), 112.8 (o), 110.8 (o), 107.9 (o), 95.3 (e), 95.0 (e), 61.4 (o), 56.2 (o), 56.1 (o), 55.7 (o), 43.0 (e), 38.9 (e), 13.4 (o), 11.8 (o); MS (EI (70 eV)) *m/e* (rel intensity) 499 (M^+, 44), 456 (6.7), 426 (99), 396 (12), 382 (6.8), 365 (7.1), 350 (100), 335 (66), 321 (39), 293 (16), 100 (27), 72 (49); HRMS (EI (70 eV)) *m/e* calcd for $C_{27}H_{33}NO_8$: 499.2206, found 499.2198.

Procedure 2. According to general procedure C2, a solution of carbamate **49d** (0.560 g, 2.630 mmol) in THF (10 mL) was added to a solution of LDA (4.53 mmol) in THF (20 mL) at 0 °C. The cooling bath was removed, and the reaction was allowed to stir for 2 h at which point LDA (2.99 mmol, 10 mL THF) was added and stirring was continued for 2 h. This process was repeated once more followed by standard workup and column chromatography (3:2 hexane/EtOAc) to afford the title compound as a foam (0.169 g, 34%), which was shown to be identical by physical and spectroscopic property comparison with material prepared by Procedure 1.

3,4-Dihydroxy-7,8-dimethoxy-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (51c). According to general procedure C1, a mixture of carbamate **49d** (0.444 g, 0.890 mmol) in THF (5 mL) was added to a solution of LDA (4.39 mmol) in THF (10 mL) at 0 °C. The reaction mixture was allowed to stir at rt for 6 h, and standard workup afforded the crude hydroxyamide **50c**, which was dissolved in MeOH (10 mL) and TsOH (0.850 g, 4.94 mmol) was added. The reaction mixture was heated at reflux for 14 h at which point it was cooled to 0 °C and the solid was removed by filtration. The filtrate was diluted with 10 mL of H_2O and cooled to 0 °C and filtered. The precipitate (two crops) was washed with MeOH affording the title compound (0.132 g, 44%) as a light-brown powder. Mp 291−294 °C (dec); IR (KBr) ν (max) 3527, 3432 (br), 2947, 1698, 1634, 1504, 1461 cm^{-1}; ^1H NMR (250 MHz, DMF-d_7) δ 10.02 (s, 2H), 8.18 (d J = 9.0 Hz, 1H), 8.01 (d J = 8.9 Hz, 1H), 7.74 (d J = 8.9 Hz, 1H), 7.75 (s, 1H), 7.59 (d J = 8.9 Hz, 1H), 7.32 (s, 1H), 4.01 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (50 MHz, DMF-d_7) δ 157.6 (e), 153.7 (e), 151.8 (e), 149.4 (e), 148.8 (e), 145.8 (e), 130.7 (e), 130.4 (e), 123.0 (o), 121.0 (o), 119.0 (e), 119.0 (o), 117.6 (o), 115.5 (e), 111.4 (e), 111.0 (o), 104.5 (o), 61.2 (o), 56.7 (o); MS (EI (70 eV)) *m/e* (rel intensity) 338 (M^+, 100), 323 (33), 309 (23), 295 (14), 280 (7.4), 265 (5.7), 252 (9.5), 237 (6.1), 196 (15), 139 (8.1); HRMS (EI (70 eV)) *m/e* calcd for $C_{19}H_{14}O_6$: 338.0790, found 338.0804.

6,7-Dimethoxy-3,4-methylenedioxy-6H-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (Arnottin I) (2). Procedure 1. A mixture of catechol **51c** (59.2 mg, 0.1751 mmol) and anhydrous CsF (0.310 g, 2.04 mmol) in dry DMF (5 mL) was allowed to stir at rt for 10 min and CH_2Cl_2 (0.1 mL, 1.56 mmol) was added and the mixture heated to 110 °C for 24 h. The reaction was quenched with H_2O, the solvents removed *in vacuo*, and the residue diluted with $CHCl_3$ (50 mL) and H_2O (50 mL) and layers separated. The organic phase was washed (brine), dried (Na_2SO_4), concentrated and the residue purified by column chromatography (3:2 hexane/EtOAc → 1:1 hexane/$CHCl_3$) affording the title compound as a fluffy colorless solid (24.0 mg, 39%). Mp 301−306 °C, lit[19] mp 293−297 °C ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.83 (d J = J = 8.8 Hz, 1H), 7.53 (d J = 8.8 Hz, 1H), 7.44 (d J = 8.8 Hz, 1H), 7.14 (s, 1H), 6.10 (s, 2H), 4.04 (s, 3H), 3.99 (s, 3H). Spectral data were found to be identical to those reported for the authentic material.[32]

Procedure 2. According to general procedure D, a solution of hydroxy amide **51c** (0.169 g, 0.338 mmol) in HOAc (7 mL) was heated at reflux for 20 min and H_2O (7 mL) was added. The reaction was heated at reflux for 1 h and cooled to rt. The resulting precipitate was filtered and washed successively with H_2O, (5 mL) EtOH (5 mL), and Et_2O (10 mL). The solid (81.7 mg) was dissolved in degassed DMF (10 mL) and K_2CO_3 (65.2 mg, 0.4717 mmol), CuO (56.5 mg, 0.710 mmol) and CH_2Br_2 (0.03 mL, 0.427 mmol) were added. The mixture was heated at reflux under Ar for 12 h, the DMF removed in vacuo and the residue diluted with H_2O (50 mL) and $CHCl_3$ (50 mL). The layers were separated and the aq phase extracted twice more with $CHCl_3$ and the combined organic layers were washed, (brine), dried (Na_2SO_4), concentrated and the residue purified by column chromatography (2:1 hexane/EtOAc → 2:2:1 hexane/$CHCl_3$/EtOAc → $CHCl_3$) affording the title compound as a colorless solid (6.2 mg, 5.2%) whose spectral properties were identical those observed for arnottin I prepared by Procedure 1.

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Supporting Information Available: Experimental details for compounds not included in main text. A detailed description of the aryne cyloaddition methods used to prepare **27a,b** and associated experimental data. ^1H NMR and ^{13}C data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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