Gold-Facilitated '6-*Exo-dig*' Intramolecular Cyclization of 2-[(2-Nitrophenyl)ethynyl]phenylacetic Acids: General Access to 5*H*-Benzo[*b*]carbazole-6,11-diones

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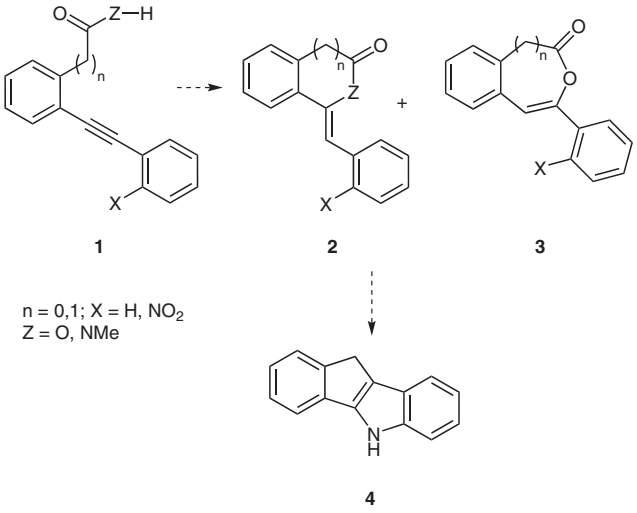
Abstract: The preliminary results of a regiospecific synthesis of (*Z*)-1-(2-nitrobenzylidene)isochroman-3-ones by gold(I)-catalyzed cycloisomerization of phenylethynylacetic acids under mild conditions is described. These novel lactones proved to be suitable starting materials for a new, general access to 5*H*-benzo[*b*]carbazole-6,11-diones.

Key words: alkynes, annulations, fused-ring systems, gold(I) chloride, indoles, lactones, nitro compounds, quinones

Alkynes are compounds of growing interest in organic synthesis due to their ease of preparation and their use in the construction of heterocycles through the intramolecular heteroannulation of carboxylic acids, amides, alcohols and amines to a carbon–carbon triple bond.[1] In recent times, this process has been widely applied in natural product synthesis for the generation of indoles from *o*-amino-diphenylacetylenes,[2] benzofurans from *o*-hydroxydiphenylacetylenes,[3] phthalides **2** (n = 0) and isocoumarins **2** (n = 1) from 2-(phenylethynyl)benzoic acids (**1**, n = 0), etc.[4] In fact, in the intramolecular cyclization of these benzoic acids, both the '5-*exo-dig*' and the '6-*endo-dig*' closures are allowed by Baldwin's rules[5] and both closure modes have been observed (Scheme 1). This route allowed regiocontrolled access to (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ones (**2**; n = 0, X = H, Z = O) and 3-phenyl-1*H*-isochromen-1-ones (**3**; n = 0, X = H), respectively, although sometimes mixtures of both compounds were obtained.[6] The regioselectivity of this process is greatly influenced by the reaction conditions and the nature of the substituents on the two aromatic rings. Several methods have been reported to promote this intramolecular reaction, including an efficient lactonization using palladium(II) acetate or gold(I) chloride as the catalyst.[6c,d]

As part of our continued interest in nitro compounds, we recently reported a synthesis of indoles **4** from 2-[(2-nitrophenyl)ethynyl]benzoic acids (**1**; n = 0, X = NO_2, Z = O) by a route in which the nitro group plays a critical role.[6a] Firstly, it promotes the stereocontrolled 5-*exo-dig* cyclization that leads to (*Z*)-3-(2-nitrobenzylidene)isobenzofuran-1(3*H*)-ones **2** (n = 0, X = NO_2, Z = O) which, under the basic reaction conditions, spontaneously rearranged to the corresponding 2-(2-nitrophenyl)-1*H*-indene-1,3(2*H*)-diones. Secondly, the nitro group provides the amino functionality required to generate the indole subunit of these targets **4**.



Scheme 1

Surprisingly, very little chemistry concerning 2-[2-(phenylethynyl)phenyl]acetic acids has been reported. In fact, at present, only a few intramolecular heteroannulations of compounds **1** (n = 1, X = H, Z = O) have been reported and they provide mixtures of lactones **2** (n = 1, X = H, Z = O) and **3** (n = 1, X = H), resulting from 6-*exo-dig* and 7-*endo-dig* closures, respectively.[6c,d] In addition, a regiospecific 6-*exo-dig* cyclization of *N*-methyl 2-[2-(phenylethynyl)phenyl]acetamide (**1**, n = 1, X = H, Z = NMe) to the corresponding derivative **2** (n = 1, X = H, Z = NMe) has been reported.[7]

As a first contribution to a synthetic program on the chemistry of diphenyl acetylenes **1**, we report here our preliminary results on the application of these compounds to the preparation of 2-phenylnaphthoquinones **9**. This work resulted in the development of a novel, general, and efficient synthesis of 5*H*-benzo[*b*]carbazole-6,11-diones **10**, a class of indole quinones with well-known antitumor activity (Scheme 2).[8]

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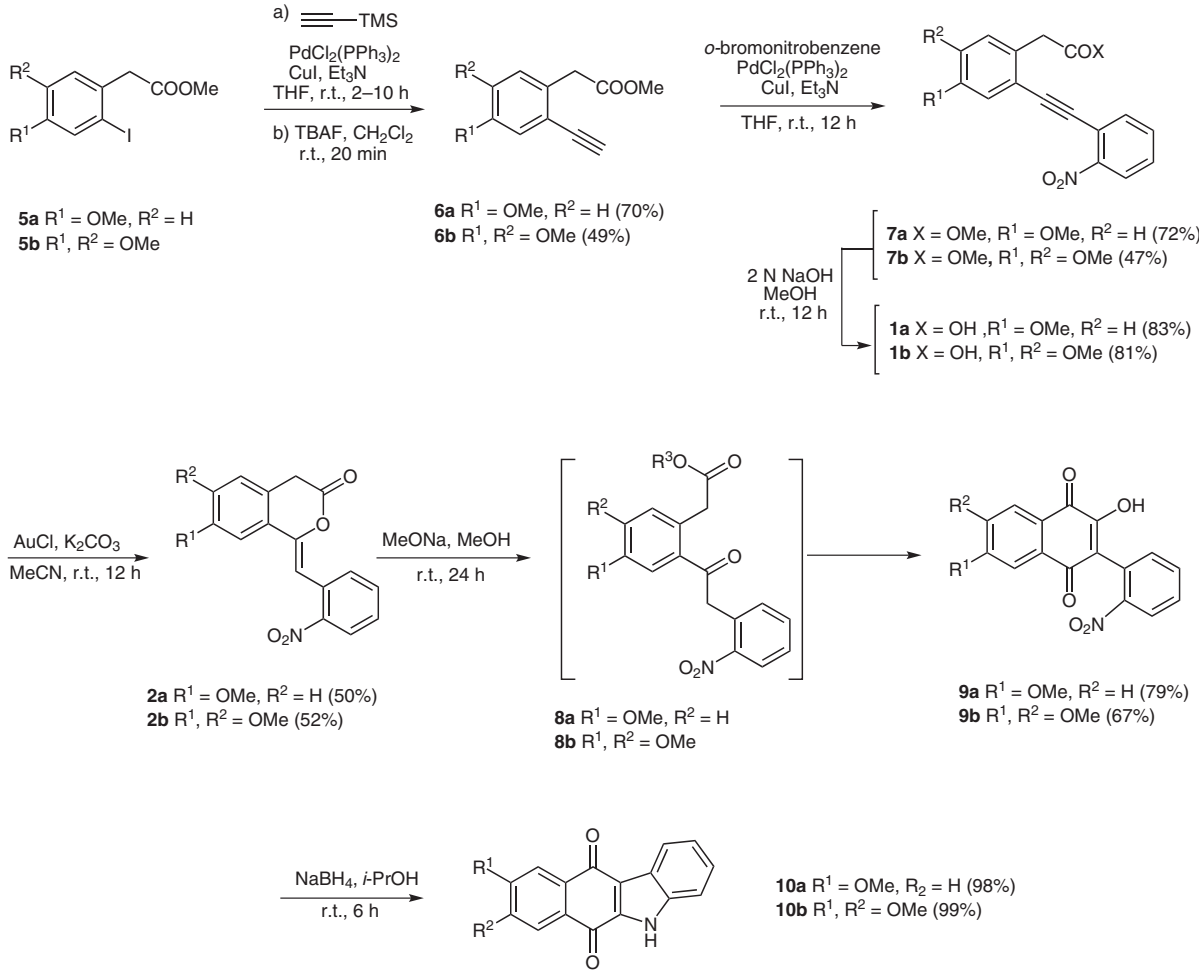
Our present study was carried out with model compounds **7a** and **7b**, which were easily obtained by Sonogashira coupling reactions. For example, Sonogashira coupling of *o*-iodophenylacetic acid ester **5a** with TMS-acetylene and subsequent removal of the TMS group by treatment with TBAF, provided the phenylacetylene derivative **6a**,[9,10] which, when subjected to a second Sonogashira reaction with commercial *o*-bromonitrobenzene, afforded the desired phenylethynylphenylacetic acid ester **7a**.[11] This compound was then subjected to basic hydrolysis in order to transform it into the phenylacetate derivative **1a**. However, attempts to promote the direct cyclization of the latter compound to the key lactone **2a** by intramolecular attack of the carboxylate group on the acetylenic functionality failed; only unreacted starting material was recovered. Nevertheless, satisfactory results were obtained when compound **1a** was allowed to react with 10 mol% solution of K_2CO_3 in acetonitrile in the presence of a catalytic amount of AuCl.[6b] Under these conditions, the desired lactone **2a** formed as the only regioisomer[12] as a result of a regiospecific 6-*exo*-*dig* cycloisomerization, which was probably facilitated by the strong resonance effect of the nitro group.

Interest in lactone **2a** lies in its structural relationship to ketoester **8a**, which was previously converted by us into *5H*-benzo[*b*]carbazole-6,11-dione **10a** via nitrophenylnaphthoquinone **9a**.[8b] This constitutes a novel approach to the synthesis of these highly functionalized indole quinones **10**, but is of limited scope because of restricted access to the required 2-{2-[2-(2-nitrophenyl)acetyl]phenyl}acetic acids **8**.

On the basis of the results discussed above, lactone **2a** was reacted with sodium methoxide in methanol in order to transform it into the known ester **8a**. However, under these reaction conditions, **2a** spontaneously underwent a mixed Claisen condensation and subsequent oxidation to provide naphthoquinone **9a** directly.

In order to establish the significance of this novel route, a second model substrate (**7b**) was studied, which was easily obtained by a double Sonogashira coupling protocol similar to that used for its analogue **7a**. Transformation of **7b** into **1b** was followed by the cycloisomerization of the potassium salt of **1b** promoted by AuCl, as described above. This led to the expected lactone **2b**, which, upon treatment with sodium methoxide in methanol, furnished the desired the nitrophenylnaphthoquinone **9b**. Finally, **9b** was easily converted into *5H*-benzo[*b*]carbazole-6,11-dione **10b** by reduction of the nitro group to an amino group with $NaBH_4$, a process that was followed by a spontaneous heteroannulation and further oxidation.



Scheme 2

In summary, we report here a novel nitro-group mediated 6-*exo-dig* regiocontrolled heteroannulation of 2-[2-(phenylethynyl)phenyl]acetic acids to (*Z*)-1-(2-nitrobenzylidene)isochroman-3-ones, which should be of general interest. These complex lactones proved to be suitable starting materials for general access to highly functionalized *5H*-benzo[*b*]carbazole-6,11-diones.

Work is currently in progress on a systematic study of this kind of alkyne heteroannulation in order to further establish its scope and limitations prior to its application to the preparation of wide sets of 5*H*-benzo[*b*]carbazole-6,11-diones and related compounds, including ellipticine and analogues with powerful antitumoral properties.[13,14]

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References and Notes

(1) (a) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505. (b) Larock, L. C. *Pure Appl. Chem.* **1999**, *71*, 1435.

(2) (a) Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339; and references cited therein. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318. (c) Kirsch, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47. (d) Reboredo, F. J.; Treus, M.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Synlett* **2003**, 1603.

(3) Larock, R. C.; Yum, E. K.; Refvick, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(4) (a) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141. (b) Le Bras, G.; Hamze, A.; Messaoudi, S.; Provot, O.; Le Calvez, P.-B.; Brion, J.-D.; Alami, M. *Synthesis* **2008**, 1607. (c) Kim, S.; Yamamoto, K.; Hayashi, K.; Chiba, K. *Tetrahedron* **2008**, *64*, 2855. (d) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62. (e) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979. (f) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933. (g) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.

(5) (a) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

(6) (a) Reboredo, F. J.; Treus, M.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Synlett* **2002**, 999. (b) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *24*, 5517. (c) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979. (d) Brady, M. G. A.; Kariuki, B.; Knight, D. W.; Mohammed, F. K. *Tetrahedron Lett.* **2009**, *50*, 1385.

(7) Yu, Y.; Stephenson, A.; Mitchell, D. *Tetrahedron Lett.* **2006**, *47*, 3811.

(8) For our contributions on these targets, see: (a) Fernandez, M.; Barcia, C.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Synlett* **2004**, 267. (b) Barcia, J. C.; Cruces, J.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **2002**, *43*, 5141. (c) Cruces, J.; Martinez, E.; Treus, M.; Martinez, L. A.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **2002**, *58*, 3015. (d) Cruces, J.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2001**, *42*, 4825. (e) Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **1993**, *34*, 6479. For other recent contributions, see: (f) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. J. *Org. Chem.* **2008**, *73*, 5022. (g) Mal, D.; Senapati, B. K.; Pahari, P. *Tetrahedron* **2007**, *63*, 3768. (h) Miguel del Corral, J. M.; Castro, M. A.; Gordaliza, M.; Martin, M. L.; Gamito, A. M.; Cuevas, C.; San Feliciano, A. *Bioorg. Med. Chem.* **2006**, *14*, 2816. (i) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958.

(9) All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data follow. Compound **6a**: oil; IR (NaCl): 3282 (C≡CH), 2106 (C≡C), 1736 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.29 (s, 1 H, CH), 3.52 (s, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.82 (d, *J* = 8.5 Hz, 1 H, ArH), 7.21 (dd, *J* = 8.5 Hz, 1 H, ArH), 7.35 (d, *J* = 2.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 39.8 (CH_2), 52.0 (OCH_3), 55.8 (OCH_3), 80.0 (CH), 81.2 (C), 110.6 (ArH), 111.1 (Ar), 125.9 (Ar), 131.0 (ArH), 134.7 (ArH), 159.6 (Ar), 171.8 (C=O); MS: *m/z* (%) = 205 (100) $[M + 1]^+$. Compound **6b**: mp 81–83 °C (CH_2Cl_2–MeOH); IR (NaCl): 3250 (C°CH), 2070 (C°C), 1722 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.24 (s, 1 H, CH), 3.69 (s, 3 H, OCH_3), 3.79 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.79 (s, 1 H, ArH), 6.98 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$): d = 38.4 (CH_2), 51.3 (OCH_3), 55.2 (OCH_3), 55.3 (OCH_3), 79.8 (CH), 81.3 (C), 112.1 (ArH), 113.6 (Ar), 114.3 (ArH), 129.4 (Ar), 147.1 (Ar), 149.1 (Ar), 171.0 (C=O); MS: *m/z* (%) = 235 (100) $[M + 1]^+$. Compound **7a**: mp 87–88 °C (CH_2Cl_2–MeOH); IR (NaCl): 2205 (C≡C), 1725 (C=O), 1565 (NO_2), 1344 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.94 (s, 2 H, CH_2), 6.83 (d, *J* = 8.5 Hz, 1 H, ArH), 6.86 (s, 1 H, ArH), 7.43 (t, *J* = 8.5 Hz, 1 H, ArH), 7.546 (m, 2 H, 2 × ArH), 7.70 (d, *J* = 9.1 Hz, 1 H, ArH), 8.08 (d, *J* = 8.2 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 40.2 (CH_2), 52.6 (OCH_3), 55.8 (OCH_3), 87.7 (C), 96.1 (C), 113.5 (ArH), 115.3 (Ar), 116.1 (ArH), 119.6 (Ar), 125.2 (ArH), 128.6 (ArH), 133.3 (ArH), 134.8 (ArH), 134.9 (Ar), 139.1 (Ar), 160.9 (Ar), 171.9 (C=O); MS: *m/z* (%) = 326 (53) $[M + 1]^+$, 207 (100). Compound **7b**: mp 142–145 °C (CH_2Cl_2–MeOH); IR (NaCl): 2201 (C≡C), 1724 (C=O), 1565 (NO_2), 1337 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.71 (s, 2 H, CH_2), 3.92 (s, 6 H, 2 × OCH_3), 3.94 (s, 3 H, OCH_3), 6.84 (s, 1 H, ArH), 7.08 (s, 1 H, ArH), 7.46 (t, *J* = 7.3 Hz, 1 H, ArH), 7.60 (t, *J* = 7.3 Hz, 1 H, ArH), 7.73 (d, *J* = 7.3 Hz, 1 H, ArH), 8.09 (d, *J* = 7.3 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 39.2 (CH_2), 52.1 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 87.7 (C), 95.7 (C), 112.6 (ArH), 114.6 (ArH), 118.9 (Ar), 124.7 (ArH), 128.2 (ArH), 130.5 (Ar), 132.8 (ArH), 134.4 (ArH), 147.8 (Ar), 148.8 (Ar), 150.2 (Ar), 171.7 (Ar), 179.2 (C=O); MS: *m/z* (%) = 356 (0.6) $[M + 1]^+$, 17 (100). Compound **1a**: mp 152–154 °C (CH_2Cl_2); IR (NaCl): 2204 (C°C), 1703 (C=O), 1564 (NO_2), 1337 (NO_2) cm^{-1}; ^1H NMR (acetone-d_6): δ = 3.85 (s, 3 H, OCH_3), 3.97 (s, 2 H, CH_2), 6.93 (dd, *J* = 8.8, 2.5 Hz, 1 H, ArH), 7.03 (d, *J* = 2.5 Hz, 1 H, ArH), 7.48 (t, *J* = 7.3 Hz, 1 H, ArH), 7.63 (t, *J* = 7.3 Hz, 1 H, ArH), 7.77 (m, 2 H, ArH), 8.10 (d, *J* = 7.3 Hz, 1 H, ArH); ^{13}C NMR (acetone-d_6): δ = 41.0 (CH_2), 56.8 (OCH_3), 89.3 (C), 97.3 (C), 114.6 (ArH), 116.6 (Ar), 118.0 (ArH), 120.3 (Ar), 126.5 (ArH), 130.7 (ArH), 134.0 (Ar), 135.1 (ArH), 135.8 (ArH), 136.3 (ArH), 141.5 (Ar), 162.6 (Ar), 173.1 (C=O); MS: *m/z* (%) = 312 (22) $[M + 1]^+$, 282 (100). Compound **1b**: mp 163–165 °C (CH_2Cl_2); IR (NaCl): 2204 (C≡C), 1710 (C=O), 1566

(NO_2), 1337 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.92 (s, 2 H, CH_2), 3.92 (s, 6 H, 2 × OCH_3), 6.89 (s, 1 H, ArH), 7.10 (s, 1 H, ArH), 7.48 (t, *J* = 7.3 Hz, 1 H, ArH), 7.63 (t, *J* = 7.3 Hz, 1 H, ArH), 7.77 (d, *J* = 7.3 Hz, 1 H, ArH), 8.10 (d, *J* = 7.3 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ = 39.9 (CH_2), 55.4 (OCH_3), 55.5 (OCH_3), 87.4 (C), 95.4 (C), 112.5 (ArH), 114.3 (Ar), 114.3 (ArH), 118.6 (Ar), 124.3 (ArH), 128.0 (ArH), 130.8 (Ar), 132.7 (ArH), 134.2 (ArH), 147.4 (Ar), 148.4 (Ar), 149.8 (Ar), 173.6 (C=O); MS: *m*/*z* (%) = 342 (0.6) $[M + 1]^+$, 33 (100). Compound **2a**: mp 141–142 °C (CH_2Cl_2); IR (NaCl): 1764 (C=O), 1514 (NO_2), 1307 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.85 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 6.68 (s, 2 H, ArH and CH), 6.91 (dd, *J* = 8.8 Hz, 1 H, ArH), 7.39 (t, *J* = 8.5 Hz, 1 H, ArH), 7.61 (m, 2 H, 2 × ArH), 7.97 (dd, *J* = 8.2 Hz, 1 H, ArH), 8.04 (dd, *J* = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 35.0 (CH_2), 55.5 (OCH_3), 101.1 (CH), 111.8 (ArH), 114.7 (ArH), 120.0 (Ar), 124.6 (ArH), 126.6 (ArH), 127.7 (ArH), 128.5 (Ar), 130.5 (Ar), 132.1 (ArH), 132.8 (ArH), 148.1 (Ar), 148.6 (Ar), 161.6 (Ar), 165.0 (C=O); MS: *m*/*z* (%) = 312 (50) $[M + 1]^+$, 282 (100). Compound **2b**: mp 163–165 °C (CH_2Cl_2); IR (NaCl): 1736 (C=O), 1518 (NO_2), 1292 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.85 (s, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 6.63 (s, 1 H, CH), 6.68 (s, 1 H, ArH) 7.09 (s, 1 H, ArH), 7.40 (t, *J* = 7.2 Hz, 1 H, ArH), 7.63 (t, *J* = 7.9 Hz, 1 H, ArH), 8.00 (d, *J* = 8.2 Hz, 1 H, ArH), 8.06 (d, *J* = 8.2 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ = 34.2 (CH_2), 56.1 (2 × OCH_3), 101.2 (CH), 106.9 (ArH), 109.4 (ArH), 112.6 (Ar), 119.5 (Ar), 121.8 (Ar), 124.7 (ArH), 127.7 (ArH), 128.5 (Ar), 132.2 (ArH), 132.9 (ArH), 148.7 (Ar), 149.0 (Ar), 151.3 (Ar), 165.0 (C=O); MS: *m*/*z* (%) = 342 (0.6) $[M + 1]^+$, 33 (100). Compound **9a**: mp 205–206 °C (MeOH); IR (NaCl): 3331 (OH), 1675 (C=O), 1637 (C=O), 1525 (NO_2), 1356 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 4.03 (s, 3 H, OCH_3), 7.41 (dd, *J* = 8.7 Hz, 1 H, ArH), 7.62–7.74 (m, 3 H, ArH), 7.80 (m, 1 H, ArH), 8.09 (d, *J* = 8.7 Hz, 1 H, ArH), 8.19 (d, *J* = 8.3 Hz, 1 H, ArH); ^{13}C NMR (DMSO-d_6): δ = 57.0 (OCH_3), 109.2 (ArH), 113.8 (Ar), 115.1 (Ar), 119.8 (ArH), 123.3 (ArH), 126.8 (Ar), 127.9 (ArH), 131.7 (ArH), 134.0 (ArH), 136.0 (ArH), 147.5 (Ar), 149.4 (Ar), 161.8 (Ar), 176.3 (Ar), 178.9 (C=O), 184.1 (C=O); MS: *m*/*z* (%) = 326 (100) $[M + 1]^+$. Compound **9b**: mp 266–268 °C (MeOH); IR (NaCl): 3349 (OH), 1642 (C=O), 1525 (NO_2), 1337 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.03 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.52–7.58 (m, 5 H, ArH + OH), 7.66 (m, 1 H, ArH), 8.17 (dd, *J* = 8.2 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 57.0 (OCH_3), 57.1 (OCH_3), 108.2 (ArH), 109.6 (ArH), 119.6 (Ar), 123.9 (Ar), 125.0 (ArH), 126.2 (Ar), 128.3 (Ar), 129.9 (ArH), 133.0 (ArH), 133.4 (ArH), 149.5 (Ar), 152.0 (Ar), 153.4 (Ar), 155.2 (Ar), 180.8 (C=O), 182.6 (C=O); MS: *m*/*z* (%) = 356 (29) $[M + 1]^+$, 309 (100).

(10) $PdCl_2(PPh_3)_2$ (0.22 mmol) was added under argon to a degassed mixture of CuI (0.22 mmol) and *o*-iodophenylacetic acid ester **5a** or **5b** (3.6 mmol) in anhydrous THF (20 mL). After 5 min stirring, Et_3N (5 mL) was first added, then TMS-acetylene (3.60 mmol) was slowly added and the resulting mixture was stirred at room temperature for 1.5 h for **6a** or 12 h for **6b**. The solids were filtered off through a Celite pad, the solvents were removed in vacuo, and the crude oil was poured into water and extracted with methylene chloride. The pooled organic liquids were washed with brine, dried over anhydrous sodium sulfate and concentrated to dryness in vacuo. Compound **6a** or **6b** were isolated by flash column chromatography.

(11) $PdCl_2(PPh_3)_2$ (0.16 mmol) was added under argon to a degassed mixture of CuI (0.16 mmol) and *o*-bromonitrobenzene (2.8 mmol) in anhydrous THF (20 mL). After 5 min stirring, Et_3N (5 mL) was first added, then a solution of **6a** or **6b** (3.85 mmol) in anhydrous THF (10 mL) was slowly added and the resulting mixture was stirred at room temperature for 12 h. The solids were filtered off through a Celite pad, the solvents were removed in vacuo and the filtrate was concentrated to dryness in vacuo. Compound **7a** or **7b** were isolated by flash column chromatography.

(12) In a flask containing **1a** or **1b** (1.00 equiv) and K_2CO_3 (0.10 equiv), acetonitrile (2 mL/0.4 mmol) was added under argon. The solution was purged with argon three times and then AuCl (0.10 equiv) was added. After stirring at room temperature for 12 h, the reaction mixture was filtered through a Celite pad and liquids from the filtrate were removed under reduced pressure. Flash column chromatography of the crude material allowed compound **2a** or **2b** to be isolated.

(13) Ferlin, M. G.; Marzano, C.; Gandin, V.; Dall'Acqua, S.; Dalla Via, L. *ChemMedChem* **2009**, *4*, 363; and references therein.

(14) Ashcroft, W. R.; Dalton, L.; Beal, M. G.; Humphrey, G. H.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2409.