Synthesis of the 3,4,5-Trimethoxy-2-(3,4-methylenedioxy-6-nitrophenyl) benzaldehyde for Divergent Preparation of Cytotoxic Biaryls

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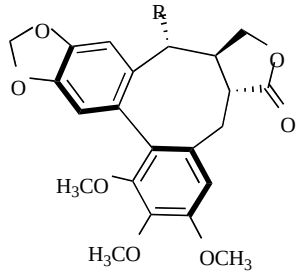
Received February 10, 2012: Revised April 22, 2012: Accepted April 22, 2012

Abstract: The regioselective synthesis of the 3,4,5-trimethoxy-2-(3,4-methylenedioxy-6-nitrophenyl)benzaldehyde as key intermediate for divergent preparation of cytotoxic biaryl lignans was achieved in three steps from commercially available starting materials. Reactivity of this synthon was illustrated by its conversion into the corresponding phenanthridine and bromomethylbenzene.

Keywords: Carbaldehydes, cytotoxic biaryls, lignans, phenanthridines, regioselective nitration, stille coupling.

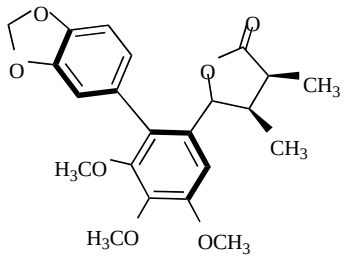
INTRODUCTION

Biphenyl molecules containing both methylenedioxyphenyl and trimethoxyphenyl moieties are common features of anti-proliferative naturally occurring biaryl lignans such as steganacin (**1**), steganone (**2**) and eupomatilone-6 (**3**) (Fig. **1**) [1]. The preparation of non-bridged molecules **4** displaying this biaryl pharmacophore was recently investigated for the development of potential antitumor agents (Fig. **1**) [2].

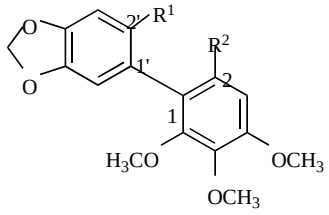


Steganacin, R = $OCOCH_3$ (**1**)

Steganone, R = =O (**2**)



Eupomatilone-6 (**3**)



Synthetic biaryls **4**

$R^1 = NO_2$, R^2 = CHO **5**

Fig. (1). Cytotoxic natural lignans and synthetic biphenyls.

Several new biaryl derivatives bearing those moieties exhibited strong cytotoxicity against multidrug resistant cancer cell lines *in vitro*. Preliminary SAR were established in this series and revealed that the highest cytotoxic effect was obtained when two bulky substituents are present on the 2,2'-positions. It was assumed that hindered groups induce a significant biphenyl tilt angle potentially important for the cytotoxic activity [2a].

As a part of a program directed toward the development of new antitumor drugs, and taking into consideration the above points, we became interested in the preparation of a useful synthon for the preparation of novel derivatives based on this essential biphenyl scaffold. In order to generate a great variety of molecules from this synthon, a nitro and an aldehyde groups were chosen as complementary substituents on the 2,2'-positions since these two functions allow a wide range of chemical reactions leading to molecular diversity. This prompted us to synthesize the 3,4,5-trimethoxy-2-(3,4-methylenedioxy-6-nitrophenyl)benzaldehyde (**5**) as key intermediate for divergent preparation of potentially cytotoxic biaryls.

Biaryl compounds are widely used by organic chemists, and strategies for biphenyl axis generation have essentially focused on palladium mediated Suzuki-Miyaura or Stille type cross couplings of two aryl precursors [3]. In this context, LaVoie *et al*. [4] first reported a Stille cross coupling reaction between an *o*-nitrophenylstannane **6** and a 2-

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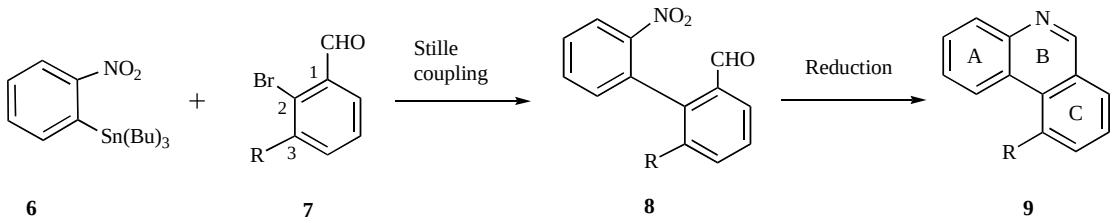
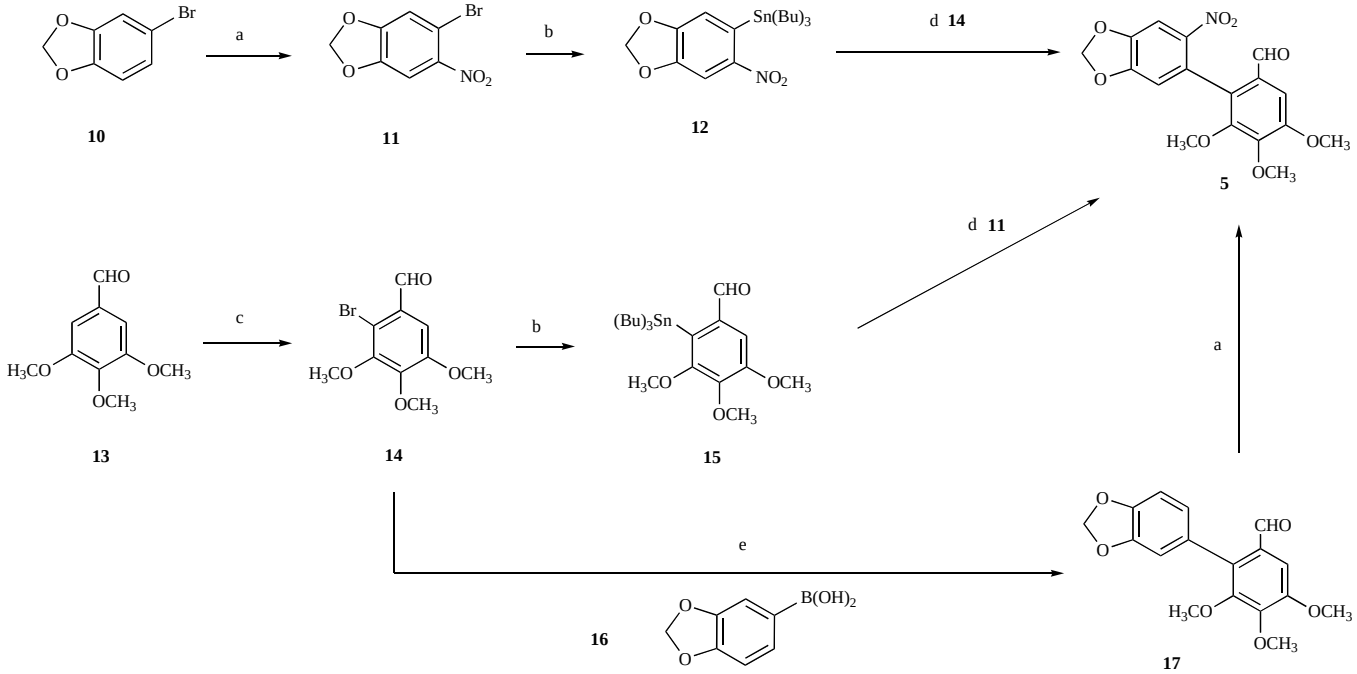


6 **7** **8** **9**

Scheme 1. General synthesis of 2-(*o*-nitrophenyl)benzaldehydes **8** by a Stille cross-coupling reaction and conversion to phenanthridines **9**.



10 **11** **12** **5**

13 **14** **15**

16 **17**

Scheme 2. Synthesis of 2-(2-nitrophenyl)benzaldehyde **5**. Reagents and reaction conditions: (**a**) 70% HNO_3, AcOH, 20 °C, 1 h, 92% for **11** and 15 min, 98% for **5**; (**b**) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, reflux, 15 h, 85% for **12** and 48h, 80% for **15**; (**c**) NBS, $CHCl_3$, reflux, 3 h, 98%; (**d**) Stille coupling; (**e**) **16**, $Pd(PPh_3)_4$, K_2CO_3, DMF, 65 °C, 48 h, 81%.

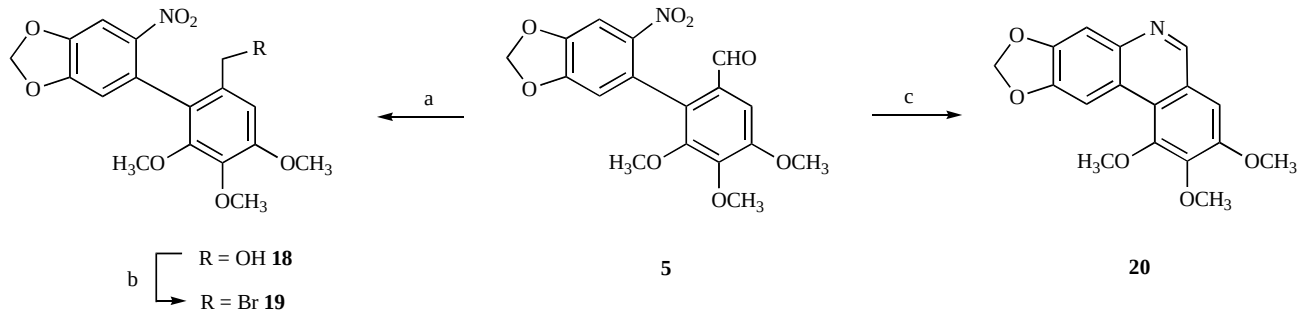
bromobenzaldehyde **7** for the preparation of 2-(2-nitrophenyl)benzaldehydes **8** as synthetic precursors of phenantridines **9** (Scheme **1**). Although Suzuki [5] and Ullman [6] cross coupling reactions have been used to generate these nitrophenylbenzaldehydes, the Stille reaction remains the method of choice because of the satisfactory yields obtained starting from several *o*-nitrophenylstannanes readily available from *o*-bromonitrobenzenes bearing various electron-donating and/or electron-withdrawing substituents [7].

RESULTS AND DISCUSSION

It was therefore legitimate to apply this method to the preparation of the target carbaldehyde **5**. The tributyl-(4,5-methylenedioxy-2-nitrophenyl)stannane (**12**) [8] was prepared using a two-step procedure and in 78% overall yield from commercially available 3,4-methylenedioxybromobenzene (**10**) as depicted in scheme **2**: nitration of **10** by nitric acid afforded the corresponding 2-nitrobromobenzene **11** [9], subsequent palladium-induced bromine-tin exchange in the presence of hexabutylditin and $Pd(PPh_3)_4$ in refluxing toluene [4,7d] led to the organotin derivative **12**. An attempt to prepare the expected biphenyl **5** by reacting **12** and the 2-bromo-3,4,5-trimethoxybenzaldehyde (**14**) (previously synthesized by bromination of the 3,4,5-trimethoxybenzaldehyde (**13**) by NBS [10]) in a Stille cross coupling process has been carried out. Conventional procedure ($CuCN/Pd(PPh_3)_4$/THF, 65°C) was unsuccessful, while promoting the equilibrium displacement of the catalytic cycle by adding CsF ($CuI/CsF/Pd(PPh_3)_4$/DMF, 45°C) [11] or CsF with an electron-rich phosphine ligand suited for ortho-substituted biaryl coupling ($CuI/CsF/PdCl_2/P(t\text{-}Bu)_3$/DMF, 45°C) [12] failed too.

A1ternatively, the 2-tributylstannyl-3,4,5-trimethoxybenzaldehyde (**15**) [13], prepared from bromobenzaldehyde **14** by bromine-tin exchange, was reacted with 4,5-methylenedioxy-2-nitrobromobenzene (**11**) under Stille cross coupling conditions. Unfortunately, no reaction occurred between these two entities even in the presence of $PdCl_2$ and $P(t\text{-}Bu)_3$. Thus, a methoxy substituent at the 3-position of the 2-bromobenzaldehyde or of the 2-stannylbenzaldehyde has a dramatic effect on these two Stille coupling reactions.

To circumvent this hurdle, we elaborated an original pathway in which the biaryl bond would be formed before the regioselective introduction of the nitro group. Thus, the biphenyl **17** was synthesized according to a previously reported Suzuki-Miyaura cross coupling procedure [14]. Selective nitration of **17** with a stoichiometric amount of nitric acid proceeded on the less sterically hindered position of the



Scheme 3. Reagents and reaction conditions: (**a**) $NaBH_4$, MeOH, 25 °C, 15 min, 95%; (**b**) PBr_3, anhydrous CH_2Cl_2, 0 °C, 45 min, 89%; (**c**) Raney Ni, 3 bars H_2, MeOH, 25 °C, 1 h, 75%.

methylenedioxyphenyl nucleus instead of the more reactive (but less accessible) 2-position of the trimethoxybenzaldehyde nucleus. The desired compound **5** [15] was exclusively obtained in 98% yield (Scheme **2**).

With synthon **5** in hand, we first decided to widen the scope of possible reactions by preparing the corresponding alcohol **18** and bromomethylbenzene derivative **19** [16], both compounds being interesting intermediates for potential nucleophilic substitutions. This synthesis was conducted in two steps with an overall yield of 85% from **5** by reduction, in the presence of $NaBH_4$, to the corresponding alcohol followed by bromination using PBr_3 (Scheme **3**).

Since the 2-(*o*-nitrophenyl)benzaldehydes are precursors for the synthesis of phenanthridines, we also attempted the intramolecular reductive cyclization of the carbaldehyde **5** to the phenanthridine **20** (Scheme **3**). Hydrogenation of **5** using Raney nickel as a catalyst provided the 8,9,10-trimethoxyphenanthridine **20** [17] in good yield. The syntheses of 8,9,10-trimethoxyphenanthridines have been previously reported but under oxidative conditions where the key step is the C-C bond formation between the A and C nuclei [18].

CONCLUSION

In summary, we have synthesized three new building blocks **5**, **18** and **19** in order to provide an easy access to various biaryl derivatives. Further studies involving these structures and their pharmacological activities are underway. The synthetic potential of the carbaldehyde **5** was also exemplified with the preparation of the phenanthridine **20**.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

R.L. was supported by the Ministère de l'Education Supérieure et de la Recherche. Dr. Daniel Dauzonne is acknowledged for helpful discussions.

REFERENCES

[1] (a) Kupchan, S.M.; Britton, R.W.; Ziegler, M.F.; Gilmore, C.J.; Restivo, R.J.; Bryan, R.F. Tumor inhibitors. LXXXX. Steganacin and steganangin, novel antileukemic lignan lactones from *Steganotaenia araliacea*. *J. Am. Chem. Soc.*, **1973**, *95*, 1335-1336; (b) Carroll, A.R.; Taylor, W.C. Constituents of *Eupomatia* species. XII. isolation of constituents of the tubers and aerial parts of *Eupomatia bennettii* and determination of the structures of new alkaloids from the aerial parts of *E. bennettii* and minor alkaloids of *E. laurina*. *Aust. J. Chem.*, **1991**, *44*, 1615-1626; (c) Mitra, S.; Gurrala, S.R.; Coleman, R.S. Total Synthesis of the Eupomatilones. *J. Org. Chem.*, **2007**, *72*, 8724-8736.

[2] (a) Wu, G.; Guo, H.-F.; Gao, K.; Liu, Y.-N.; Bastow, K.F.; Morris-Natschke, S.L.; Lee, K.-H.; Xie, L. Synthesis of unsymmetrical biphenyls as potent cytotoxic agents. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 5272-5276; (b) Jain, N.; Yada, D.; Shaik, T.B.; Vasantha, G.; Reddy, P.S.; Kalivendi, S.V.; Sreedhar, B. Synthesis and antitumor evaluation of nitrovinyl biphenyls: anticancer agents based on allocolchicines. *ChemMedChem*, **2011**, *6*, 859-868.

[3] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl-Aryl bond formation one century after the discovery of the ullmann reaction. *Chem. Rev.*, **2002**, *102*, 1359-1469.

[4] Li, D.; Zhao, B.; LaVoie, E.J. Nitroarylstannanes as synthons for the preparation of phenanthridine and benzo[*i*]phenanthridine derivatives. *J. Org. Chem*., **2000**, *65*, 2802-2805.

[5] Li, H.-L.; Wu, Z.-S.; Yang, M.; Qi, Y.-X. Sulfur-ligand/Pd-catalyzed cross-coupling reactions of aryl halides with arylboronic acids under aerobic conditions. *Catal. Lett.*, **2010**, *137*, 69-73.

[6] (a) Banwell, M.G.; Lupton, D.W.; Ma, X.; Renner, J.; Sydnes, M.O. Synthesis of quinolines, 2-quinolones, phenanthridines, and 6(5*H*)-phenanthridinones *via* palladium[0]-mediated ullmann cross-coupling of 1-bromo-2-nitroarenes with β-halo-enals, -enones, or -esters. *Org. Lett.*, **2004**, *6*, 2741-2744; (b) Some, S.; Ray, J.K.; Banwell, M.G.; Jones, M.T. New protocols for the synthesis of 3,4-annulated and 4-substituted quinolines from β-bromo-α,β-unsaturated aldehydes and 1-bromo-2-nitrobenzene or 2-bromoacetanilide. *Tetrahedron Lett.*, **2007**, *48*, 3609-3612.

[7] (a) Makhey, D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L.F.; LaVoie, E.J. Substituted benzo[*i*]phenanthridines as mammalian topoisomerase-targeting agents. *Bioorg. Med. Chem.*, **2003**, *11*, 1809-1820; (b) Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L.F.; LaVoie, E.J. 8,9-Methylenedioxybenzo[*i*]phenanthridines: topoisomerase I-targeting activity and cytotoxicity. *Bioorg. Med. Chem.*, **2003**, *11*, 3795-3805; (c) Zhang, W.; Wilke, B.I.; Zhan, J.; Watanabe, K.; Boddy, C.N.; Tang, Y. A new mechanism for benzopyrone formation in aromatic polyketide biosynthesis. *J. Am. Chem. Soc.*, **2007**, *129*, 9304-9305; (d) Zhao, H.; Su, S.; Cui, J.; Song, X.; Qin, X.; Li, H.; Yan, H.; Zhong, R.; Hu, L. Asymmetric synthesis and structural elucidation of C_2-symmetrical optically active macrocycles consisting of two biaryl and two α-amino acid moieties. *Synlett*., **2010**, *17*, 2557-2560.

[8] Preparation of tributyl-(4,5-methylenedioxy-2-nitrophenyl)stannane (**12**): To a stirred solution of nitrobenzene **11** (1 g, 4.06 mmol) and Bu_6Sn_2 (3.2 mL, 6.10 mmol) in anhydrous toluene (10 mL) under N_2, was added $Pd(PPh_3)_4$ (235 mg, 0.20 mmol). The resulting mixture was then refluxed for 15 h and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2 as eluent to afford **12** as a yellowish oil (1.57 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (t, J = 7 Hz, 9 H), 1.05-1.50 (m, 18 H), 6.10 (s, 2 H), 7.00 (s, 1

H), 7.80 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.3, 13.7, 27.3, 29.0, 102.7, 105.4, 114.6, 137.0, 148.7, 152.7 ppm. Anal. Calcd for $C_{19}H_{31}NO_4Sn$: C, 50.03; H, 6.85; N, 3.07. Found: C, 50.40; H, 7.17; N, 2.83.

[9] Dallacker, F.; Wagner, A. Derivatives of 1,3-benzodioxole, 52. Preparation and reactions of 1,3-dioxolo[4,5-*b*]phenazines. *Z. Naturforsch*., **1984**, *39b*, 936-949.

[10] Molander, G.A.; George, K.M.; Monovich, L.G. Total synthesis of (+)-isoschizandrin utilizing a samarium(II) iodide promoted 8-endo ketyl-olefin cyclization. *J. Org. Chem*., **2003**, *68*, 9533-9540.

[11] Mee, S.P.H.; Lee, V.; Baldwin, J.E. Stille coupling made easier-the synergic effect of copper(I) salts and the fluoride ion. *Angew. Chem. Int. Ed*., **2004**, *43*, 1132-1136.

[12] Littke, A.F.; Schwarz, L.; Fu, G.C. Pd/P(*t*-Bu)$_3$: A mild and general catalyst for stille reactions of aryl chlorides and aryl bromides. *J. Am. Chem. Soc*., **2002**, *124*, 6343-6348.

[13] Preparation of 2-tributylstannyl-3,4,5-trimethoxybenzaldehyde (**15**): To a stirred solution of benzaldehyde **14** (858 mg, 3.12 mmol) and Bu_6Sn_2 (2.4 mL, 4.70 mmol) in anhydrous toluene (10 mL) under N_2, was added $Pd(PPh_3)_4$ (185 mg, 0.16 mmol). The resulting mixture was then refluxed for 48 h and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using a CH_2Cl_2/cyclohexane mixture (9:1) as eluent to afford **15** as a clear oil (1.21 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (t, *J* = 7 Hz, 9 H), 1.05-1.50 (m, 18 H), 3.85 (s, 3 H), 3.90 (s, 6 H), 7.25 (s, 1 H), 9.80 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.6, 13.8, 27.4, 29.3, 56.2, 60.7, 60.9, 110.2, 133.5, 137.9, 147.0, 154.3, 159.0, 192.7 ppm. Anal. Calcd for $C_{22}H_{38}O_4Sn$: C, 54.45; H, 7.89. Found: C, 54.81; H, 8.18.

[14] Preparation of 3,4,5-trimethoxy-2-(3,4-methylenedioxy-6-nitrophenyl)benzaldehyde (**5**): A 70% nitric acid solution (0.23 mL, 2.59 mmol) was added dropwise to a solution of carbaldehyde **17** (820 mg, 2.59 mmol) in acetic acid (20 mL). The mixture was stirred at room temperature for 15 min and was poured onto ice. The resulting precipitate was filtered, washed with saturated aq. $NaHCO_3$ solution and recrystallized from a ligroin/Et_2O mixture to afford **5** as a slightly colored solid (916 mg, 98%), mp (ligroin/Et_2O) 126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.70 (s, 3 H), 4.00 (s, 6 H), 6.20 (s, 2 H), 6.70 (s, 1 H), 7.35 (s, 1 H), 7.70 (s, 1 H), 9.70 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.2, 61.0, 103.3, 105.5, 106.4, 112.0, 125.3, 128.9, 129.8, 143.5, 147.2, 148.0, 150.3, 151.3, 153.7, 189.7 ppm. Anal. Calcd for $C_{17}H_{15}NO_8$: C, 56.51; H, 4.18; N, 3.88. Found: C, 56.41; H, 4.05; N, 3.88.

[15] Gurjar, M.K.; Cherian, J.; Ramana, C.V. Synthesis of the putative structure of eupomatilone-6. *Org. Lett.*, **2004**, *6*, 317-319.

[16] Preparation of 3,4,5-trimethoxy-2-(3,4-methylenedioxy-6-nitrophenyl)bromomethylbenzene (**19**): To a stirred suspension of carbaldehyde **5** (500 mg, 1.38 mmol) in MeOH (50 mL), was added $NaBH_4$ (105 mg, 2.76 mmol). The mixture was stirred at room temperature for 15 min and then water (20 mL) was added. MeOH was removed under reduced pressure and the aqueous phase was extracted with CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using a CH_2Cl_2/AcOEt mixture (8:2) as eluent to afford slightly unstable alcohol **18** as a yellow oil (478 mg, 95%) which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 1 H), 3.65 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.30 (d, *J* = 12 Hz, 1 H), 4.35 (d, *J* = 12 Hz, 1 H), 6.15 (s, 2 H), 6.65 (s, 1 H), 6.85 (s, 1 H), 7.55 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.0, 60.9, 62.9, 103.2, 105.3, 107.1, 111.4, 123.6, 127.6, 133.7, 141.1, 143.3, 147.4, 150.2, 151.3, 153.4 ppm; A 1 M solution of PBr_3 in CH_2Cl_2 (1.32 mL, 1.32 mmol) was added dropwise to a stirred solution of freshly purified alcohol **18** (478 mg, 1.32 mmol) in anhydrous CH_2Cl_2 (35 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 min. The mixture was poured onto ice and the organic phase was washed with saturated aq. $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2 as eluent to afford **19** as a yellowish solid (500 mg, 89%), mp 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.65 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.10 (d, *J* = 9 Hz, 1 H), 4.30 (d, *J* = 9 Hz, 1 H), 6.15 (s, 1 H), 6.20 (s, 1 H), 6.80 (s, 1 H), 6.85 (s, 1 H), 7.65 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 32.1, 56.0, 60.9, 103.2, 105.5, 109.0, 111.4, 125.4, 127.0, 130.3, 142.2, 143.1, 147.7, 150.6, 151.3, 153.6 ppm. Anal. Calcd for $C_{17}H_{16}BrNO_8$: C, 47.91; H, 3.78; N, 3.29. Found: C, 47.99; H, 4.01; N, 3.38.

[17] Preparation of 2,3-(methylenedioxy)-8,9,10-trimethoxyphenanthridine (**20**): A solution of **5** (73 mg, 0.46 mmol) in MeOH (12 mL) was hydrogenated for 1 h under pressure (3 bars) and in the presence of washed Raney nickel. The reaction mixture was solubilized with CH_2Cl_2 (5 mL) and filtered through a pad of Celite which was rinsed using 3 × 2 mL of a CH_2Cl_2/AcOEt mixture (1:1) to afford **20** as a white solid (47 mg, 75%), mp 197 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.05 (2s, 6 H), 4.10 (s, 3 H), 6.15 (s, 2 H), 7.20 (s, 1 H), 7.55 (s, 1 H), 8.80 (s, 1 H), 9.05 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.1, 60.5, 61.3, 101.7, 103.5, 104.7, 107.1, 119.1, 122.3, 123.4, 141.1, 146.3, 148.2, 148.3, 149.8, 150.8, 153.1 ppm. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.79; H, 5.08; N, 4.28.

[18] (a) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartín, R.; Domínguez, E. Novel applications of hypervalent iodine: PIFA mediated synthesis of benzo[*c*]phenanthiridines and benzo[*c*]phenanthridinones. *Tetrahedron*, **2001**, *57*, 5403-5411; (b) Bunnell, A.E.; Flippin, L.A.; Liu, Y. Total Synthesis of (±)-Roserine. *J. Org. Chem.*, **1997**, *62*, 9305-9313.