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A Total Synthesis of the Marine Alkaloid Discoipyrrole D

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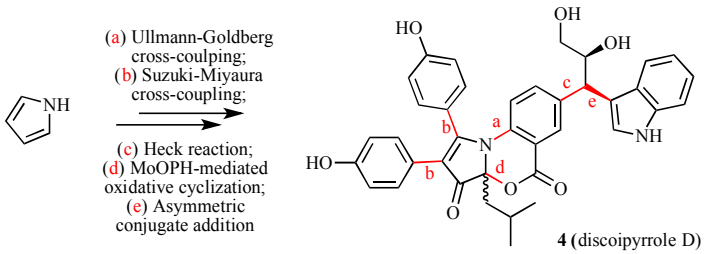
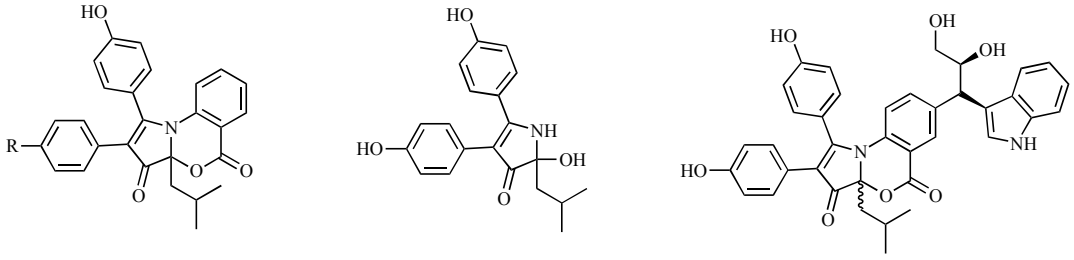


4 (discoipyrrole D)

ABSTRACT: A total synthesis of the diastereoisomeric pair of compounds, **4**, assigned to the marine alkaloid discoipyrrole D is reported. A series of palladium-catalysed cross-coupling and other reactions was employed to assemble the relevant 1,2,3,4-tetra-substituted pyrrole (**16**) that was engaged in MoOPH-mediated oxidative cyclization then conjugate addition and redox processes to complete the synthesis. This work serves to confirm the structure (**4**) originally assigned to discoipyrrole D.

INTRODUCTION

In 2013 MacMillan and co-workers reported on the isolation (from a marine bacterium) and structural elucidation of the alkaloids **1**-**4** (Figure 1), named discoipyrroles A-D respectively.[1] The occurrence of these compounds as racemic or (in the case of compound **4**) diastereoisomeric mixtures suggested that they were produced by non-enzymatic means and the same group was able to mimic the proposed biogenesis in a one-pot total synthesis of compound **1**. This involved "incubating" a DMSO solution of *p*-hydroxysattabacin, *p*-hydroxybenzalehyde and anthranilic acid at 50 °C in the presence of 1% trifluoroacetic acid.[1,2] The generation of analogues of the discoipyrroles by related means could well lead to the identification of compounds that show even more potent inhibition of the discoidin domain receptor-2 signalling pathway than the natural products themselves. In a similar vein, May and co-workers were able to produce a brominated analogue of discoipyrrole A bis-*O*-methyl ether and elaborate this, through Heck-type chemistry followed by, inter alia, an organocatalyzed asymmetric conjugate addition of an indole trifluoroborate, to discoipyrrole D bis-*O*-methyl ether.[3]



1 (R = OH, discoipyrrole A)
2 (R = H, discoipyrrole B)

3 (discoipyrrole C)

4 (discoipyrrole D)

Figure 1: Discoipyrroles A-D (**1**-**4**, respectively).

Seemingly, however, the sensitivity of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core associated with this last compound to the conditions normally used to cleave aryl methyl ethers prevented the completion of a synthesis of the natural product, viz. discoipyrrole D.[3]

In 2016 we reported[4] a distinctly different route to compounds **1** and **2** that involved the assembly, through Ullmann-Goldberg[5] and Suzuki-Miyaura cross-coupling chemistries,[6] of a tetra-substituted pyrrole that could be engaged in an oxoperoxymolybdenum (pyridine) hexamethylphosphoric triamide[7] or MoOPH-mediated oxidative cyclization reaction[8] resulting in the assembly of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core of discoipyrroles A and B. We have since used this modular approach to the discoipyrroles in the construction of a range of analogues.[9] As an extension of such work we now report on the amalgamation of this chemistry with certain aspects of May's approach[3] to discoipyrrole D in the successful synthesis of this natural product that serves to confirm the structure originally assigned to it by MacMillan and co-workers.[1]

RESULTS AND DISCUSSION

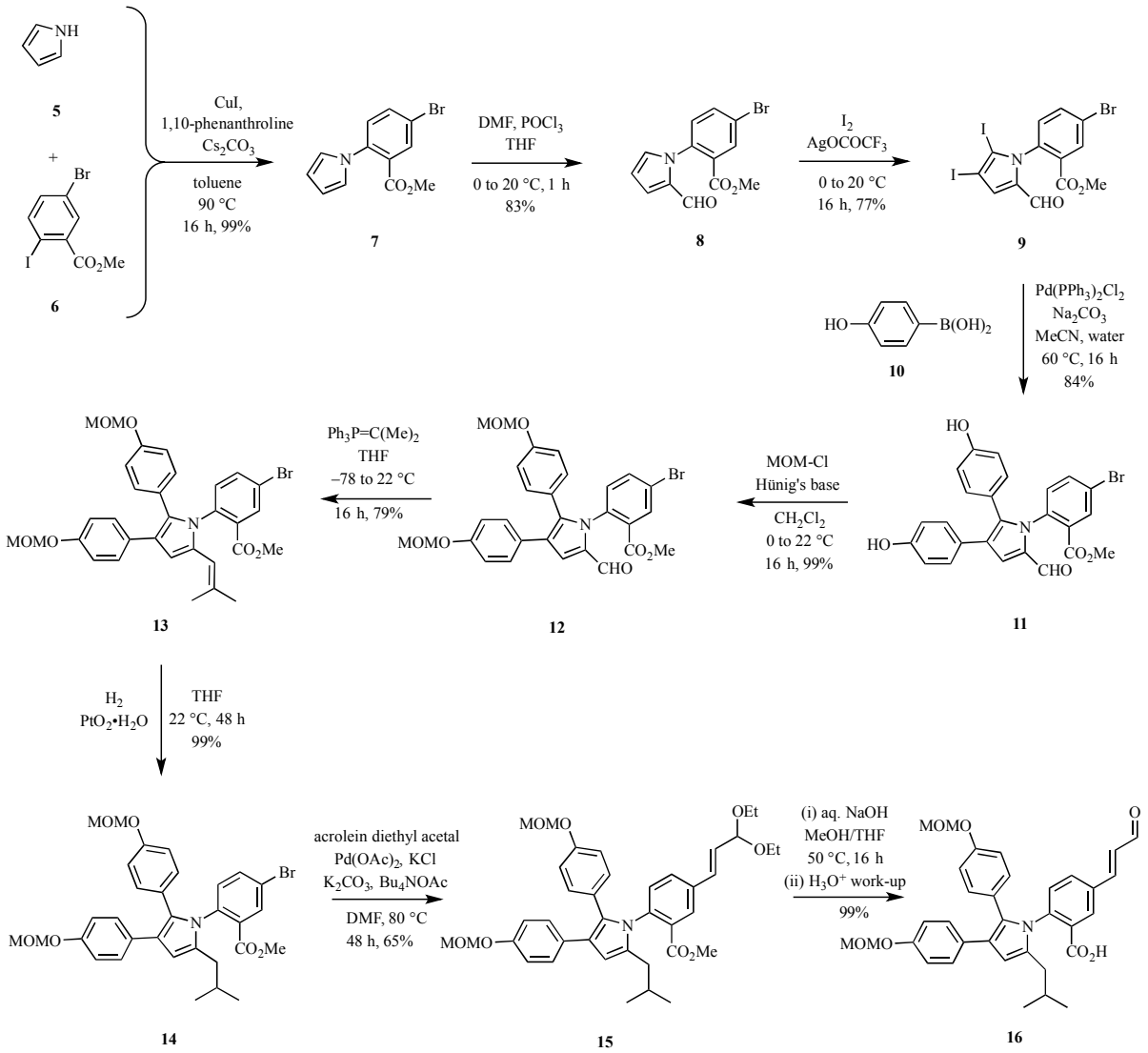
The two major considerations associated with our devising an approach to discoipyrrole D were, (i), the nature of the protecting group to be used to mask the phenolic hydroxyl groups present in the target and, (ii), the timing of MoOPH-mediated oxidative cyclization reaction that establishes the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core associated with compound **4**. After some preliminary experimentation we elected to employ the MOM group to protect the phenolic hydroxyls and to also delay the key oxidative cyclization reaction as

long as possible because of the seemingly "fragile" nature of the core heterocyclic ring system associated with the discoipyrroles.[3]

The reaction sequence leading to the tetrasubstituted pyrrole that was to be engaged in the pivotal oxidative cyclization reaction is shown in Scheme 1 and started with the regioselective Ullmann-Goldberg arylation of the parent heterocycle **5** with methyl 5-bromo-2-iodobenzoate (**6**) under conditions reported by Buchwald and co-workers.[5] Product **7** (99%) obtained by this means was subjected to a Vilsmeier-Haack reaction[10] and thus affording the pyrrole-2-carboxaldehyde **8** (83%) that was itself subjected to a regiocontrolled di-iodination reaction using molecular iodine in the presence of silver trifluoroacetate and thereby producing compound **9** (77%). Two-fold Suzuki-Miyaura cross coupling of di-iodide **9** with commercially available *p*-hydroxyphenylboronic acid (**10**) then gave the tri-arylated pyrrole **11** (84%) that was protected, under conventional conditions, as the corresponding bis-MOM ether **12** (99%). Wittig olefination of the aldehyde residue associated with the last compound was accomplished using in situ generated isopropylenetriphenylphosphorane[11] and by such means the olefin **13** (79%) was obtained. This was immediately hydrogenated using dihydrogen in the presence of Adam's catalyst and so affording the isobutylated pyrrole **14** (99%) that was itself engaged in a Heck reaction with 3,3-diethoxyprop-1-ene using $Pd(OAc)_2$ as the catalyst source. The ester residue associated with product **15** (65%) was saponified using sodium hydroxide in methanol and upon acidification of the ensuing mixture with aqueous HCl, so as to generate the free acid, the acetal moiety was also hydrolyzed and thus affording the cinnamaldehyde **16** (99%), the substrate required for the

pivotal oxidation reaction. All the spectral data acquired on this tetrasubstituted pyrrole were in complete accord with the illustrated structure.

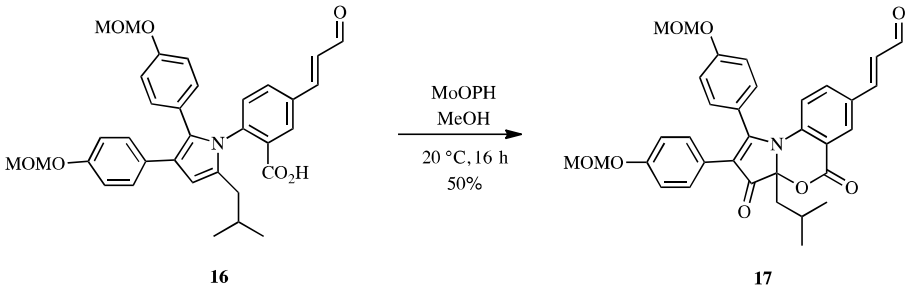
Scheme 1: Synthesis of pyrrole **16** required for the pivotal oxidative cyclization reaction.



In keeping with earlier observations,[4] when compound **16** was treated with freshly prepared MoOPH in methanol at ambient temperatures the anticipated oxidative cyclization reaction took place and after chromatographic purification of the major reaction product compound **17**

was obtained in 50% yield as a yellow oil (Scheme 2). No other characterizable materials could be isolated from the reaction mixture. The ^{13}C NMR spectrum of compound **17** displayed twenty-nine of the expected thirty resonances including three at δ_C 193.8, 193.2 and 167.4 ppm that are attributed to carbonyl carbons associated with the ketone, aldehyde and lactone residues, respectively. In the corresponding infra-red spectrum C=O stretching bands are evident at 1740, 1702 and 1679 cm^{-1} while molecular associated ions at *m/z* 606 $[(M + Na)^+]$ and 584 $[(M + H)^+]$ dominate the EI mass spectrum.

Scheme 2: MoOPH-mediated oxidative cyclization of pyrrole **16** leading to the formation of 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione **17**



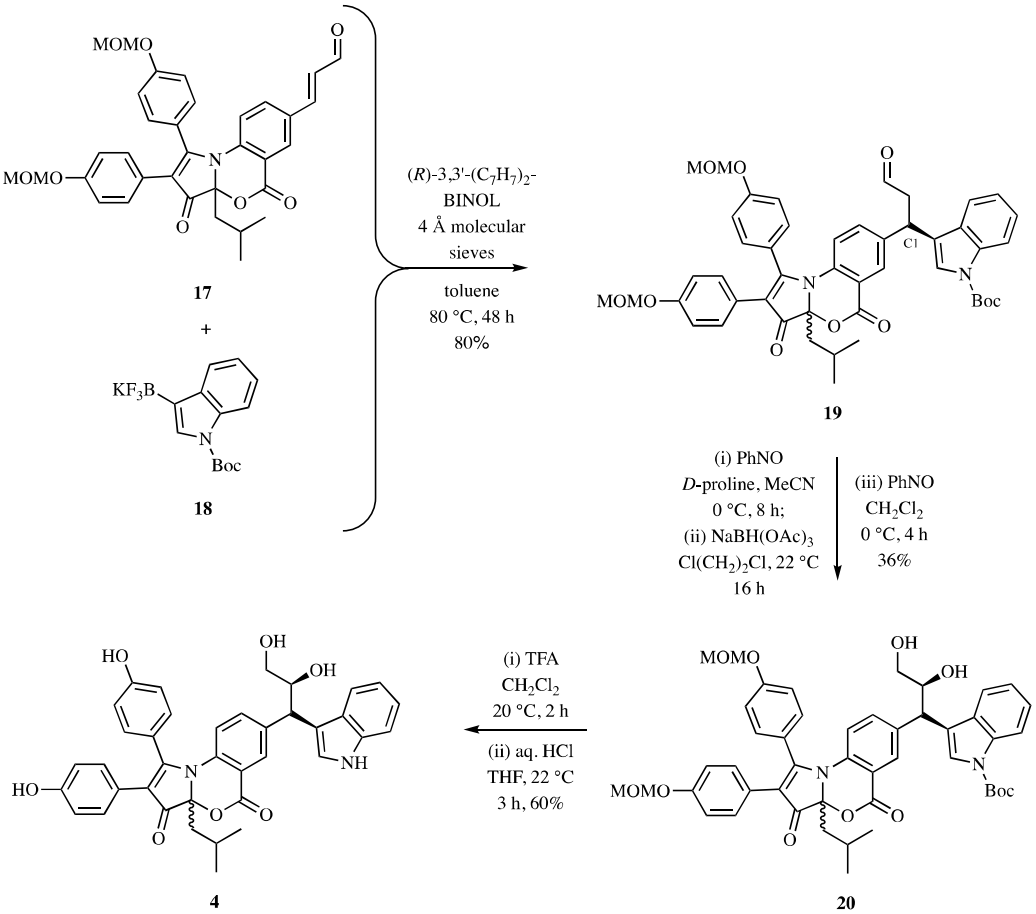
16 **17**

The completion of the synthesis of target compound **4** is shown in Scheme 3 and proved to be a rather straightforward matter. Thus, following the protocols reported by May and co-workers,[3] compound **17** was subjected to a reaction with the readily prepared and *N*-Boc-protected indole C3-trifluorborate salt **18**[12] in the presence of the freshly prepared catalyst (*R*)-3,3'-$(C_7F_7)_2$-BINOL[3] and so affording the rather unstable product **19** as a 1:1 mixture of diastereoisomers. This outcome clearly indicates that the existing stereogenic center within substrate **17** has no impact on the configuration of C1 established during the conjugate addition reaction. By analogy with the work of May, this addition reaction is presumed to

have proceeded with a high degree of stereochemical control and such that the illustrated *S*-configuration has been established at the new stereogenic center. May's three-step protocol was then employed to manipulate the indole-bearing carbon side-chain of compound **19** so as introduce the associated hydroxyl groups. Specifically, then, a *D*-proline-controlled oxidation involving nitrosobenzene[13] was used to introduce a 2°-phenyaminoxy moiety in a stereocontrolled fashion and this was followed by reduction of the aldehyde moiety using sodium triacetoxyborohydride. Treatment of the ensuing 2-aminoxyalcohol with nitrosobenzene resulted in cleavage of the aminoxy residue and so producing diol **20** (36%) that was also obtained as a 1:1 mixture of diastereoisomers. Subjection of this material to analysis on chiral HPLC column very similar to that used by May and co-workers and using a range of solvent systems only showed peaks due to two diastereoisomers and none attributable to the corresponding enantiomers. In the final steps of the reaction sequence, compound **20** was treated with trifluoroacetic acid (to cleave to Boc group) and then aqueous HCl (to cleave the MOM ethers) and thereby affording compound **4** in 60% yield and as a light-yellow oil. ^{1}H and ^{13}C NMR spectroscopic analyses of this material revealed the presence of aliphatic impurities although the aromatic regions of each spectrum were very clean. The origins of these impurities probably reflect the fragile nature of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core of the compound and its partial degradation under the acidic conditions necessarily employed in the final steps of the synthesis. Much cleaner samples of compound **4** were obtained after purification under reverse-phase HPLC conditions.

All the spectral data acquired on the HPLC-purified sample of compound **4**, which indicated that it had been generated as a 1:1 mixture of diastereoisomers, proved a good match with those reported by MacMillan and co-workers[1] on discoipyrrole D (see SI for a tabulated comparison of the ^{13}C NMR spectral data sets). Subjection of this material to analysis on chiral HPLC column very similar to that used as described above (and, once again, using a range of solvent systems) only showed peaks due to two diastereoisomers and none attributable to the corresponding enantiomers.

Scheme 3: Completion of the synthesis of discoipyrrole D (**4**)



The synthetic material was optically active {$[\alpha]_D^{25}$ = +25 (*c* 0.2, MeOH)}. However, in the absence of any published specific rotation data on the title natural product not much more can be said about the absolute configuration of the alkaloid.

CONCLUSION

The total synthesis of discoipyrrole D reported here serves to confirm the basic structure (but not the absolute configuration) assigned to it by MacMillan and co-workers. This work also highlights the capacity of the protocols reported by May and his colleagues to effect the organocatalyzed asymmetric conjugate addition of hetereoaryl trifluoroborates to cinnamaldehydes (in particular). In addition, the present study reveals more about the functionality that can be tolerated during the MoOPH-mediated formation of the above-mentioned heterocyclic core and the various reaction conditions that can be used without adversely affecting this same and often rather fragile motif.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates or as neat material resting on the sampling port. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double-focusing, triple-sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in either positive or negative ion mode. Melting points are uncorrected. HPLC analyses were performed on a HPLC system equipped with a photodiode array detector and either a C18 reversed phase (150 mm x 4.6 mm, 3 μM silica gel), Chiralpak IA (250 mm × 4.6 mm, amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μM silica gel) or Chiralpak IC (250 mm × 4.6 mm, cellulose tris (3,5-dichlorophenylcarbamate) coated on 5 μM silica gel) column. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g : 7.5 g : 37.5 g : 720 mL), potassium

permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g : 20 g : 5 mL : 300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid (conc.)/ethanol (15 g : 2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[14] with silica gel 60 (40-63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[15] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. **Methyl 5-Bromo-2-(1*H*-pyrrol-1-yl)benzoate (7).** A magnetically stirred and degassed mixture of pyrrole (**2**) (1.39 g, 20.8 mmol), commercially available compound **4** (6.45 g, 18.9 mmol), CuI (359 mg, 1.9 mmol), 1,10-phenanthroline (680 mg, 3.8 mmol) and Cs_2CO_3 (9.30 g, 28.4 mmol) in anhydrous toluene (40 mL) was heated at 100 °C under a nitrogen atmosphere for 48 h. The cooled reaction mixture was then passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue so formed was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 8:1 v/v hexane/ethyl acetate), compound **7** (5.21 g, 99%) as a clear, colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.5 and 2.4 Hz, 2H), 7.18 (m, 1H), 6.71 (m, 2H), 6.25 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 139.4, 135.3, 133.5, 129.4, 128.3, 122.0, 120.5, 110.2, 52.8; IR ν_{max} 2950, 1729, 1594, 1563, 1498, 1435, 1400, 1329, 1288, 1267, 1238, 1123, 1094, 1015, 966, 922, 826, 727 cm^{-1}; MS

(ESI, +ve): *m/z* 282 and 280 [$(M+H)^+$, both 50%], 250 and 248 (96 and 100); HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{12}H_{11}{}^{79}BrNO_2$ 279.9973; Found 279.9972.

Methyl 5-Bromo-2-(2-formyl-1*H*-pyrrol-1-yl)benzoate (8). Anhydrous DMF/THF (90 mL of a 4:5 v/v mixture) maintained with magnetic stirring at 0 °C under a nitrogen atmosphere was treated with $POCl_3$ (5.50 mL, 59.5 mmol) and the resulting orange reaction mixture was stirred at 0 °C for 0.75 h before being treated, dropwise, with a solution of compound **7** (6.47 g, 23.2 mmol) in anhydrous THF (40 mL). The mixture so-formed was warmed to 22 °C then stirred at this temperature for 3 h before being quenched with ice (100 g). The ensuing mixture was neutralized using $NaHCO_3$ (saturated aqueous solution) then extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with brine (1 × 300 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 12:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 4:1 v/v hexane/ethyl acetate), compound **8** (5.89 g, 83%) as a clear, colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 8.3 and 2.4 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (dd, J = 4.0 and 1.7 Hz, 1H), 6.94 (m, 1H), 6.43 (broadened s, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 164.1, 138.5, 135.6, 134.0, 133.2, 131.6, 130.4, 129.9, 123.8, 122.5, 110.9, 52.6; IR ν_{max} 3100, 2843, 1727, 1646, 1489, 1415, 1361, 1284, 1246, 1088, 1075, 1039, 836, 761, 745 cm^{-1}; MS (ESI, +ve): *m/z* 332 and 330 [$(M+Na)^+$, 95 and 100%], 310 and 308 (both 6); HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{13}H_{11}{}^{79}BrNO_3$ 307.9922; Found 307.9927.

Methyl 5-Bromo-2-(5-formyl-2,3-diiodo-1*H*-pyrrol-1-yl)benzoate (9). A magnetically stirred mixture of compound **8** (5.89 g, 19.2 mmol) and CF_3COOAg in dry THF (80 mL)

maintained at 0 °C under a nitrogen atmosphere was treated with molecular iodine (9.99 g, 39.3 mmol) and the resulting deep-red reaction mixture was warmed to 22 °C over 16 h while being protected from light. After this time the reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/THF elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **9** (8.21 g, 77%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.27 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 8.4 and 2.3 Hz, 1H), 7.21 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 163.2, 139.4, 138.5, 136.3, 134.7, 131.8, 130.0, 129.7, 124.0, 100.2, 78.1, 52.9; IR ν_{max} 3446, 3110, 2950, 1730, 1670, 1488, 1435, 1380, 1351, 1287, 1254, 1096, 835 cm^{-1}; MS (ESI, +ve) *m/z* 584 and 582 [$(M+Na)^+$, 100 and 97%], 562 and 560 [$(M+H)^+$, both 33]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{13}H_9{}^{79}Br^{127}I_2NO_3$ 559.7855; Found 559.7855.

Methyl 5-Bromo-2-(5-formyl-2,3-bis(4-hydroxyphenyl)-1*H*-pyrrol-1-yl)benzoate (11). A magnetically stirred and degassed mixture of compound **9** (1.62 g, 2.91 mmol), commercially available boronic acid **10** (910 mg, 6.40 mmol), $Pd(PPh_3)_2Cl_2$ (163 mg, 0.23 mmol) and Na_2CO_3 (1.23 g, 11.64 mmol) in acetonitrile/water (75 mL of a 3:2 v/v mixture) was heated at 60 °C for 48 h while being maintained under a nitrogen atmosphere throughout this period. The cooled reaction mixture was passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate), compound **11** (1.20 g, 84%) as a pale-yellow foam. ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.00 (d, J = 2.3

Hz, 1H), 7.69 (dd, J = 8.3 and 2.3 Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 8.6 Hz, 2H), 3.69 (s, 3H) (signals due to protons of phenolic hydroxyl groups not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 180.1, 165.6, 159.0, 157.2, 142.0, 138.7, 136.3, 134.3, 133.9, 133.6, 133.3, 132.5, 130.2, 127.1, 127.0, 124.5, 123.0, 122.3, 116.2, 116.1, 53.0; IR ν_{max} 3315, 2954, 2873, 1732, 1712, 1636, 1612, 1457, 1434, 1419, 1258, 1230, 1159, 1100, 830, 736 cm^{-1}; MS (ESI, +ve) *m/z* 516 and 514 [$(M+Na)^+$, 93 and 100%], 494 and 492 [$(M+H)^+$, 20 and 19]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{25}H_{18}{}^{79}BrNO_5Na$ 514.0266; Found 514.0265.

Methyl 5-Bromo-2-(5-formyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)benzoate (12). A magnetically stirred solution of compound **11** (1.26 g, 2.57 mmol) and *N*,*N*-diisopropylethylamine (3.32 g, 25.7 mmol) in dry dichloromethane (25 mL) maintained at 0 °C under a nitrogen atmosphere was treated with freshly prepared MOMCl (12 mL of an 2.14 M solution in dry dichloromethane, 25.7 mmol). The resulting light-yellow reaction mixture was warmed to 22 °C over 16 h then treated, successively, with NH_4Cl (50 mL of a saturated aqueous solution) and water (100 mL) before being extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (1 × 150 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/ethyl acetate) gave compound **12** (1.51 g, 99%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.04 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.4 and 2.3 Hz, 1H), 7.24 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.95–6.89 (complex m, 4H), 6.81 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 3.70 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

178.5, 164.0, 157.4, 156.0, 139.5, 137.2, 135.3, 133.8, 132.5, 132.2, 132.0, 130.9, 129.2, 128.2, 125.2, 123.4, 123.0, 122.4, 116.2, 116.0, 94.5, 94.4, 56.3, 56.1, 52.6; IR ν_{max} 2953, 2902, 2827, 1732, 1662, 1461, 1286, 1235, 1151, 1077, 994, 836 cm^{-1}; MS (ESI, +ve) *m/z* 604 and 602 [$(M+Na)^+$, 100 and 97%], 582 and 580 [$(M+H)^+$, 33 and 28]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{29}H_{26}{}^{79}BrNO_7Na$ 602.0790; Found 602.0794.

Methyl 2-(2,3-bis(4-(Methoxymethoxy)phenyl)-5-(2-methylprop-1-en-1-yl)-1*H*-pyrrol-1-yl)-5-bromobenzoate (13). A magnetically stirred suspension of *i*-$PrPPh_3I$ (1.44 g, 3.16 mmol) in dry THF (20 mL) maintained at −78 °C under a nitrogen atmosphere was treated with *n*-BuLi (1.82 mL of a 1.6 M solution in hexane, 2.91 mmol), and the ensuing red suspension stirred at −78 °C for 0.5 h before being added, over 0.17 h, to a magnetically solution of compound **12** (1.41 g, 2.43 mmol) in dry THF (40 mL) maintained at −78 °C. The reaction mixture thus formed was transferred to an ice-water bath and maintained at *ca*. 0 °C for 1 h then treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (40 mL) before being extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **13** (1.16 g, 79%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 8.4 and 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (m, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H), 5.49 (s, 1H), 5.14 (s, 2H), 5.11 (s, 2H), 3.64 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 1.97 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 156.4, 155.3, 137.6, 135.3, 135.0, 133.6, 132.8, 132.3, 132.2(4), 132.2(0), 130.4, 129.5, 129.1, 126.0, 122.8,

121.4, 116.1, 115.9, 114.5, 109.4, 94.7, 94.6, 56.2, 56.0, 52.6, 27.0, 20.3; IR ν_{max} 2951, 2900, 1733, 1515, 1486, 1284, 1232, 1151, 1077, 999, 834, 731 cm^{-1}; MS (ESI, +ve) *m/z* 630 and 628 [$(M+Na)^+$, 100 and 90%], 608 and 606 [$(M+H)^+$, 38 and 40]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{32}H_{33}{}^{79}BrNO_6$ 606.1491; Found 606.1494.

Methyl 5-bromo-2-(5-isobutyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)benzoate (14). A magnetically stirred mixture of compound **13** (4.72 g, 7.80 mmol) in dry THF (100 mL) was treated with $PtO_2 \bullet H_2O$ (573 mg, 2.34 mmol) and the ensuing black suspension stirred at 22 °C under a balloon of hydrogen for 48 h then filtered through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **14** (4.70 g, 99%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.4 Hz, 1H), 7.60 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.18–7.11 (complex m, 3H), 6.91–6.85 (complex m, 4H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.24 (s, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 3.64 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 2.25 (dd, *J* = 15.2 and 7.0 Hz, 1H), 2.16 (dd, *J* = 15.2 and 7.2 Hz, 1H), 1.70 (m, 1H), 0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 156.3, 155.1, 138.0, 135.2, 133.9, 133.8, 132.8, 132.3, 132.2, 130.7, 129.6, 128.9, 126.4, 122.0, 121.6, 116.1, 115.8, 107.8, 94.7, 94.6, 56.3, 56.1, 52.6, 36.3, 27.8, 22.7(8), 22.7(5); IR ν_{max} 2952, 2899, 1737, 1515, 1486, 1283, 1233, 1151, 1078, 999, 836 cm^{-1}; MS (ESI, +ve) *m/z* 610 and 608 [$(M+H)^+$, 100 and 92%], 632 and 630 [$(M+Na)^+$, 90 and 88]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{32}H_{35}{}^{79}BrNO_6$ 608.1648; Found 608.1647.

Methyl (*E*)-5-(3,3-Diethoxyprop-1-en-1-yl)-2-(5-isobutyl-2,3-bis(4-(methoxymethoxy)-phenyl)-1*H*-pyrrol-1-yl)benzoate (15). A magnetically stirred mixture of compound **14**

(647 mg, 1.06 mmol), acrolein diethyl acetal (1.38 g, 10.6 mmol), tetra-*n*-butylammonium acetate (640 mg, 2.12 mmol), K_2CO_3 (220 mg, 1.59 mmol), KCl (80 mg, 1.06 mmol) and $Pd(OAc)_2$ (120 mg, 0.53 mmol) in anhydrous DMF (10 mL) was heated at 100 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **15** (453 mg, 65%) as a clear, yellow oil. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.86 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.80 (m, 3H), 6.36 (dd, J = 16.2 and 4.9 Hz, 1H), 6.27 (s, 1H), 5.15 (s, 2H), 5.10 (m, 3H), 3.73–3.64 (complex m, 5H), 3.55 (m, 2H), 3.43 (s, 3H), 3.39 (s, 3H), 2.33 (dd, J = 15.0 and 7.1 Hz, 1H), 2.23 (dd, J = 15.0 and 7.2 Hz, 1H), 1.70 (m, 1H), 1.20 (m, 6H), 0.89 (m, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 166.5, 157.4, 156.2, 138.9, 137.4, 134.5, 133.3, 132.8, 132.2, 131.9, 131.4, 130.7, 129.7, 129.5, 127.7, 122.6, 116.9, 116.5, 108.5, 101.9, 95.4, 95.3, 61.7, 56.3, 56.1, 52.7, 37.2, 28.6, 23.1, 15.9, 15.8; IR ν_{max} 2853, 2898, 1719, 1515,1302, 1232, 1198, 1150, 1077, 997, 921, 837, 788 cm^{-1}; MS (ESI, +ve): *m/z* 680 [$(M+Na)^+$, 15%], 658 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{39}H_{48}NO_8$ 658.3380; Found 658.3389.

(*E*)-2-(5-Isobutyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)-5-(3-oxoprop-1-en-1-yl)benzoic acid (16). A magnetically stirred solution of compound **15** (453 mg, 0.69 mmol) in THF/water/ethanol (20 mL of a 1:1:2 v/v/v mixture) was treated with KOH (386 mg, 6.9 mmol) and the ensuing mixture stirred at 22 °C for 24 h then acidified, using HCl (2 M aqueous solution), to pH 2. The mixture thus obtained was diluted with brine (50 mL) and

then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (3 × 100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/acetone elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/acetone), compound **16** (353 mg, 90%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 8.3 and 2.1 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.91–6.84 (complex m, 4H), 6.75 (dd, J = 16.0 and 7.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 6.24 (s, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 3.46 (s, 3H), 3.41 (s, 3H), 2.29 (dd, J = 15.2 and 7.0 Hz, 1H), 2.19 (dd, J = 15.2 and 7.2 Hz, 1H), 1.66 (m, 1H), 0.85 (m, 6H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 169.1, 156.3, 155.1, 150.1, 141.7, 133.6(3), 133.5(9), 132.5, 131.9, 131.8, 130.5, 130.2, 129.6, 129.0, 126.3, 122.3, 116.1, 115.9, 108.4, 94.7, 94.6, 56.2, 56.1, 36.4, 27.9, 22.7(2), 22.6(8); IR ν_{max} 2954, 1680, 1515, 1232, 1198, 1150, 1121, 1078, 999, 920, 837, 731 cm^{-1}; MS (ESI, +ve) *m/z* 570 [$(M+H)^+$, 100%]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{34}H_{36}NO_7$ 570.2492; Found 570.2496.

(*E*)-3-(3a-Isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrole[2,1-*b*][1,3]oxazin-7-yl)acrylaldehyde (17). A magnetically stirred solution of compound **16** (540 mg, 0.95 mmol) in dry methanol (25 mL) maintained under a nitrogen atmosphere at 22 °C was treated with MoOPH (825 mg, 1.9 mmol). The ensuing yellow-colored reaction mixture was stirred, while being protected from light, at 22 °C for 16 h then filtered through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 2:1 v/v

hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate), compound **17** (277 mg, 50%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.8 and 2.2 Hz, 1H), 7.40 (d, J = 16.0 Hz, 1H), 7.19–7.06 (complex m, 6H), 6.88 (d, J = 8.8 Hz, 2H), 6.66 (dd, J = 16.0 and 7.5 Hz, 1H), 6.34 (d, J = 8.6 Hz, 1H), 5.26–5.21 (complex m, 2H), 5.14–5.09 (complex m, 2H), 3.53 (s, 3H), 3.44 (s, 3H), 2.35 (dd, J = 14.1 and 5.7 Hz, 1H), 1.97 (dd, J = 14.1 and 7.0 Hz, 1H), 1.83–1.71 (complex m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.2, 167.4, 161.3, 159.4, 156.5, 149.8, 139.1, 133.4, 131.7, 130.4, 130.2(9), 130.2(7), 129.3, 122.3, 122.1, 122.0, 118.4, 117.0, 116.4, 116.1, 94.6, 94.4, 91.2, 56.6, 56.2, 42.4, 24.1, 23.1; IR ν_{max} 2959, 1740, 1702, 1679, 1607, 1498, 1389, 1237, 1152, 1121, 1079, 989 cm^{-1}; MS (ESI, +ve) *m/z* 606 [$(M+Na)^+$, 90%], 584 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{34}H_{33}NO_8Na$ 606.2104; Found 606.2107.

Potassium [1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]trifluoroborate (18). Following a procedure reported by Aggarwal,[16] a magnetically stirred mixture of 3-Bpin-*N*-Boc-indole[17] (9.60 g, 28 mmol) in methanol/THF (90 mL of a 7:2 v/v mixture) was treated, dropwise at 0 °C, with a solution of KHF_2 (9.93 g, 126 mmol) in water (33 mL) and the ensuing white suspension was stirred at 20 °C for 3 h then concentrated under reduced pressure. The residue thus obtained was re-dissolved in methanol/water (50 mL of a 1:1 v/v mixture) and all the volatile materials were again removed under reduced pressure. This evaporation-dissolution cycle was repeated a further four times and the white solid thereby obtained was treated with acetone (100 mL) and ensuing mixture then filtered (through filter paper) and the filtrate so-obtained concentrated under reduced pressure. The resulting solid was then dried over P_2O_5

for 16 h to afford compound **18**[12] (8.99 g, 99%) as a colorless solid, m.p. = 168-176 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 150.7, 137.0, 136.6, 127.7, 123.8, 122.9, 121.9, 114.8, 82.5, 28.2 (one signal obscured or overlapping); ^{11}B NMR (128 MHz, $(CD_3)_2CO$) δ 3.48; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –138.3; IR ν_{max} 2984, 1724, 1706, 1455, 1370, 1250, 1161, 1127, 1084, 983, 928, 900, 754 cm^{-1}; MS (ESI, +ve) *m/z* 362 [$(M+K)^+$, 100%]; HRMS (ESI, +ve): $(M+K)^+$ Calcd for $C_{13}H_{14}BF_3NO_2K$ 362.0344; Found 362.0340.

***tert*-Butyl 3-((1*R*)-1-(3a-Isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)-3-oxopropyl)-1*H*-indole-1-carboxyl-ate (19)**. A magnetically stirred mixture of compound **17** (41 mg, 0.07 mmol), (*R*)-3,3'-$(C_7F_7)_2$-BINOL (25 mg, 0.035 mmol), compound **18** (68 mg, 0.21 mmol) and molecular sieves (200 mg of 4 Å powdered material) in dry toluene (3 mL) was heated at 80 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **19** (45 mg, 80%) as a 1:1 mixture of diastereoisomers and as a clear, light-yellow oil, $[\alpha]_D^{24}$ = +60 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.19–8.03 (complex m, 2H), 7.49 (s, 1H), 7.34–6.99 (complex m, 10H), 6.88 (m, 2H), 6.28 (m, 1H), 5.27–5.17 (complex m, 2H), 5.11 (m, 2H), 4.80 (m, 1H), 3.57–3.49 (complex m, 3H), 3.46 (m, 3H), 3.42–3.07 (complex m, 2H), 2.32 (m, 1H), 2.00–1.87 (complex m, 1H), 1.77–1.66 (complex m, 10H), 0.96–0.90 (complex 3H), 0.84–0.77 (complex m, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 199.9, 199.8, 194.1(0), 194.0(7), 168.5(3), 168.5(1), 161.9, 161.8, 159.1, 156.2, 149.7, 139.4(2), 139.3(6), 136.2, 136.1, 135.9, 134.7, 134.5, 130.6, 130.3, 130.2, 130.1, 129.7(1), 129.6(5), 129.2(0), 129.1(5), 124.9, 122.9, 122.8(4), 122.7(8), 122.6(2), 122.6(0), 122.4, 122.3, 122.2, 122.0, 121.7, 121.6, 119.3(3), 119.2(7), 118.2, 118.1, 116.8, 116.7, 116.0, 115.6(0), 115.5(7), 115.2(8), 115.2(7), 94.5(4), 94.5(2), 94.4, 91.3, 91.2, 84.2, 56.5, 56.1, 49.0, 48.9, 42.1, 42.0, 35.9, 35.8, 29.8, 28.3, 24.0, 23.9, 23.1; MS (ESI, +ve) *m/z* 801 [$(M+H)^+$, 100%]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{47}H_{49}N_2O_{10}$ 801.3387; Found 801.3381.

***tert*-Butyl 3-((1*R*,2*S*)-2,3-Dihydroxy-1-(3a-isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)propyl)-1*H*-indole-1-carboxylate (20)**. A magnetically stirred mixture of compound **19** (67 mg, 0.083 mmol) and nitrosobenzene (8.9 mg, 0.083 mmol) in acetonitrile (0.5 mL) was cooled to 4 °C then treated with *D*-proline (2.9 mg, 0.025 mmol). The ensuing and initially green-colored mixture was stirred at 4 °C for 6 h during which time the color of the mixture turned to yellow (and thus marking the end-point of the α-aminoxylation reaction) and at which stage it was diluted with 1,2-dichloroethane (2 mL) and treated with $NaBH(OAc)_3$ (145 mg, 0.66 mmol). The resulting yellow suspension was stirred at 22 °C for 16 h then treated, successively, with $NaHCO_3$ (2 mL of a saturated aqueous solution) and water (10 mL) before being extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in dry dichloromethane (2 mL) and the resulting solution cooled to 4 °C before being treated with nitrosobenzene (17 mg, 0.16 mmol). The ensuing green-colored was mixture was stirred at 4 °C for 4 h and then subjected to flash chromatography (silica,

2:3 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v hexane/ethyl acetate), compound **20** (24.7 mg, 36%) as a clear, yellow oil and a 1:1 mixture of diastereoisomers, $[\alpha]_D^{24}$ = –29 (*c* 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, CD_3OD) δ 8.13 (d, *J* = 2.1 Hz, 0.5H), 8.11 (d, *J* = 2.1 Hz, 0.5H), 8.10 (m, 1H), 7.77 (s, 0.5H), 7.75 (s, 0.5H), 7.51 (m, 0.5H), 7.49 (m, 0.5H), 7.38 (d, *J* = 7.9 Hz, 0.5H), 7.35 (d, *J* = 7.8 Hz, 0.5H), 7.26 (m, 1H), 7.19–7.12 (complex m, 3H), 7.08 (m, 1H), 7.05–7.01 (complex m, 3H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.38 (d, *J* = 8.5 Hz, 0.5H), 6.36 (d, *J* = 8.5 Hz, 0.5H), 5.23 (s, 1H), 5.19 (m, 1H), 5.11 (s, 2H), 4.42–4.36 (complex m, 2H), 3.52–3.45 (complex m, 2H), 3.48 (s, 1.5H), 3.44 (s, 1.5H), 3.40 (s, 3H), 2.22–2.14 (complex m, 1H), 2.04–1.93 (complex m, 1H), 1.80–1.71 (complex m, 1H), 1.69 (s, 4.5H), 1.68 (s, 4.5H), 0.93 (d, *J* = 6.7 Hz, 1.5H), 0.92 (d, *J* = 6.7 Hz, 1.5H), 0.82 (d, *J* = 6.7 Hz, 1.5H), 0.81 (d, *J* = 6.7 Hz, 1.5H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 196.3(1), 196.2(9), 172.1(0), 172.0(9), 163.5, 163.4, 160.7, 160.6, 157.7, 151.1, 139.6(2), 139.5(7), 137.6, 137.5, 137.0, 132.5, 132.4, 131.6, 131.5, 131.4, 131.2, 125.6, 124.3, 124.1, 123.5(9), 123.5(7), 123.4(2), 123.3(8), 123.1, 122.9, 122.8, 122.7, 120.4, 120.3, 118.8(2), 118.7(9), 117.7(1), 117.6(7), 116.9, 116.2(0), 116.1(8), 116.1(5), 116.1, 95.5(0), 95.4(7), 95.4, 92.7, 92.6, 85.0, 74.4, 74.2, 65.6, 65.5, 56.5(9), 56.5(6), 56.2, 45.0, 43.0, 42.9, 28.4(3), 28.4(2), 25.2, 25.1, 24.2(1), 24.1(7), 23.5(1), 23.4(9); IR ν_{max} 3449, 2925, 1735, 1611, 1499, 1453, 1371, 1240, 1155, 1080, 996 cm^{-1}; MS (ESI, +ve) *m/z* 841 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{47}H_{50}N_2O_{11}Na$ 841.3312; Found 841.3312.

7-((1*R*,2*S*)-2,3-Dihydroxy-1-(1*H*-indol-3-yl)propyl)-1,2-bis(4-hydroxyphenyl)-3a-isobut-yl-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (Discoipyrrole D, 4). A

magnetically stirred solution of compound **20** (24.5 mg, 0.03 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (460 μL, 6 mmol) and the ensuing brown-colored reaction mixture was stirred at 22 °C for 2 h before being treated, successively, with $NaHCO_3$ (1 × 2 mL of a saturated aqueous solution) and water (1 × 10 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in THF (2 mL), the resulting solution treated with HCl (2 mL of a 4.0 M aqueous solution) and the mixture thus obtained stirred at 22 °C for 3 h before being diluted with $NaHCO_3$ (2 mL of a saturated aqueous solution) and water (10 mL) then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 12:1 v/v ethyl acetate/isopropanol elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **4** (11 mg, 60%) as a clear, light-yellow oil and a 1:1 mixture of diastereoisomers, $[\alpha]_D^{25}$ = +25 (*c* 0.2, MeOH). For the purposes of spectroscopic analysis, a portion of this material was subjected to further purification by reversed phase HPLC using 3:7 v/v acetonitrile/water as the eluting solvent at a flow rate of 1 mL/min. ^{1}H NMR (800 MHz, CD_3OD) δ 8.13 (d, *J* = 2.1 Hz, 0.5H), 8.10 (d, *J* = 2.1 Hz, 0.5H), 7.52 (td, *J* = 8.8 and 2.1 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 0.5H), 7.40 (d, *J* = 8.0 Hz, 0.5H), 7.33 (d, *J* = 8.1 Hz, 0.5H), 7.32 (d, *J* = 8.1 Hz, 0.5H), 7.31 (s, 0.5H), 7.30 (s, 0.5H), 7.07 (m, 1H), 7.05–7.02 (complex m, 2H), 6.97–6.90 (complex m, 3H), 6.82 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.62 (dm, *J* = 8.8 Hz, 1H), 6.61 (dm, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 0.5H), 6.38 (d, *J* = 8.5 Hz, 0.5H), 4.43–4.40 (complex m, 1H), 4.36 (d, *J* = 8.1

Hz, 0.5H), 4.35 (d, J = 8.1 Hz, 0.5H), 3.56 (m, 1H), 3.45 (complex m, 1H), 2.15 (m, 1H), 1.99 (m, 0.5 H), 1.95 (m, 0.5 H), 1.73 (m, 1H), 0.91 (t, J = 6.4 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H) (signals due to OH and NH group protons not observed); ^{13}C NMR (200 MHz, CD_3OD) δ 196.6, 196.5, 172.4(4), 172.4(2), 163.8, 161.0(6), 161.0(5), 157.6, 141.8(4), 141.8(1), 137.9(8), 137.9(6), 137.3, 137.2, 136.5, 132.0, 131.9, 131.6, 131.4, 128.0, 123.3(2), 123.3(1), 122.9(2), 122.8(7), 122.5(9), 122.5(8), 121.8, 121.0(6), 121.0(5), 119.8(3), 119.8(2), 119.5(4), 119.5(0), 118.6, 118.5, 116.8(8), 116.8(6), 116.7(4), 116.6(7), 116.1, 116.0, 115.9, 112.4, 112.3, 92.6(4), 92.6(2), 75.3, 75.1, 66.1, 66.0, 46.1(2), 46.0(9), 42.9(6), 42.9(5), 25.2, 24.2(2), 24.1(9), 23.4(2), 23.4(0) (seventeen signals obscured or overlapping); IR ν_{max} 3364, 2959, 2927, 1720, 1612, 1498, 1387, 1273, 1240, 1172, 1070, 1042 cm^{-1}; MS (ESI, +ve) *m/z* 653 [$(M+Na)^+$, 40%], 631 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{38}H_{35}N_2O_7$ 631.2444; Found 631.2441.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXXX. Tabular comparison of the ^{13}C NMR data reported for discoipyrrole D with those recorded on the synthetically derived compound **4**. ^{1}H and ^{13}C NMR spectra of compounds **7**-**9**, **11**-**20** and **4** (PDF).

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Notes

The authors declare no competing financial interest.

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