Organic LETTERS

Letter

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Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway

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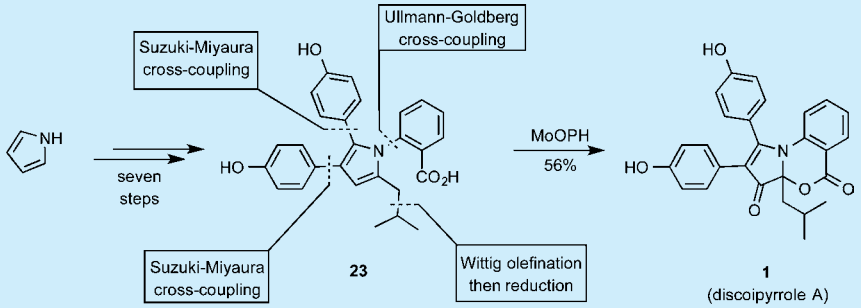
Supporting Information



ABSTRACT: The title natural product **1** has been synthesized by treating the 1,2,3,5-tetrasubstituted pyrrole **23** with oxoperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH). Compound **23** was itself prepared in seven steps from parent pyrrole using Ullmann−Goldberg and Suzuki−Miyaura cross-coupling, Vilsmeier−Haack formylation, electrophilic bromination, and Wittig olefination reactions as key steps. Related chemistry has been used to prepare discoipyrrole B (**2**).

In 2013 MacMillan and co-workers reported[1] the isolation, using a functional signature-based ontology (FUSION) map approach,[1,2] of four new alkaloids from the marine-derived *Bacillus hunanensis* strain SNA-048. Using a range of relatively conventional spectroscopic techniques, they assigned structures **1**−**4** (Figure 1) to these compounds and named them discoipyrroles A−D, respectively.[1] Each was isolated as the racemate and the structure of the first (viz. **1**) was confirmed by single-crystal X-ray analysis of the bis-*p*-bromobenzoate derivative of the (−)-enantiomer obtained using chiral-phase HPLC techniques.

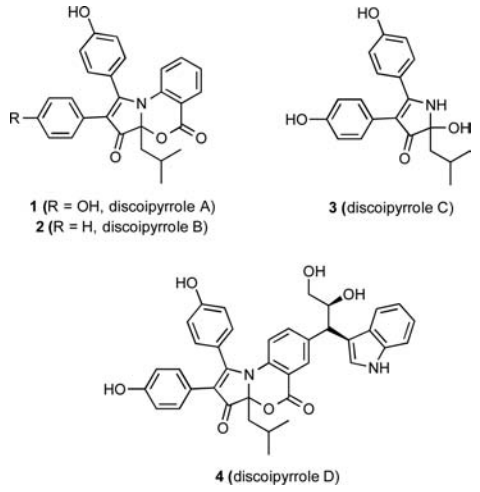


Figure 1. Discoipyrroles A−D.

Discoipyrroles **1**, **2**, and **4** are the first examples of natural products that embody a 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core. All four compounds proved to be particularly strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts.[1] They also showed selective cytotoxicity toward DDR2 mutant lung cancer cell lines (IC_{50} 120−400 nM). As such, these natural products and their analogues could provide important new tools for interrogating the DDR2 signaling pathway, one that has been implicated in various cancers,[3] fibroblast migration and proliferation,[4] as well as obstructive diseases of blood vessels.[5]

The biogenesis of the racemic discoipyrroles is believed to be nonenzymic in nature and involves, in the case of compound **1**, for example, oxidative coupling of 2-hydroxy-1-(*p*-hydroxyphenyl)-5-methylhexan-3-one and *p*-hydroxybenzaldehyde with the resulting 1,3,4-trione engaging in successive inter- then intramolecular condensation reactions with the amine and carboxylic acid residues, respectively, of anthranilic acid.[1] Various feeding experiments have served to support such proposals, and by mixing the three reaction partners just mentioned in dimethyl sulfoxide containing 1% trifluoroacetic acid at 50 °C then modest amounts of discoipyrrole A were obtained as an admixture with a number of side products.[1] A variation on this theme has been

Received: December 27, 2015
Published: February 2, 2016

DOI: 10.1021/acs.orglett.5b03672
Org. Lett. 2016, 18, 704−707

employed by May and co-workers in an approach to discoipyrrole D (**4**).[6]

The fascinating origins, structures, and biological activities of the discoipyrroles together with the potential for "tuned" analogues to serve as molecular probes of the DDR2-mediated cellular signaling processes prompted us to investigate means for establishing completely modular (and rational) syntheses of such systems. Herein, we report the assembly, via successive cross-coupling and alkenylation chemistries, of compounds of the general form **5** (Figure 2) and their successful oxidative

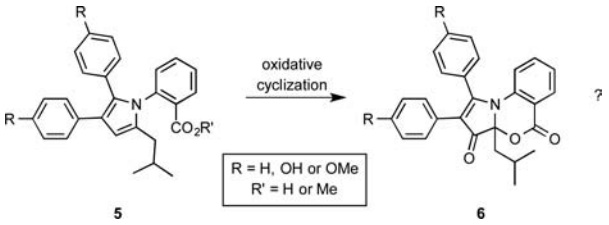
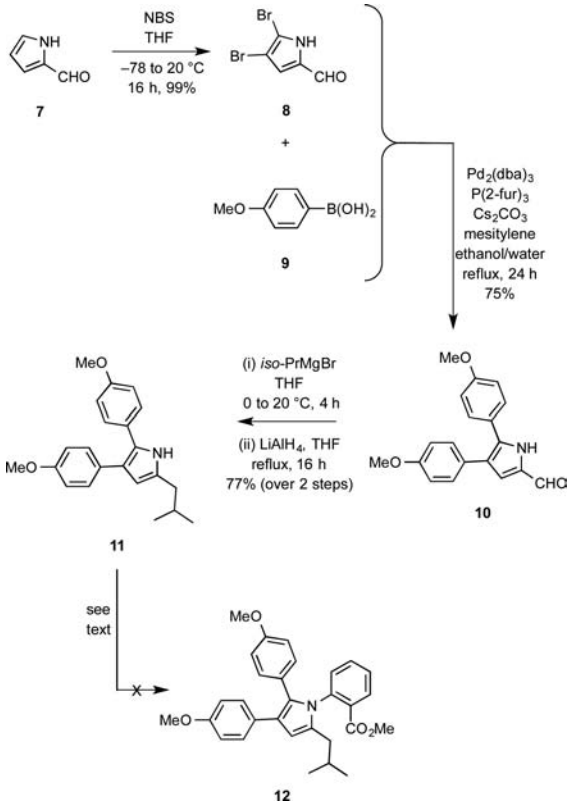


Figure 2. Proposed oxidative cyclization of a 1,2,3,5-tetrasubstituted pyrrole **5** to afford the 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione framework **6** of discoipyrroles A, B, and D.

cyclization to generate the corresponding 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-diones **6** including discoipyrroles A and B (**1** and **2**, respectively).[7]

The first approach used in attempts to prepare pyrroles of the general form **5** is shown in Scheme 1 and started with the 2-fold electrophilic bromination of readily available 1*H*-pyrrole-2-carboxaldehyde (**7**) using *N*-bromosuccinimide (NBS) and so affording the previously reported[8] dibromo-derivative **8** in 99% yield. Suzuki–Miyaura cross coupling of this last compound with 5 molar equiv of commercially available *p*-methoxyphenylboronic acid (**9**) provided the previously unreported, diarylated pyrrole **10** in 75% yield.[9]

Scheme 1. Attempted Synthesis of the 1,2,3,5-Tetrasubstituted Pyrrole 12 via *N*-Arylation of Precursor 11



On reaction with isopropylmagnesium bromide in THF aldehyde **10** afforded the expected but unstable secondary alcohol that was treated, in situ, with lithium aluminum hydride ($LiAlH_4$), thereby effecting reductive cleavage of the hydroxy group to produce the isobutyl-substituted pyrrole **11** in 77% yield (from **10**).[10]

Unfortunately, all attempts to effect the *N*-arylation of compound **11** using various methyl *o*-halobenzoates under a range of different conditions, including modern variants of the Ullmann–Goldberg reaction,[11] failed. Such outcomes are attributed to the sterically congested environment about the nitrogen of pyrrole **11** resulting from the presence of the flanking aryl and isobutyl groups at C2 and C5, respectively.

In an effort to address the difficulties described immediately above, a reordering of the cross-coupling and alkylation processes was investigated as shown in Scheme 2. Thus, pyrrole (**13**) was cross-coupled with methyl *o*-iodobenzoate (**14**) using conditions very similar to those reported by Buchwald[11a,b] and thereby affording the anticipated and previously reported product **15**[12] (99%). Subjection of the latter compound to a standard Vilsmeier–Haack formylation reaction using *N*,*N*-dimethylformamide (DMF) and $POCl_3$ afforded aldehyde **16**[13] (59%), which could be dibrominated with NBS under the same conditions as described earlier and so delivering the dihalogenated product **17** in 99% yield.

Two-fold Suzuki–Miyaura cross-coupling of this last compound with boronic acid **9** then gave the 1,2,3-triarylated pyrrole-2-carboxaldehyde **18** (73%) that was itself subjected to a Wittig olefination reaction using the ylide obtained by treating isopropyltriphenylphosphonium iodide with potassium *tert*-butoxide. The isobutene **19** (78%) so formed was subjected to hydrogenation at atmospheric pressures using palladium on carbon as catalyst and the targeted C5-isobuylated and triaryl-substituted pyrrole **12** thereby obtained in 95% yield.

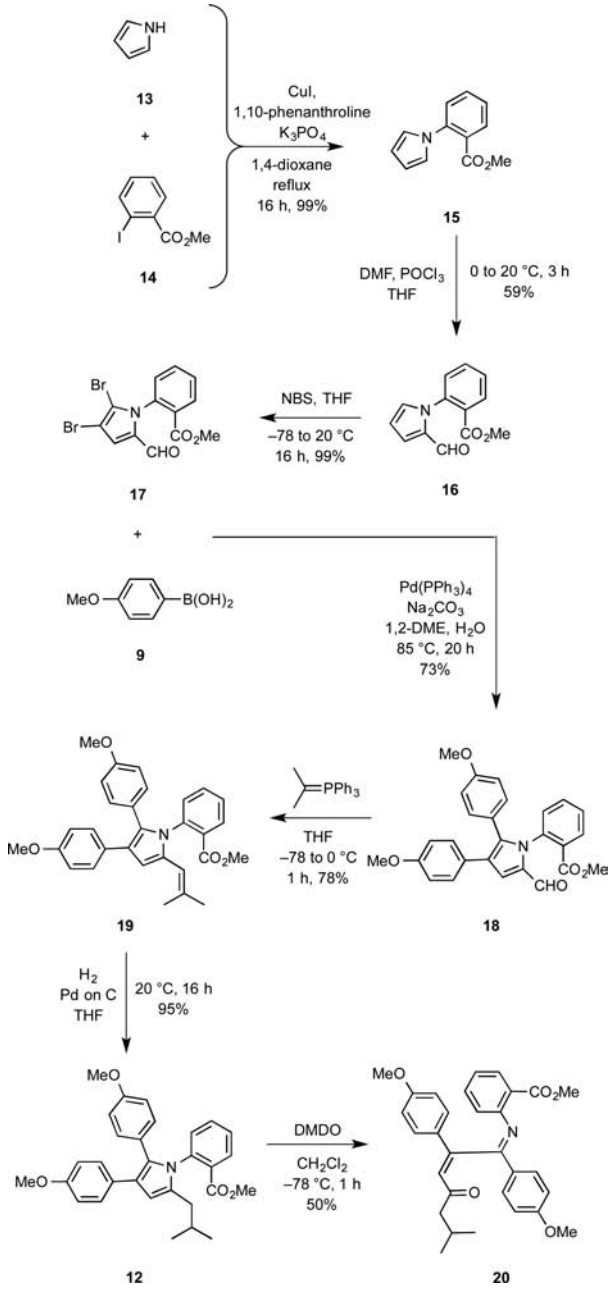
On the basis that the pyrrole ester **12** might undergo an oxidative cyclization reaction of the type shown in Figure 2, it was treated with a freshly prepared solution of dimethyldioxirane (DMDO) in acetone at −78 °C. A rather complex mixture of products was formed and, after chromatography, the oxidatively ring-cleaved product **20** was obtained in 50% yield. The structure of this rather unstable compound was secured by single-crystal X-ray analysis (details provided in the SI). This conversion is believed to involve initial epoxidation of the $\Delta^{4,5}$-double bond within substrate **12** with the resulting oxirane then fragmenting, via successive C–O and C–N bond cleavages, to give the observed product.

Various studies have been conducted on the oxidation of the indole C2–C3 double bond using MoO_5-based systems, and the primary products so-generated have been trapped by a range of external nucleophiles such as methanol so as to generate, for example, 2-methoxyindolin-3-ones.[14] No analogous studies appear to have been carried out with pyrroles or with any systems incorporated internal nucleophiles. Since a carboxylic acid residue was required as an internal nucleophile in the present instance, the ester **12** was saponified (Scheme 3) using potassium hydroxide and, after workup with aqueous HCl, the corresponding carboxylic acid **21** was obtained in 99% yield.

Gratifyingly, when a solution of compound **21** in dichloromethane/methanol was treated, at 20 °C for 16 h, with freshly

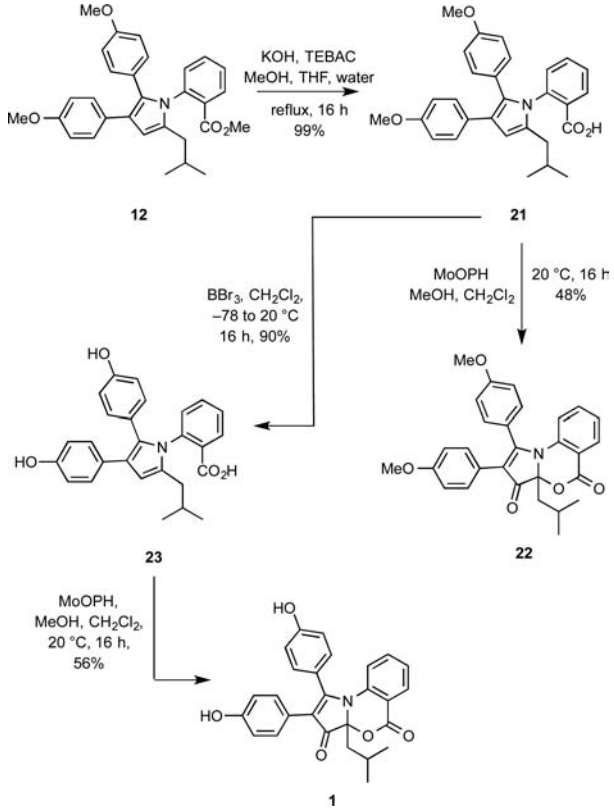
DOI: 10.1021/acs.orglett.5b03672
Org. Lett. 2016, 18, 704–707

Scheme 2. Synthesis of the 1,2,3,5-Tetrasubstituted Pyrrole 12 and an Attempt To Effect Its Oxidative Cyclization



prepared oxoperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH),[15] the desired 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione **22** was obtained in 48% yield after chromatographic purification. All of the spectroscopic data acquired on this oxidative cyclization product (see the SI for details) were in complete accord with the assigned structure. Most particularly, the ^{13}C NMR spectrum displayed the expected 25 resonances, including ones at δ_C 194.3 and 168.6 that are assigned to the ketone and lactone carbonyl carbons, respectively. Furthermore, the infrared spectrum of compound **22** displayed carbonyl stretching bands at 1740 and 1700 cm^{-1}, while the electrospray ionization mass spectrum revealed molecular associated ions at *m*/*z* 470 [(M + H)$^+$] and 492 [(M + Na)$^+$].

Scheme 3. Successful Oxidative Cyclization Reactions Leading to Discoipyrrole A (1) and Its Bis-*O*-methyl Ether 22



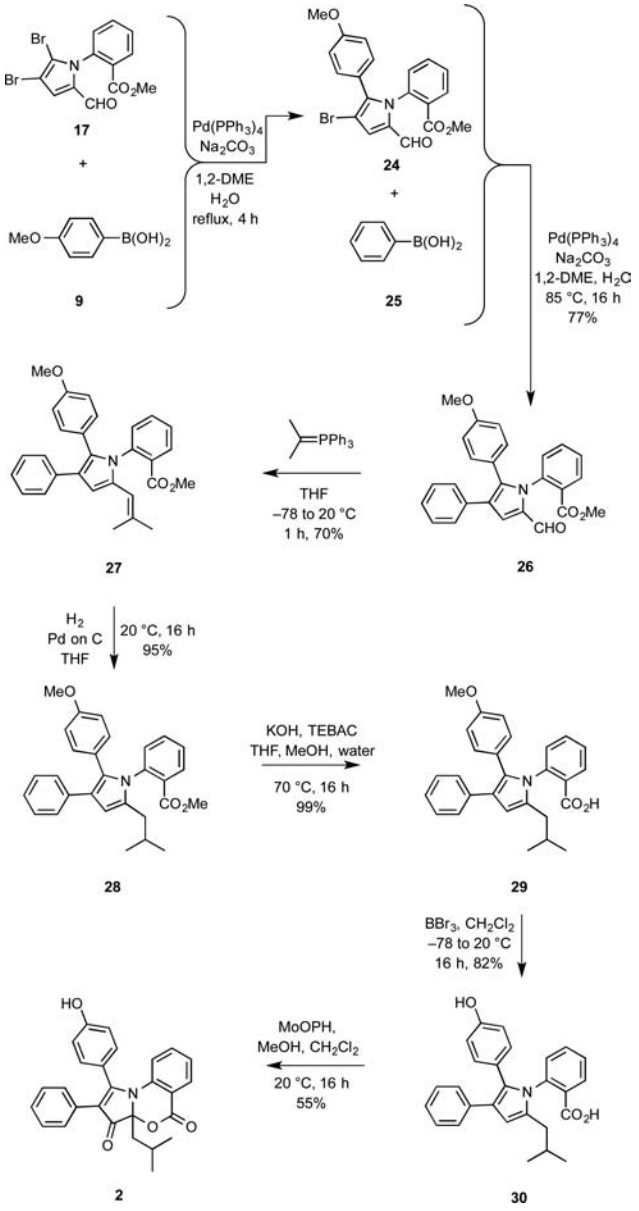
A second substrate, bis-phenol **23**, used to examine the scope of the oxidative cyclization process was obtained in 90% yield through the boron tribromide-mediated demethylation of compound **21**. On treatment with MoOPH in dichloromethane, compound **23** was converted into discoipyrrole (**1**)[1] (56%), the derived spectral data for which proved an excellent match with those reported for the natural product (see the SI for the ^{1}H and ^{13}C NMR spectral data sets).

The utility of the modular syntheses of 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-diones reported here is enhanced by the observation that regioselective Suzuki−Miyaura arylation reactions of the dibromopyrrole **17** are possible (Scheme 4).[8a,16] Thus, for example, when this compound was cross-coupled with 1.2 molar equiv of boronic acid **9**, the diarylated pyrrole **24** (not isolated) was obtained and immediately engaged in a second cross-coupling reaction with phenylboronic acid (**25**) to give the triarylated pyrrole **26** in 77% yield.

The acquisition of the differentially triarylated pyrrole **26** allowed for the completion of a total synthesis of discoipyrrole B (**2**) using the same protocols as described above for the assembly of congener A (**1**). Specifically then, compound **26** was converted into olefin **27** (70%) using the same ylide as employed previously and the double bond associated with the latter hydrogenated under conventional conditions to afford the isobutyl-substituted pyrrole **28** in 95% yield. Saponification of the last compound then gave, after acidic workup, benzoic acid **29** (99%), the structure of which was confirmed by single-crystal X-ray analysis. When treated with boron tribromide, aryl methyl ether **29** was cleaved to give the phenol **30** (82%) that upon reaction with MoOPH in dichloromethane afforded lactone **2** in 55% yield. The structure of compound **2** was confirmed by single-crystal X-ray analysis. Furthermore, the derived NMR and

DOI: 10.1021/acs.orglett.5b03672
Org. Lett. 2016, 18, 704−707

Scheme 4. Regioselective Diarylation of Dibromopyrrole 17 and Completion of a Synthesis of Discoipyrrole B (2)



IR spectral data were in excellent agreement with those reported[1] for discoipyrrole B.

While the scope and limitations of the biomimetic route to the discoipyrroles developed by MacMillan[1] have yet to be delineated, the distinct mode of assembly of the natural product framework reported here almost certainly means that the two pathways are likely to be quite complementary in nature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03672.

Experimental procedures, spectroscopic and analytical data, NMR spectra of compounds **1**, **2**, **8**, **10**–**12**, **15**–**19**, **21**–**23**, and **26**–**30** together with X-ray data for compounds **2**, **20**, **21**, and **29** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. Y.Z. gratefully acknowledges the China Scholarship Council for support.

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DOI: 10.1021/acs.orglett.5b03672
Org. Lett. 2016, 18, 704–707