Organic LETTERS

Letter

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Total Synthesis of (±)-Distomadines A and B

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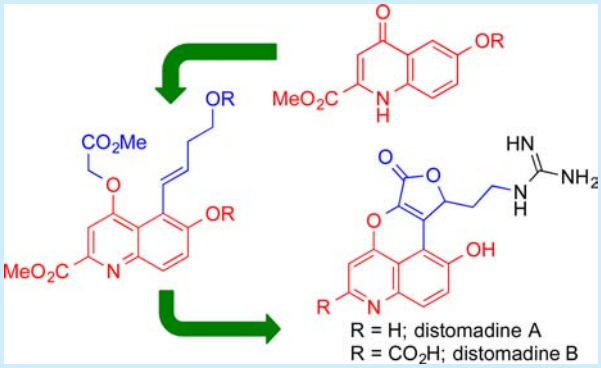
Supporting Information

ABSTRACT: The total synthesis of distomadines A and B, two structurally unique tetracyclic quinolines, is described. The route features a three-step process to access the pyranoquinoline butenolide rings via a Suzuki cross coupling of a 5-bromo-4-methoxycarbonylmethoxyquinoline with a vinyl boronate, followed by an α-ketohydroxylation and double cyclization by intramolecular aldol condensation and lactonization. Subsequent manipulation of the side chain to introduce the guanidine fragment completed the synthesis of distomadine B, whereas the distomadine A congener resulted from decarboxylation of a late-stage intermediate.



As part of our ongoing studies into the synthesis of structurally unique heterocyclic natural products,[1−3] we developed an interest in the distomadines, isolated from the New Zealand ascidian *Pseudodistoma aureum* by Copp and co-workers.[4] Although distomadine B was isolated in a 1:1 admixture with 2′-deoxyadenosine, the structure of the A congener was fully elucidated by NMR spectroscopy, although the absolute stereochemistry remained unknown. These unusual structures possess a unique tetracyclic core that comprises a pyrano[2,3,4-*de*]quinoline fused to a butenolide (Figure 1), and only one compound has been reported which possesses a similar pyranoquinoline core, a synthetic compound related to the aaptamine alkaloids.[5] The 2-quinolinecarboxylic acid present in distomadine B is also quite uncommon in marine natural products,[6−8] although the first example, 3,4-dihydroxyquinoline-2-carboxylic acid, was isolated from *Aplysina aerophoba* in the early 1970s.[9] Kynurenic and xanthurenic acid are two of the best known examples of 2-quinolinecarboxylic acid natural products (Figure 1), although distomadine B is the most complex isolated to date. We now report the first syntheses of these unusual heterocyclic natural products.

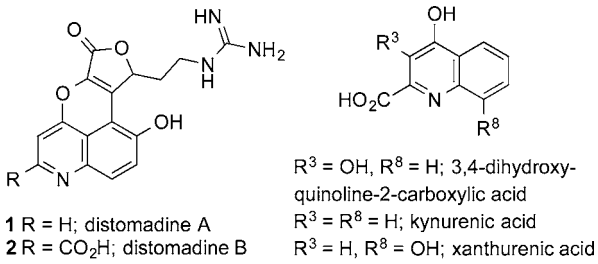
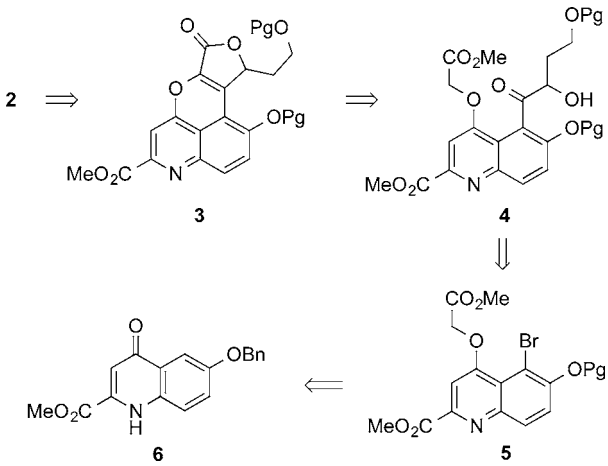


Figure 1. Structures of distomadines A and B and kynurenic and xanthurenic acids.

We initially focused on synthesizing distomadine B (**2**), anticipating that distomadine A could be accessed by a late-stage decarboxylation. We also planned to introduce the guanidine during the final stages from a protected alcohol **3**. The butenolide could be formed by a one-step aldol-condensation−lactonization from the corresponding α-ketol **4**, which could be accessed by oxidation of an alkene, available via a Suzuki− Miyaura cross-coupling between the 5-bromoquinoline **5** and the corresponding alkenylboronic ester as outlined in Scheme 1.

The synthesis began with the known 6-benzyloxy-4-quinolone **6**, previously prepared via a modified Conrad−

Scheme 1. Retrosynthesis Analysis of Distomadine B (Pg = Protecting Group)



Received: December 12, 2013
Published: February 8, 2014

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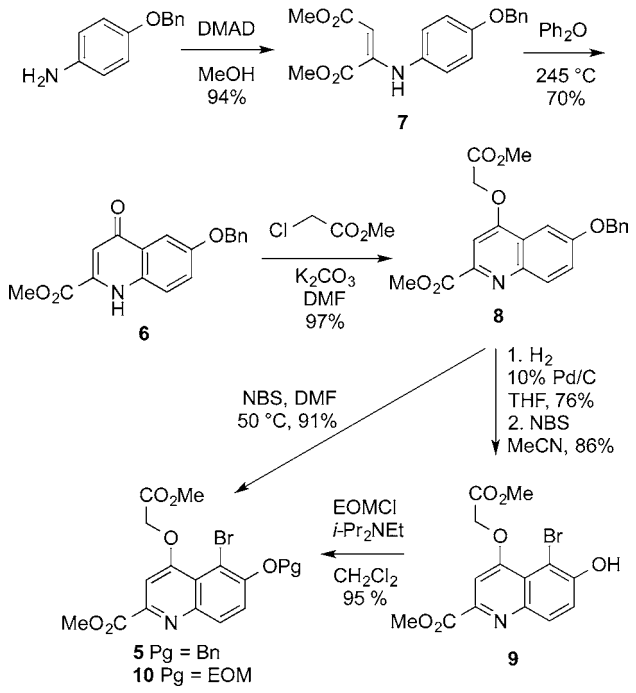
Limpach reaction[10] from the commercially available 4-benzyloxyaniline hydrochloride. Thus, aza-Michael addition to dimethyl acetylenedicarboxylate (DMAD), followed by heating in diphenyl ether at 245 °C, afforded the 4-quinolone **6** in 70% yield. Alkylation with methyl chloroacetate followed by bromination with NBS in DMF gave the desired 5-bromoquinoline **5** in excellent yield (Scheme 2).

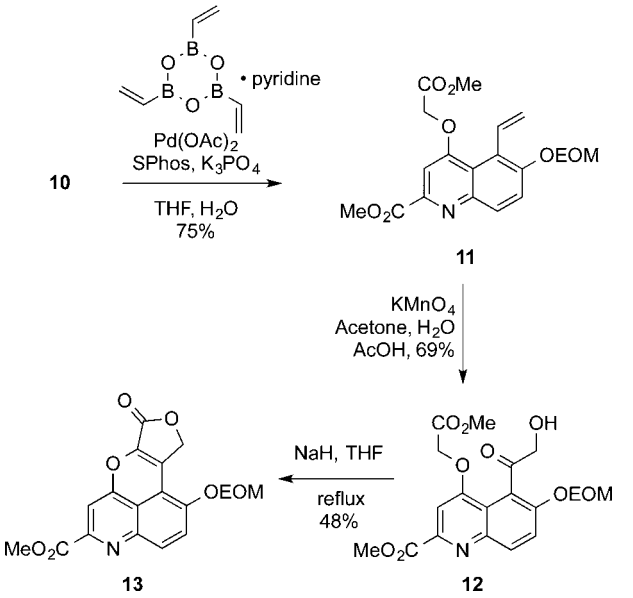
Scheme 2. Synthesis of 5-Bromoquinolines 5 and 10



It was thought that 5-bromoquinoline **5** would then participate in Suzuki–Miyaura cross-coupling, but this gave poor results, possibly due to steric hindrance by the benzyloxy protecting group in addition to the *peri*-substituent at C-4. As a result, it was envisioned that deprotection, followed by installation of a smaller protecting group, could improve the yield of the cross-coupling. Deprotection of the benzyl ether **8** followed by bromination with NBS in acetonitrile afforded **9**, which was protected as the ethoxymethyl ether **10**. The Suzuki–Miyaura cross-coupling was initially attempted using trivinylboroxine as a model for the requisite terminal alkene (Scheme 3). Thus, reaction of **10** and vinyl boroxine pyridine complex using $Pd(OAc)_2$ and SPhos[11] gave coupled product **11** in 75% yield. Oxidation of the alkene with $KMnO_4$ in acetone, water, and acetic acid[12] allowed access to the α-ketol **12** in good yield, allowing us to attempt a model butenolide formation. Previous syntheses of butenolides have been reported by condensation between dimethyl malonate and α-hydroxy ketones with sodium hydride or sodium methoxide.[13,14] The cyclization of model α-ketol **12** with sodium hydride afforded the desired butenolide **13** in 48% yield, X-ray crystallographic analysis of which confirmed the tetracyclic structure (Figure 2).

In proceeding with our synthesis toward distomadine B, it was first necessary to synthesize a suitable boronic ester to be used as a coupling partner in the Suzuki–Miyaura reaction. Due to the harsh conditions of the formation of the butenolide, a benzyloxymethyl (BOM)-protected alcohol was selected for the side chain. But-3-yn-1-ol was protected with BOMCl and

Scheme 3. Synthesis of the Model Tetracyclic Core of Distomadine B



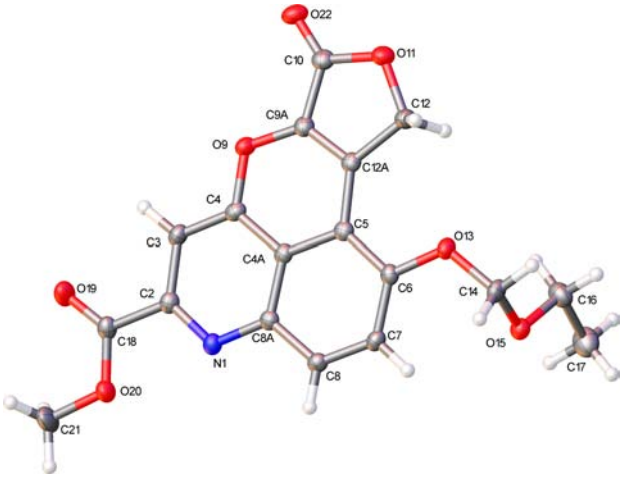


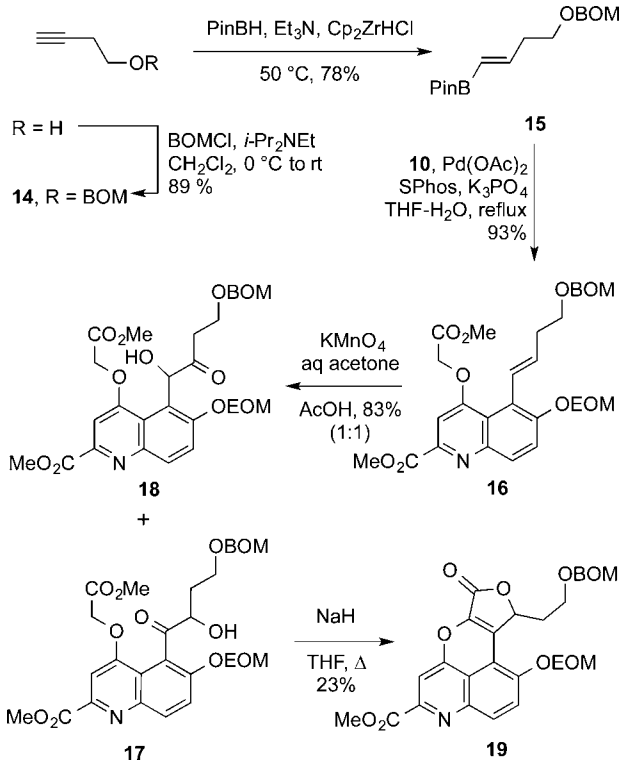
Figure 2. X-ray crystal structure of tetracyclic pyrano[2,3,4-*de*]-quinoline **13**.

Hunig's base to afford **14**. The hydroboration of the alkyne was performed by following the reported modification of Srebnik's conditions[15,16] for the Schwartz's reagent catalyzed hydroboration, affording the boronic ester **15** in 78% yield. Suzuki–Miyaura cross-coupling between bromoquinoline **10** and boronic ester **15** with $Pd(OAc)_2$ and SPhos gave **16** in excellent yield. However, the previously employed oxidation with $KMnO_4$ resulted in a mixture (ca. 1:1) of the α-hydroxy ketones **17** and **18**. Attempts to selectively synthesize the desired regioisomer **17** by either selective oxidation of the corresponding diol or by a Rubottom oxidation of an enol ether were unsuccessful. However, treatment of the mixture of α-ketols **17** and **18** with sodium hydride resulted in the tetracyclic core **19** in a moderate 23% yield (Scheme 4).[17]

With access to the tetracyclic core, the synthesis could be completed by introduction of the guanidine and removal of the protecting groups. Deprotection of the BOM group in tetracycle **19** by transfer hydrogenation using formic acid and palladium black gave the deprotected alcohol that could be

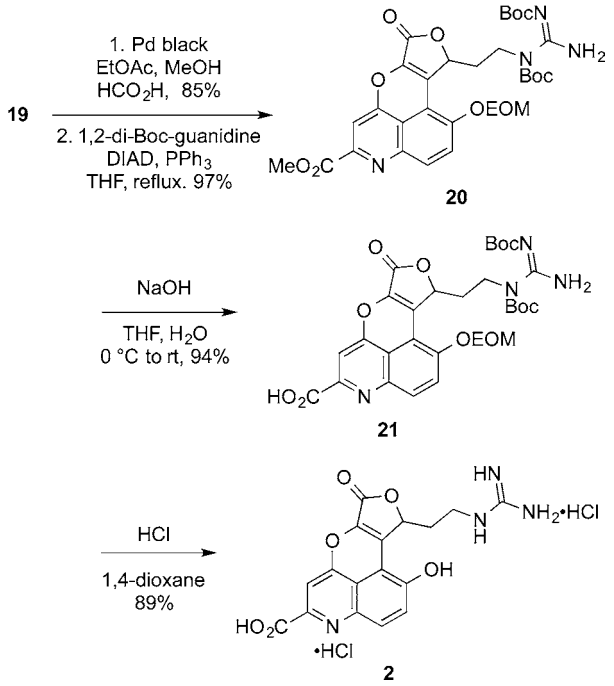
dx.doi.org/10.1021/ol403598k | *Org. Lett.* 2014, 16, 1064–1067

Scheme 4. Synthesis of γ-Butenolide 19 Core of Distomadine B (PinB = 4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)



coupled with 1,2-di-Boc-protected guanidine under Mitsunobu conditions[18] to afford **20** in nearly quantitative yield. Hydrolysis of the ester with NaOH provided the acid **21**, X-ray crystallography confirming the structure (Figure 3). Finally, treatment of the acid **21** with HCl in dioxane gave the dihydrochloride salt of distomadine B in 89% yield (Scheme 5). Although natural distomadine B was only reported as a mixture with 2′-deoxyadenosine, we were able to compare the NMR spectroscopic data with our synthetic sample. Thus, treatment

Scheme 5. Completion of Synthesis of Distomadine B (2)



of the dihydrochloride salt with concentrated ammonia in methanol gave the monohydrochloride salt; ^{1}H NMR in CD_3OD with a drop of concentrated ammonia matched the reported data for the natural product.

In order to complete the synthesis of distomadine A, the late-stage intermediate **19** was first hydrolyzed to give the acid which then underwent decarboxylation on heating in diphenyl ether at 190 °C to give quinoline **22** in 77% yield over two steps. The structure of the decarboxylated tetracycle **22** was confirmed by X-ray crystallography (Figure 4). Transfer hydrogenation with palladium black and formic acid gave the alcohol **23** that was coupled to 1,2-di-Boc-protected guanidine

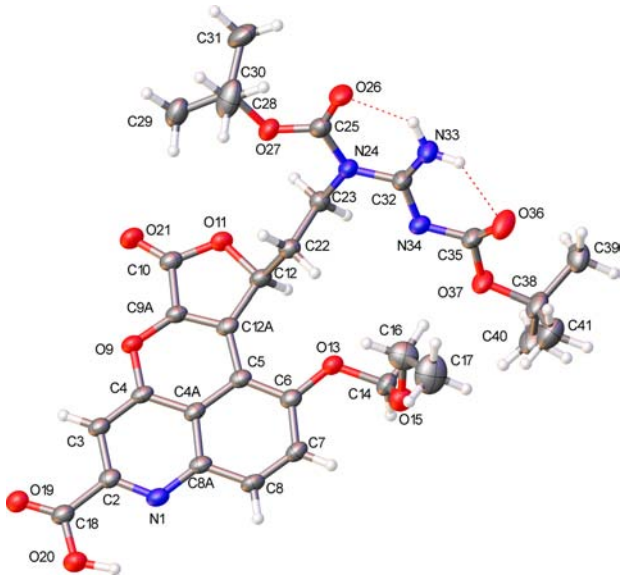


Figure 3. X-ray structure of **21**.

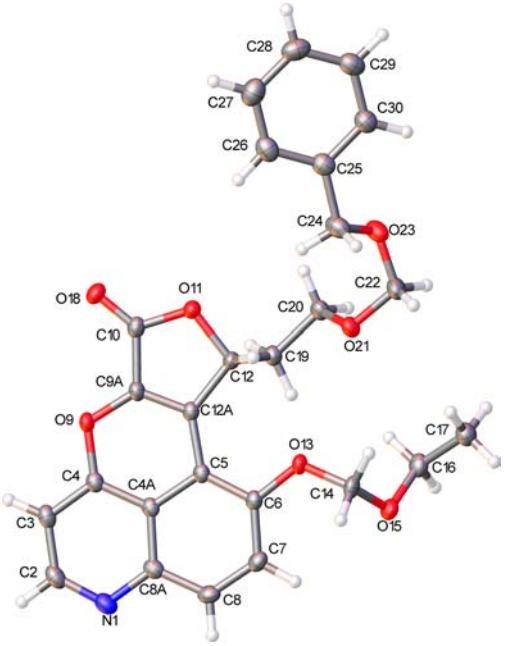
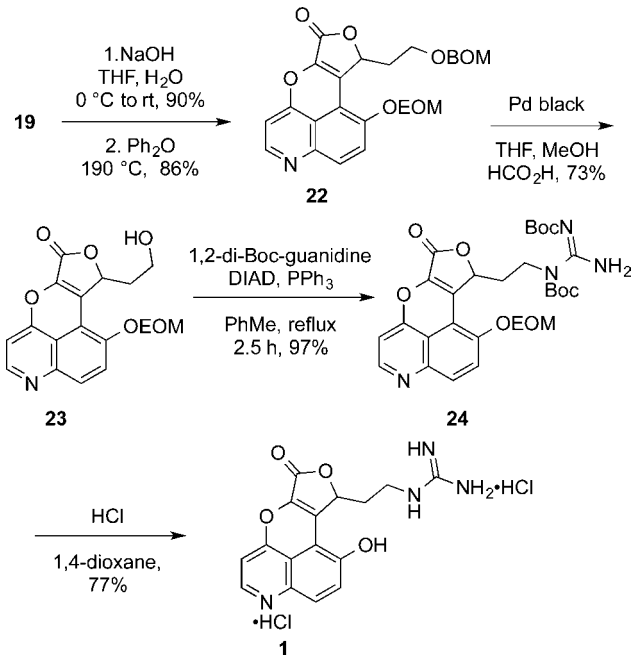


Figure 4. X-ray crystal structure of decarboxylated tetracycle **22**.

dx.doi.org/10.1021/ol403598k | Org. Lett. 2014, 16, 1064−1067

to give **24** in nearly quantitative yield. Finally, **24** was treated with HCl in dioxane to give the dihydrochloride salt of distomadine A (**1**) in 77% yield (Scheme 6). Treatment with

Scheme 6. Completion of the Synthesis of Distomadine A (1)



concentrated ammonia gave material whose ^{1}H and ^{13}C NMR spectra in CD_3OD were identical with a sample of the authentic natural product, although the ^{13}C NMR data appeared to be concentration dependent.[19]

In summary, we have achieved the first total syntheses of distomadines A and B in 14 steps (3.5% yield) and 13 steps (5.6% yield), respectively, with key intermediate structures being confirmed by X-ray crystallography. The pivotal steps of the syntheses are the construction of the butenolide by Suzuki cross-coupling, oxidation of the resulting alkene, and the intramolecular aldol lactonization sequence. The syntheses confirm the unusual tetracyclic pyranoquinoline structure of the natural products.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures, copies of ^{1}H and 1^{3}C NMR spectra, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Nottingham for funding and Drs Brent Copp and Norrie Pearce (University of Auckland) for copies of NMR spectra of the distomadines and a sample of natural distomadine A.

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