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Concise, stereocontrolled and modular syntheses of the anti-influenza rubrolides R and S

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Abstract – The fungal metabolites rubrolide R and S were synthesized in concise, entirely stereoselective fashion through the combined use of bromine-stereodirected vinylogous aldol condensation (SVAC) and Suzuki cross-coupling. A bioinspired, high-yield conversion of rubrolide R to rubrolide S is also reported.

Introduction

Influenza, or flu, is a highly contagious viral infection causing recurrent epidemics that bring about an enormous burden to the economy along with significant morbidity and mortality, particularly in young children and the elderly [1]. According to the World Health Organization (WHO), annual epidemics result in 3-5 million cases of severe illness, millions of hospitalizations and up to 650,000 deaths worldwide [2]. Because vaccination provides only modest protection against seasonal influenza (typically 10-60%) and no protection against novel strains [3], small molecule therapeutics are vital to control the spread of the disease [4]. However, like antibiotics, antiviral drugs are loosing their efficacy due to the emergence of resistant viral strains [5]. Consequently, there is a pressing need for new anti-influenza agents, especially those with modes of action that circumvent existing resistance mechanisms [6,7].

The diverse biological properties and distinctive β–aryl–γ–benzylidenebutenolide framework associated with the rubrolide family of natural products have attracted considerable attention since the 1990s [8-10], when the first such compounds were isolated from the marine ascidian *Ritterella rubra* [8a]. While the vast majority of the members of this family come from ascidia [8], a pair of prenylated analogues, named rubrolide R and S (**1**-**2**, Figure 1), have recently been isolated from marine and terrestrial-derived *Aspergillus* fungi [11a,b].

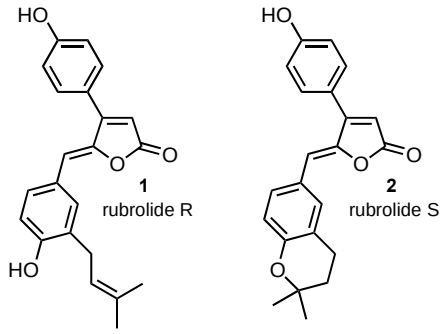
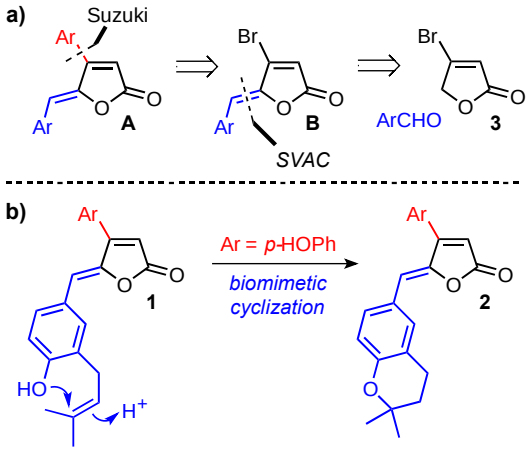


Figure 1. Structure of rubrolides R and S.

Besides possessing an unprecedented carbon skeleton, **1** and **2** display significant antiviral activities, being superior to the nucleoside drug ribavirin against seasonal and pandemic influenza A viruses (cf. H3N2 and pH1N1) [11a,12b]. One of these molecules, rubrolide S (**2**), was also shown to be a potent uncompetitive inhibitor of α–glucosidase (K_i = 1.42 μM) [11c]. Inhibitors of this enzyme are believed to exert their anti-influenza effects by targeting the host glycosylation machinery. This indirect mechanism of action not only allows broad-spectrum antiviral activity, but also provides protection against the development of drug resistance [7].

To date, two syntheses of rubrolide R and S have been reported, one by Jun and the other by Schützenmeister. That of Jun begins from 4-methoxyacetophenone and requires a deprotection-reprotection-deprotection cycle to reach rubrolides in 6 steps [12a]. Schützenmeister's route is shorter and protecting group-free (3-steps from tetronic acid) but leads to mixtures of *Z*/*E*-isomers, requiring sequential purification by silica gel and reversed-phase C18 chromatography to obtain *Z*-rubrolides [12b]. Furthermore, direct comparison of the anti-influenza activities of the *Z*/*E*-mixtures with those of isomerically pure **1** and **2** revealed that the *Z*-stereochemistry is crucial for high potency against both H3N2 and pH1N1 viruses [12b].

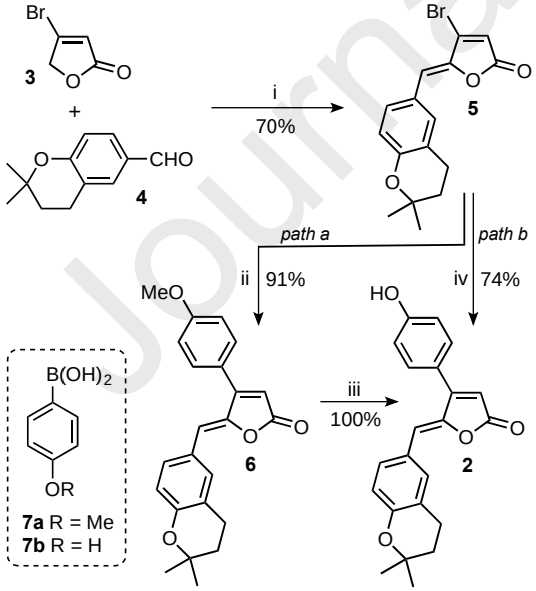
Herein, we report a strategically distinct approach to rubrolides and their analogues (cf. **A**, Scheme 1a) that is concise and entirely stereoselective. A key objective in our approach was to introduce the β–aryl substituent late in the synthesis, so as to facilitate future SAR studies on the importance of this substituent. Retrosynthetically, we envisioned generating **A** through Suzuki arylation of (*Z*)–γ–benzylidene–β–bromobutenolides **B** which would in turn arise from β–bromobutenolide **3** by utilizing our laboratory's previously described bromine-stereodirected vinylogous aldol condensation (SVAC) methodology [13,14]. Crucially, bromine was to serve a dual role in the synthesis, first as a stereocontrol element enabling the benzylidene appendage to be installed with the desired *Z*-configuration, and second, as a leaving group in the ensuing coupling event. We now describe the successful execution of this plan (cf. Scheme 1a) and further demonstrate the hitherto unrealized, bioinspired [15] cationic cyclization of rubrolide R to rubrolide S (**1** → **2**, Scheme 1b).



Scheme 1. Our synthesis plan.

Results and discussion

The development of a rapid route to rubrolide S (**2**) began from commercially available or inexpensively prepared β–bromobutenolide **3** [16] and 2,2-dimethylchromane-6-carbaldehyde **4** [17] (Scheme 2). Assemblage of the pivotal (*Z*)–γ–benzylidenebutenolide **5** was best accomplished by application of our one-pot vinylogous aldol condensation procedure [13]. Thus, sequential treatment of **3** with TBSOTf, Hünig's base and aldehyde **4**, followed by *in situ* β–elimination of the aldol adduct(s) with DBU, afforded **5** as a single stereoisomer in 70% yield after flash column chromatography. In contrast, subjection of **3** and **4** to classical Knoevenagel conditions, e.g. piperidine or sodium carbonate in MeOH at 25-50 ºC, which had previously worked well with some carbon-substituted butenolides and benzaldehydes [12a,18], led to complex mixtures containing only traces of **5** (<10%). Clearly, the serviceability of conventional procedures depends to a considerable degree upon the structure of the reactants [19].



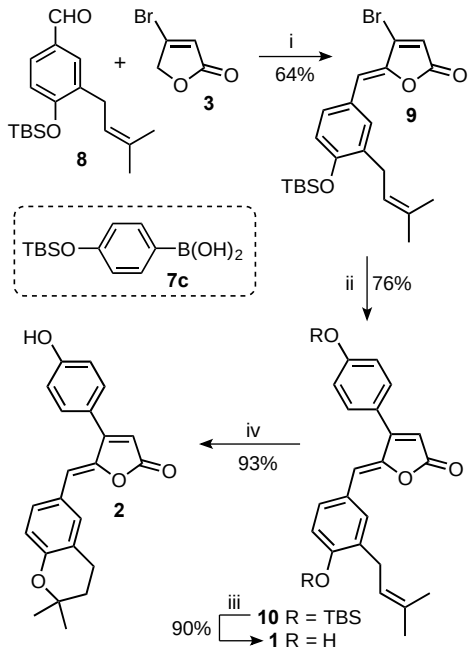
Scheme 2. Reagents and conditions: (i) **3**, TBSOTf, *i*-Pr_2NEt, DCM, 0 ºC, 30 min, then **4**, -78 ºC, 1 h, then DBU, -78 ºC to rt, 3 h, 70%; (ii) *method A*: **7a**, $PdCl_2(PPh_3)_2$, CsF, Et_3NBnCl, $PhMe/H_2O$, rt, 36 h, 91%, *method B*: **7a**, $PdCl_2(MeCN)_2$, Ag_2O,

$AsPh_3$, THF, reflux, 36 h, 85%; (iii) BBr_3, DCM, 0 ºC to rt, 2 h, 100%; (iv) As in (ii)-*method A* but using **7b**, 110 ºC, 36 h, 74%.

With reliable access to **5**, attention turned to its Suzuki coupling with 4-methoxyphenylboronic acid **7a** (Scheme 2, *path a*). Being mindful of the susceptibility of γ–□□kylidenebutenolides to alkaline hydrolysis [20], our exploration of the Suzuki reaction focused on protocols employing mild, essentially nonbasic conditions. Among those tried, the best consisted in the use of $PdCl_2(PPh_3)_2$/CsF/phase-transfer technology at room temperature (cf. method A) [21], or $PdCl_2(MeCN)_2/Ag_2O/AsPh_3$ in THF under reflux (method B) [10a,22], affording the cross-coupled product **6** in yields of 91 and 85%, respectively. Demethylation of **6** with boron tribromide, followed by standard aq. $NaHCO_3$ work-up, delivered isomerically pure rubrolide S **2** quantitatively without recourse to chromatography.

We also explored the possibility of cutting-off a step in the synthesis of **2** by replacing **7a** with 4-hydroxyphenylboronic acid **7b** (Scheme 2, *path b*). Initial attempts to couple **7b** with **5** using the optimal conditions identified in path a (cf. method A, room temperature) failed to deliver **2**. This negative result was not wholly unexpected considering the low reactivity of **7b** compared to that of **7a** [9i,23]. Whereas the desired coupling was ultimately achieved under harsher conditions, product yields were not as high as those obtained with **7a**. Indeed, the yield of **2** was maximized at 74% (method A, 110 ºC, 36 h), making the 2-step route somewhat less efficient overall than its 3-step variant (52% vs 64%).

With a practical synthesis of rubrolide S achieved, attention turned to establishing a unified route to both rubrolides R and S (Scheme 3). Subjection of the easily prepared aldehyde **8** [24] to our SVAC protocol afforded *Z*-configured γ–benzylidenebutenolide **9** in 64% yield after flash chromatography. Suzuki arylation of **9** with commercially available 4-(*tert*-butyldimethylsilyloxy) phenylboronic acid **7c** [25] was best performed using $PdCl_2(MeCN)_2/Ag_2O/AsPh_3$ (cf. method B) to furnish cross-coupled product **10** (76%), whose desilylation uneventfully delivered rubrolide R **1** in 90% isolated yield. Happily, rubrolide R, as well as intermediates **9** and **10**, were obtained as single stereoisomers, suggesting that no *Z* to *E* isomerization occurred during the synthesis or flash chromatography on silica gel [9i,26].



Scheme 3. Reagents and conditions: (i) **3**, TBSOTf, *i*-Pr_2NEt, DCM, 0 ºC, 30 min, then **8**, -78 ºC, 1 h, then DBU, -78 ºC to rt, 3 h, 64%; (ii) **7c**, $PdCl_2(MeCN)_2$, Ag_2O, $AsPh_3$, THF, reflux, 36 h, 76%; (iii) TBAF, THF, 0 ºC, 15 min, 90%; (iv) TfOH (0.8 equiv), THF, rt, 12 h, 93%.

At this point, all that remained was to trigger cationic cyclization of the *ortho*-prenylphenol in **1** to generate rubrolide S **2** (cf. Scheme 1b). After screening several acids at different temperatures, including the commonly employed HCl [15], TsOH [24a], and $BF_3{\cdot}OEt_2$ [27], and the superacid TfOH, we were pleased to find that the latter was uniquely effective in promoting cyclization at ambient temperature, cleanly providing rubrolide S **2** in an excellent 93% isolated yield (Scheme 3).

Conclusion

In conclusion, we have developed practical, entirely stereoselective syntheses of the antiviral natural products rubrolide R and S from commercially available β–bromobutenolide and easily prepared benzaldehydes. The foregoing work demonstrates (i) the serviceability of a new strategy for constructing *Z*–□□□□□□□□□□ β–aryl–γ–benzylidenebutenolides combining bromine-stereodirected vinylogous aldol condensation with Suzuki cross-coupling (cf. Scheme 1a), and (ii) the previously unrealized biomimetic transformation or rubrolide R to rubrolide S. Furthermore, because the β–aryl substituent is introduced at a late stage, the present approach should facilitate SAR studies on the importance of this substituent.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

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Highlights:

- Bromine-stereodirected vinylogous aldol condensation led uniquely to *Z*-configured γ–benzylidenebutenolides.
- The β–aryl substituent is introduced late in the synthesis.
- Triflic acid enables highly efficient biomimetic conversion of rubrolide R to rubrolide S.

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