Iridium-Catalysed C–H Borylation Facilitates a Total Synthesis of the HRV 3C Protease Inhibitor (±)-Thysanone

Katrin Schünemann,[a,b] Daniel P. Furkert,[a] Stephen Connelly,[c] John D. Fraser,[b] Jonathan Sperry,[a] Margaret A. Brimble*[a]

[a] School of Chemical Sciences, The University of Auckland, 23 Symonds St., Auckland 1142, New Zealand
Fax +64(9)3737422; E-mail: m.brimble@auckland.ac.nz

[b] Department of Molecular Medicine and Pathology, The University of Auckland, 85 Park Road, Auckland 1142, New Zealand

[c] Department of Molecular Biology, The Scripps Research Institute, BCC 265, 10550 Torrey Pines Road, La Jolla, CA 92037, USA

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Abstract: A new total synthesis of the HRV 3C protease inhibitor (±)-thysanone is described. The synthetic route hinges on an iridium-catalysed borylation to install the resorcinol-derived component of the natural product.

Key words: thysanone, oxa-Pictet–Spengler reaction, pyranonaphthoquinone, HRV 3C protease, CH activation

Human rhinoviruses (HRV) are the main cause of the common cold worldwide and currently only symptomatic treatment is available. Infection occurs in the upper respiratory tract, preferably by targeting the nasal epithelial cells.[1] Upon uncoating of the virion and replication of the viral RNA, translation of the genome of the HRV is not initiated by a (5′)G-cap as usual, but rather is initiated by one single internal ribosome entry site (IRES) and thus one single polyprotein precursor is produced. To produce active viral proteins and enzymes, the polyprotein is processed mainly by one virally encoded protease, designated as 3C.[2] Therefore, HRV 3C protease is an attractive target for potential treatment of the common cold.

During a screening process aimed at identifying potential chemotherapeutic agents to treat the common cold, Singh and coworkers isolated the pyranonaphthoquinone (–)-thysanone (**1**, Figure 1) from the fungus *Thysanophora penicilloides*.[3] (–)-Thysanone was subsequently demonstrated to be an effective inhibitor of HRV 3C protease with an IC_{50} of 13 μg/mL (47 μM).[3]

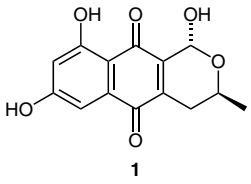

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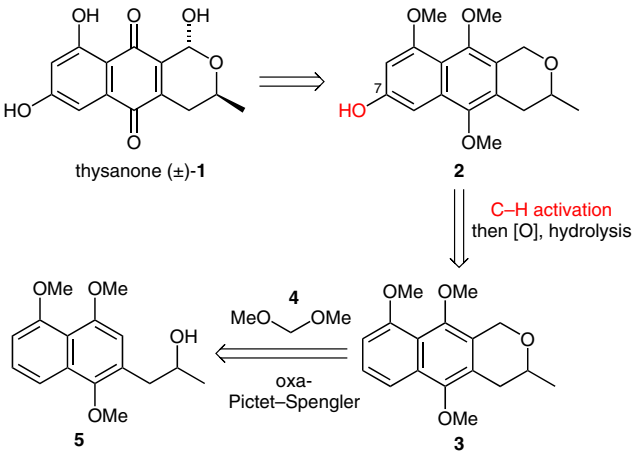
Figure 1 (–)-Thysanone (**1**)

Currently, two total syntheses of the natural product (–)-thysanone (**1**) have been published.[4] Gill and coworkers published the first total synthesis of (–)-thysanone (**1**) using a key Diels–Alder reaction,[4a,b] and we reported the total synthesis of (–)-thysanone using a Staunton–Weinreb annulation to forge the carbon framework of the natural product.[4c,d] Despite our successful synthesis, issues with scale up have prohibited the accumulation of sufficient quantities of the natural product required for extensive biological evaluation. Accordingly, we sought an alternative synthetic route to thysanone (**1**), the successful results of which are reported herein.

We have recently shown that the oxa-Pictet–Spengler reaction between homobenzylic alcohol **5** with dimethoxymethane **4** gives the naphthopyran **3** (Scheme 1).[5] With a stock of **3** to hand, we considered a C–H activation reaction to install the phenol at C7, thus providing the full oxygenation pattern present in thysanone (**1**). Based on our own work regarding the C–H activation chemistry of related naphthalenes,[6] we were confident that the regiochemical outcome required to complete the total synthesis of (±)-**1** would be observed.



Scheme 1 Retrosynthetic analysis of thysanone [(±)-**1**]

Our attention turned to installation of the C-7 phenol from the corresponding boronate using the proposed C–H activation process. Applying the methodology developed by Hartwig,[7] treatment of naphthopyran **3** with freshly prepared pinacolborane in the presence of catalytic amounts of $[Ir(cod)OMe]_2$ and dtbpy resulted in the boronate regio-

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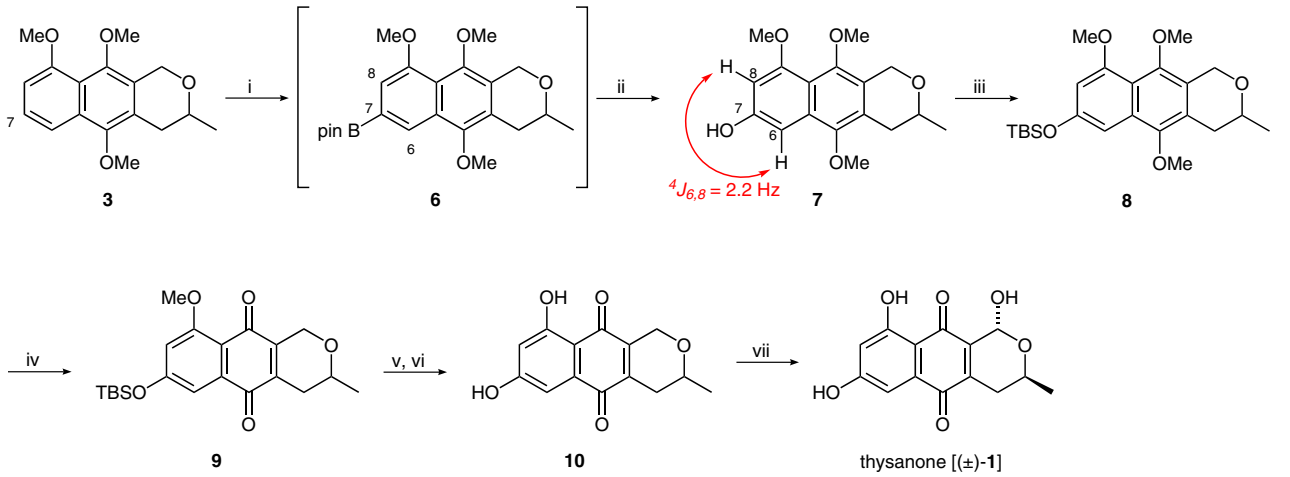

Scheme 2 *Reagents and conditions*: i) $[Ir(cod)OMe]_2$, BHpin, dtbpy, THF, 80 °C; ii) NMO, DCE, 100 °C, sealed tube, 30 min, 72% over two steps; iii) NaH, TBSCl, THF, 73%; iv) AgO, HNO_3, THF–H_2O, 75%; v) BCl_3, CH_2Cl_2, –78 °C to r.t., 80%; vi) TBAF, THF, quant.; vii) a) Br_2, $(BzO)_2$, CCl_4; b) H_2O–THF, 71%.

isomer **6**, as suggested by NMR analysis of the crude reaction mixture (Scheme 2). Pleasingly, the desired regiochemical outcome was confirmed upon oxidation–hydrolysis of boronate **6** to naphthol **7** for which a $^4J_{6,8}$ coupling constant of 2.2 Hz in the ^{1}H NMR spectrum was observed, confirming the *meta* substitution pattern.[6]

With the resorcinol-derived component of the natural product successfully installed using a C–H activation process, we proceeded to complete the total synthesis of racemic thysanone [(±)-**1**]. Unfortunately, pyranonaphthol **7** did not undergo oxidative demethylation to the corresponding pyranonaphthoquinone. Pyranonaphthol **7** was therefore protected as its TBS ether to afford **8** which did undergo oxidative demethylation using freshly prepared silver(II) oxide, giving the pyranonaphthoquinone **9** in good yield. Attempting to effect one-pot deprotection of both the TBS and methyl ethers in **9** was not successful using boron trichloride, instead giving the TBS-protected pyranonaphthoquinone which could be subsequently treated with TBAF affording **10**. Finally, bromination–hydrolysis of **10** as previously described[4c,d] gave thysanone [(±)-**1**], the NMR data of which were identical to synthetic (–)-thysanone (**1**)[9] previously obtained by our research group.[4c,d]

In conclusion, we have achieved a distinct total synthesis of thysanone [(±)-**1**] that circumvents some of the issues encountered in our previous synthetic route.[4c,d] A novel C–H activation process was used to install the C-7 phenol and thus the resorcinol-derived component of the natural product.[8] Due to the widespread abundance of this 1,3-dihydroxybenzene motif in natural products, we envisage the methodology presented herein will find widespread application for the synthesis of related resorcinol derivatives.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) To a mixture of (±)-1-deoxythysanone (13 mg, 50 μmol) in CCl_4 (8 mL) was added bromine (50 μL, 1 M in CCl_4, 50 μmol). The mixture was heated at reflux under irradiation with a desk lamp for 30 min. The mixture was concentrated in vacuo, and THF (1 mL) and H_2O (0.5 mL) were added. The resulting mixture was stirred for 1 h at r.t. Then CH_2Cl_2 (5 mL) and H_2O (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL/mmol$_{SM}$). The combined organic extracts were washed with brine (5 mL) and dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative TLC (SiO_2, toluene–ethyl formate–formic acid = 50:49:1) to afford the title compound (6.09 mg, 22 μmol, 44%) as a yellow solid. ^{1}H NMR (400 MHz, acetone-d_6): δ = 12.26 (1 H, s, OH), 9.93 (1 H, s, OH), 7.08 (1 H, d, *J* = 2.4 Hz, H-6), 6.62 (1 H,

d, J = 2.4 Hz, H-8), 5.91 (1 H, dd, J = 18.2, 5.8 Hz, H-1), 4.39–4.29 (1 H, m, H-3), 2.70 (1 H, dd, J = 19.2, 3.4 Hz, H-4A), 2.18–2.08 (1 H, m, H-4B), 1.31 (3 H, d, J = 6.3 Hz, H-Me), lactol OH not observed. R_f = 0.74 (hexanes–EtOAc, 1:2). The spectroscopic data were in agreement with those reported[4c] in the literature.

