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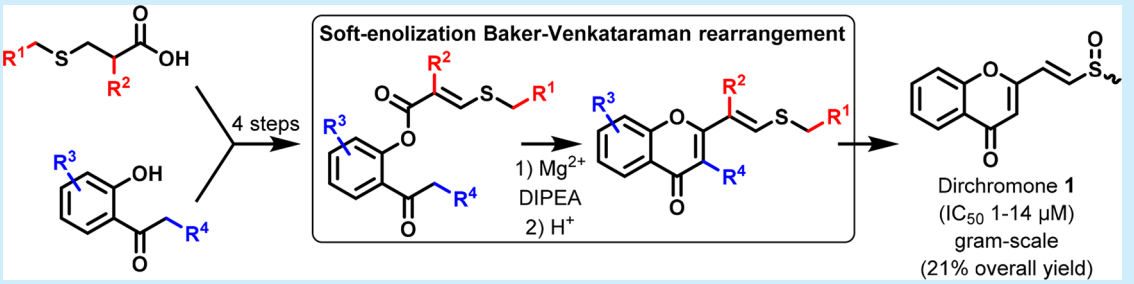
Soft-enolization Baker−Venkataraman Rearrangement Enabled Total Synthesis of Dirchromones and Related 2-Substituted Chromones

Alexis St-Gelais,[†] Jérôme Alsarraf,[†] Jean Legault,[†] Charles Gauthier,[†,‡] and André Pichette*[,†]

[†]Chaire de recherche sur les agents anticancéreux d'origine naturelle, Laboratoire d'analyse et de séparation des essences végétales (LASEVE), Département des Sciences Fondamentales, Université du Québec à Chicoutimi, 555, boulevard de l'Université, Chicoutimi, Québec, G7H 2B1, Canada

[‡]INRS-Institut Armand-Frappier, Université du Québec, 531, boulevard des Prairies, Laval, Québec H7V 1B7, Canada

Supporting Information



ABSTRACT: A seven-step total synthesis of the original scaffold of cytotoxic dirchromones involving an unprecedented soft-enolization Baker−Venkataraman rearrangement was designed. The methodology enabled access to naturally occurring dirchromone **1** (21% overall yield) at gram-scale, which was screened for cytotoxicity against 13 cancer cell lines. The scope of the soft-enolization Baker−Venkataraman rearrangement encompasses diversely substituted dirchromones, including flavonoids, 2-styrylchromones, and 2-phenylethylchromones.

Dirchromones are a series of sulfur-containing compounds that were isolated from *Dirca palustris* L. bark and wood.[1] Some of these compounds exhibited a moderately selective cytotoxicity against human colorectal adenocarcinoma (DLD-1) cells, with dirchromone **1** (Figure 1) being the most active (IC_{50} 1.0 μM). However, only a limited number of derivatives were characterized, and they were isolated in minute quantities. For instance, 12.5 kg of dried wood and bark of *D. palustris* was required to obtain 36 mg of dirchromone **1**, which was isolated after an extensive purification process. A synthetic route toward dirchromone **1** and analogues is thus needed for any further studies to be conducted on the mechanism of action and/or structure−activity relationships (SARs) of this peculiar class of compounds. Dirchromones are structurally similar to two other groups of biologically active molecules. The group of 2-styrylchromones **2** is uncommonly found in nature, but within a large diversity of organisms, and has been the focus of several synthetic efforts, with a variety of reported biological activities such as cytotoxic, anti-inflammatory, and neuroprotective effects.[2] As for the second group, several of the large number of 2-phenylethylchromones **3** found in agarwood, the fungi-infected wood of several Thymelaeaceae,[3] were reported to exhibit interesting *in vitro* anti-inflammatory properties.[4,5]

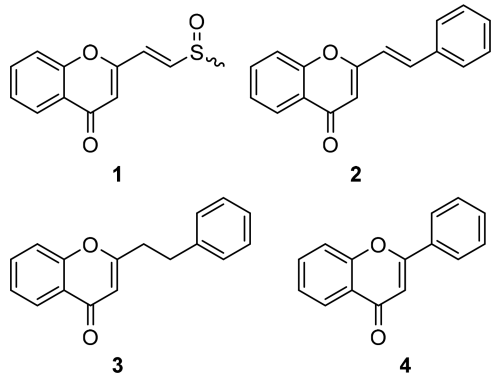


Figure 1. Parent structures of 2-substituted chromones: dirchromone **1**, 2-styrylchromone **2**, 2-phenylethylchromone **3**, and flavone **4**.

Among the reported synthetic approaches toward these biologically active 2-substituted chromones, including the ubiquitous flavone scaffold **4**, the Claisen condensation of activated cinnamates onto 2′-hydroxyacetophenone[6] is the most common route. More specifically, its intramolecular counterpart, i.e., the Baker−Venkataraman (B−V) rearrangement of cinnamoyl ester of 2′-hydroxyacetophenone,[2,7] is

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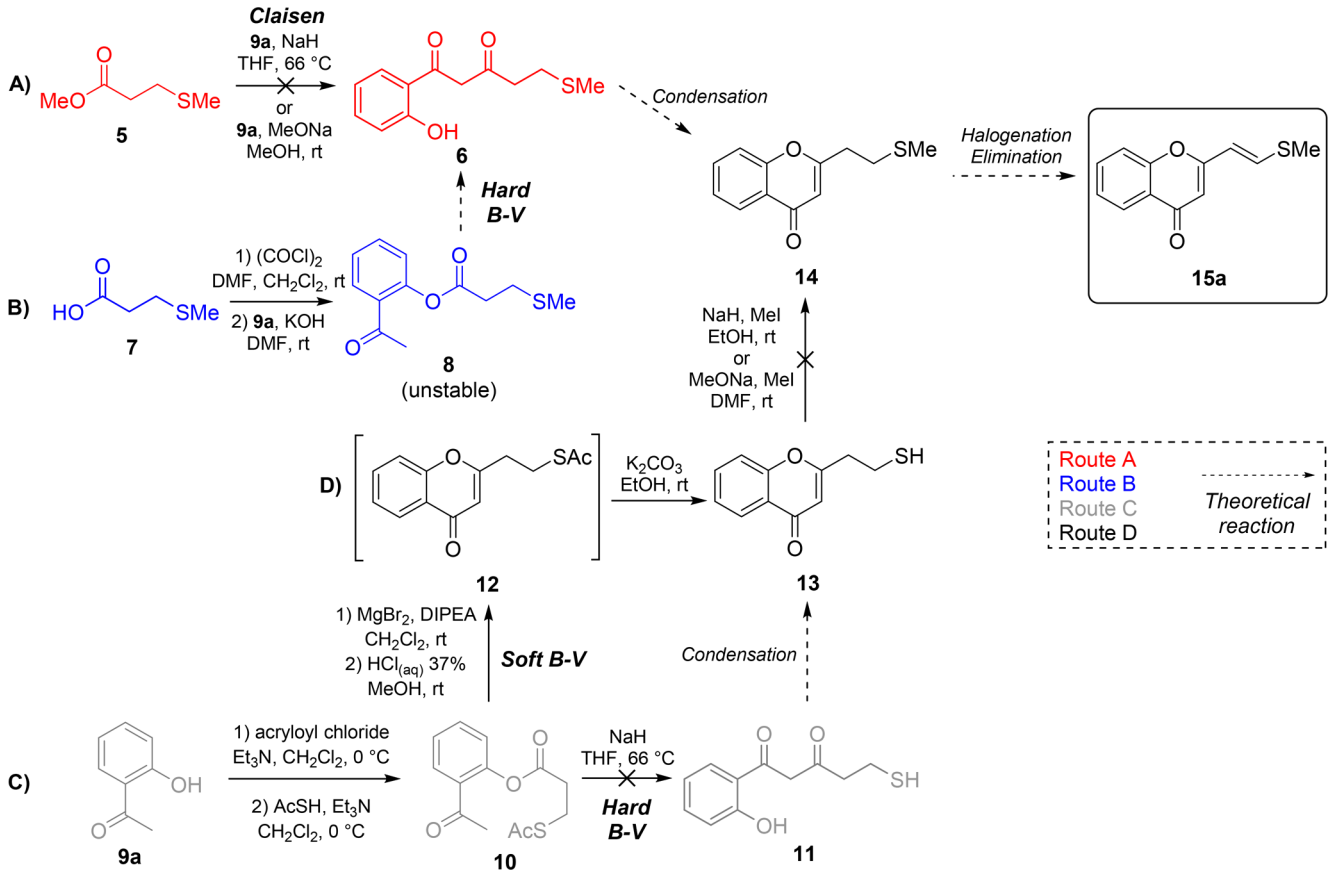
Scheme 1. Failed Synthetic Routes Explored for the Preparation of (*S*)-Deoxydirchromone 15a



widely used. This reaction requires the formation of an enolate[8] that is typically produced by deprotonation of acetophenone using a strong base.[9] The scope of the reaction is therefore restricted to substrates that tolerate strongly basic conditions, which are referred to as "hard" enolization conditions.[10] However, "soft" enolization conditions, where a Lewis acid is used to enable the formation of enolates in the presence of a weak base,[10,11] have never been applied to the B−V rearrangement.[12] Along these lines, we demonstrate that hard enolization conditions proved inapplicable to the synthesis of dirchromones, which prompted the development of the first soft-enolization B−V rearrangement. This strategy specifically enabled a facile and scalable synthesis of diversely substituted dirchromone derivatives from readily available and affordable buildings blocks. Illustrating the utility of the proposed synthesis, it gave access to gram-scale preparation of dirchromone **1**. Its cytotoxicity was then screened against 13 cancer cell lines.

The preparation of (*S*)-deoxydirchromone **15a** was the main focus of the initial investigation, provided that it could then be readily oxidized to racemic sulfoxide **1** using 3-chloroperbenzoic acid (*m*-CPBA).[13] The first explored strategy was modeled based on classical syntheses of 2-substituted chromones through a Claisen condensation[6,14] of methyl 3-methylthiopropionate **5** and 2′-hydroxyacetophenone **9a** (Scheme 1, route A). This would have been followed by acidic dehydrative cyclization to compound **14** and oxidation to generate vinylsulfide **15a**. The Claisen condensation, under classical hard conditions involving strong bases such as sodium hydride[6,9,15] or sodium alcoolate,[16] however, failed to afford the desired intermediate. A methodological change was thus required.

We then envisioned an intramolecular version of this transformation involving a B−V rearrangement of ester **8** followed by acidic cyclization (Scheme 1, route B). However, ester **8** was found to readily degrade, preventing its isolation in sufficient amount and purity to pursue this strategy. Construction of a different sulfur-bearing chain via the easily prepared ester **10** (Scheme 1, route C) was found to be an acceptable workaround. The conversion of ester **10** to diketone intermediate **11** under classical B−V conditions, however, gave phenone **9a** and starting ester as the main products.

The hard conditions involved in either the Claisen condensation or classical B−V rearrangement were suspected to interfere with the reaction. We thus envisioned applying the soft-enolization Claisen reaction developed by Lim et al.[10] to the case of dirchromone synthesis. After screening various Lewis acids, including $ZnCl_2$, $CuOTf_2$, and NiI_2 in different solvents such as THF or toluene, the authors showed that room temperature Claisen condensations could be efficiently conducted using acetophenone and a variety of activated acylating agents. The optimized conditions were demonstrated to involve *N*-acylbenzotriazoles or pentafluorophenyl esters as acylating reagents in the presence of magnesium bromide diethyl etherate in reagent-grade CH_2Cl_2 open to air and using diisopropylethylamine (DIPEA) as a base.[17] Yet, when 2′-hydroxyacetophenone **9a** was used as the substrate, the reported yields were significantly reduced. Furthermore, preparing activated acyl groups from sulfide bearing carboxylic acid **7** to perform a Claisen condensation would involve significant work, and our preliminary testing showed that the

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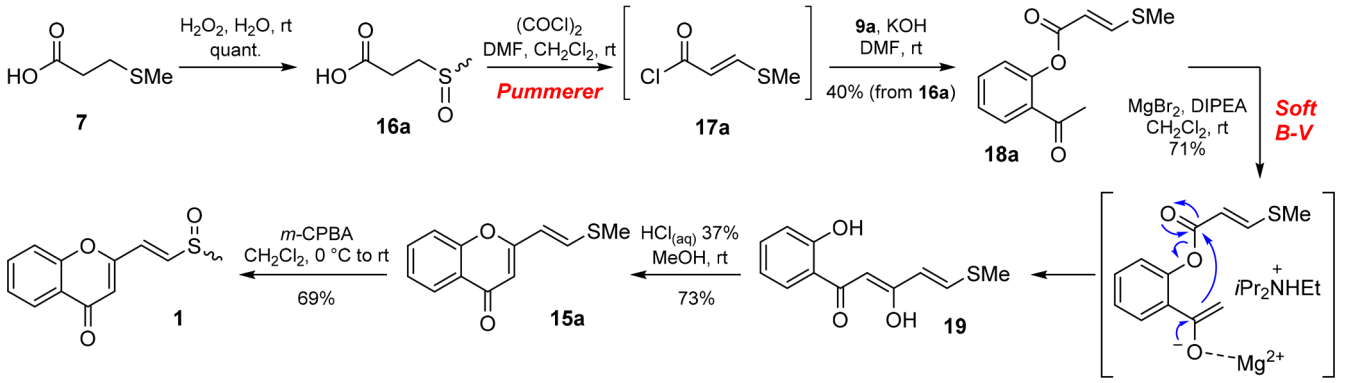
Scheme 2. Soft Baker–Venkataraman Enabled Synthesis of (*S*)-Deoxydirchromone and Preparation of Dirchromone 1



yields were very low (data not shown). For these reasons, the soft-enolization intermolecular Claisen condensation seemed not to be a relevant strategy for the preparation of dirchromone precursors. However, an intramolecular soft-enolization B–V rearrangement appeared as an attractive alternative. Indeed, direct esterification of 2′-hydroxyacetophenone **9a** would yield a proper substrate for a B–V rearrangement, leading to chromone precursors in an atom-economical fashion. Applying Lim's conditions to ester **10** (Scheme 1, route D), which could be described as the first reported soft-enolization B–V reaction (soft B–V), followed by acidic cyclization and cleavage of the crude thioester **12** with K_2CO_3, provided the thiol **13** in satisfactory yield. Yet, subsequent methylation of thiol **13** to afford compound **14** did not proceed under classical conditions.[18,19]

In search of a more efficient alternative, sulfide **7** was first quantitatively oxidized to crude sulfoxide **16a**[20] (Scheme 2). The latter was then reacted with oxalyl chloride in anhydrous CH_2Cl_2, which had two purposes. Not only was the acyl chloride generated but a Pummerer rearrangement followed by an elimination led to an oxidation transfer from the sulfur atom to the lateral chain, providing a vinyl sulfide with complete *E*-selectivity. The formation of a vinylsulfide in such a way is, to the best of our knowledge, quite uncommon,[21,22] sometimes observed as a side product in the course of other Pummerer-type reactions.[23] As such, our procedure proved to be a straightforward route to useful vinylsulfide building blocks.[24] The overall reaction to yield derivative **17a** was completed faster when a catalytic amount of DMF was added. Once gas evolution had ceased, coupling the formed reactant with an excess of the conjugated base of 2′-hydroxyacetophenone **9a** yielded stable vinylsulfide ester **18a** in a convenient 40% yield, given the relatively complex one-pot sequence. Ester **18a** was then submitted to the soft B–V conditions (2.5 equiv of $MgBr_2$ etherate, 3 equiv of DIPEA, CH_2Cl_2 open to air, overnight at room temperature) to afford enol **19** (71%). Mechanistically, the reaction is likely to proceed through the coordination of Mg^{2+} to the ketone function of ester **18a** that would decrease the pK_a of the α-proton and promote deprotonation by the weak base DIPEA. The generated enolate would then undergo the B–V rearrangement to afford enol **19**. The latter was then successfully cyclized into (*S*)-deoxydirchromone **15a** (73%). These two steps were found to be applicable consecutively, omitting isolation of the enol, with an identical overall yield (52% over two steps).

Since this overall strategy secured straightforward access to the dirchromone scaffold, it was applied to several substituted dirchromones to explore its scope (Scheme 3). The acyl chloride formation/Pummerer rearrangement/esterification step gave moderate overall yields. Pleasingly, the reaction still proceeded well with ethylsulfoxide **18b** even though the elimination step could have been expected to occur on both sides of the sulfide following the Pummerer rearrangement, which could explain the decreased yield. However, the sequence failed for isopropylsulfoxide **18c**, indicating that only unbranched alkylsulfides can be transformed by this method. When a benzoate protecting group was present (**18g**), generation of the phenolate had to be conducted with NaH instead of KOH, resulting in decreased esterification efficiency. For other dirchromones, at best, use of potassium phenolate of ketone **9a** in excess as both the substrate and the base was found to slightly increase the yield by 5–10%, compared to an alternative approach using 1.5 equiv of ketone **9a** in the presence of triethylamine. It thus seems that a stronger conjugated base leads to more convenient yields. The excess phenone could be almost quantitatively retrieved by chromatography, so this procedure was preferred for preparation of compounds **18a–b**, **18d–f**, and **18h**. The Pummerer rearrangement itself rather than the acyl chloride generation or esterification steps is presumed to be the most yield-limiting part of the sequence since transposition of the same protocol starting with *E*-cinnamic acid **20** toward the synthesis of chromone **3** gave a good 76% yield of ester **21**. When commercial acyl chlorides **21** and **22** were used, a milder esterification with ketone **9a** in the presence of triethylamine was satisfactory, providing the expected ester with yields ranging from 58 to 88%.

For the second step, it was found that the soft B–V proceeded similarly well when generating a substituted enol, starting from 2′-hydroxypropiophenone toward **15e**. Substituted vinylsulfide **18d** afforded the corresponding methylated deoxydirchromone **15d** in a very good 81% yield, showing that steric hindrance did not interfere with the soft B–V rearrangement. Also of interest was the possibility to conduct the reaction while retaining a benzoyl group **15g**, indicating the compatibility of the soft conditions with base-sensitive functionalities. The reaction was also readily scalable. The gram-scale soft B–V, which enabled conversion of vinylsufide **18a** into chromone **15a**, proceeded even better than at the mmol scale (52%), with a yield reaching 67%, without changing the protocol. The conditions used for the soft B–V rearrangement represent, to the best of our knowledge, a novel approach to this classical reaction, enabling the formation of a wider scope of compounds featuring sensitive functional

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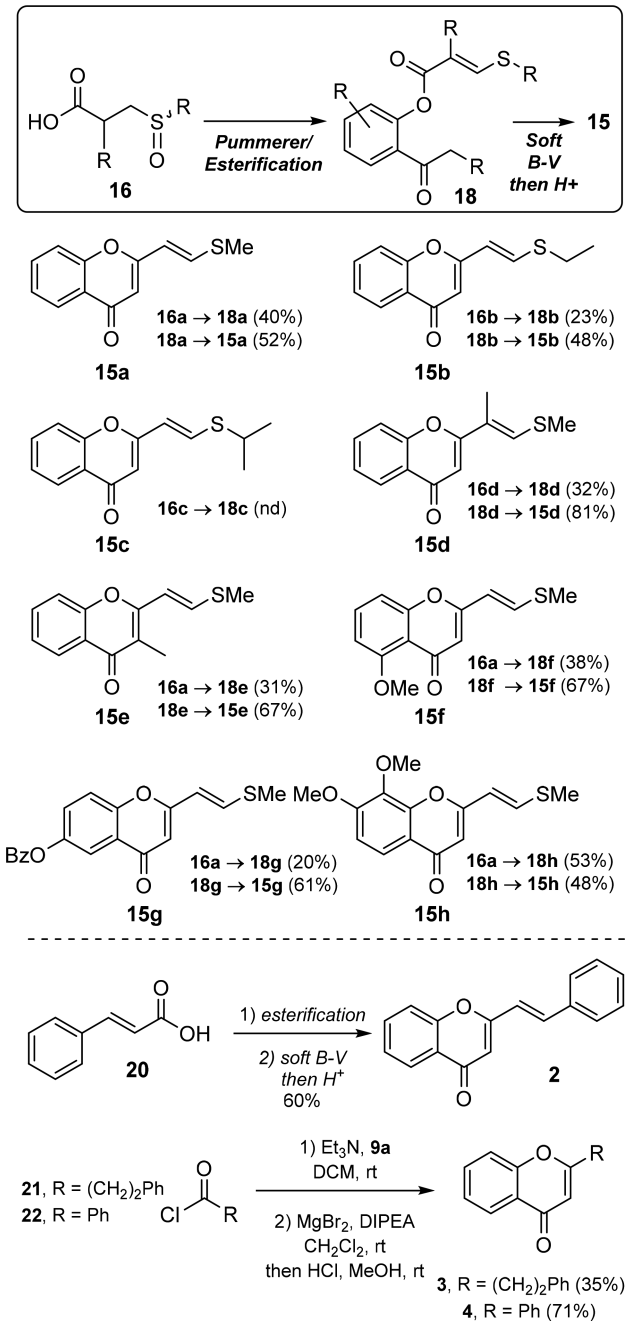
Scheme 3. Scope of the Soft B–V Rearrangement



groups that are not compatible with classical hard conditions. Upon investigation, the reaction offered similarly useful conditions for the preparation of 2-styrylchromone **2**, 2-phenylethylchromone **3**, and flavone **4** in 79, 61, and 81% yields, respectively. In comparison, 2-styrylchromone **2** was obtained in 43% yield (from phenone **9**) when the B–V rearrangement was conducted with K_2CO_3 in refluxing acetone;[25] or in 73% yield (from cinnamoyl chloride) following a KOH-mediated B–V rearrangement procedure.[26] These backbones of a large number of biologically relevant compounds are, as far as we are aware, always formed under strongly basic conditions.[12] The softer base/magnesium system was here demonstrated to be applicable to the same reactions in high yields, foretelling that soft B–V could be usefully applied in the future to a broad variety of syntheses, especially if base-sensitive groups are present.

Oxidation of sulfide **15a** to sulfoxide **1** was completed in good yields (69–87%) using *m*-CPBA, overall offering a straightforward and efficient synthesis of dirchromone **1** whose NMR data were in full agreement with the reported structure.[1] With no significant modification to experimental protocols, the seven-step sequence, i.e., oxidation, acyl chloride generation, Pummerer rearrangement, esterification, soft B–V rearrangement, condensation, and oxidation, was consecutively and successfully applied to the synthesis of 1.5 g of dirchromone **1**, with an overall yield of 21%. With such quantity at hand, cytotoxic activity screening of dirchromone **1** was broadened to 13 cancer cell lines. As presented in Table 1, dirchromone **1** was found to be cytotoxic against all cancer cell lines tested, with IC_{50} ranging from 1.5 to 14.1 μM. The range of activity (μM) is similar to etoposide used as positive control. DLD-1 and PC-3 are the most sensitive cancer cell lines to dirchromones **1** with IC_{50} of 1.5 and 1.7 μM, respectively. The results confirm the previously reported activity for DLD-1 and A-549.[1]

Table 1. Cytotoxic Activity of Synthesized Dirchromone 1 against a Panel of Cancer Cell Lines

		IC_{50} (μM)[a]	
cell line	type	dirchromone (**1**)	etoposide
DLD-1	colorectal adenocarcinoma	1.5 ± 0.2	5.1 ± 1.0
Caco-2	colorectal adenocarcinoma	6.5 ± 0.5	>50
HT-29	colorectal adenocarcinoma	13.7 ± 0.8	10 ± 2
PC-3	prostate adenocarcinoma	1.7 ± 0.1	4.4 ± 0.7
MCF-7	mammary adenocarcinoma	3.0 ± 0.3	>50
PA-1	ovarian teratocarcinoma	3.1 ± 0.8	<0.4
PANC 05.04	pancreatic adenocarcinoma	3.6 ± 0.3	>50
SK-Mel-2	skin melanoma	3.7 ± 0.5	3.5 ± 0.4
SAOS2	osteosarcoma	3.8 ± 0.2	3.5 ± 0.4
HEP-G2	hepatocarcinoma	4.1 ± 0.7	0.6 ± 0.1
U-87	brain glioblastoma	4.3 ± 0.1	>50
A-549	lung carcinoma	11.9 ± 0.7	1.7 ± 0.3
U251	glioma	14.1 ± 0.6	3.4 ± 0.7

[a]IC_{50} values ± SD (n = 3) are representative of two different experiments.

In summary, we have reported the first soft B–V, which can be applied to base-sensitive substrates. Combined to a vinylsulfide-generating Pummerer reaction, this in turn enabled the total synthesis of biologically active dirchromone **1**, in an amount that would have required over four tons of dried *D. palustris* wood to be isolated. Synthetic preparation of dirchromone **1** proceeded from two cheaply available substrates (**7** and **9a**). It is expected that this work will pave the way to a detailed study of mechanism of action of dirchromone **1** and SAR. The vinylsulfide-generating Pummerer rearrangement described herein will also be further studied to broaden its field of application. Investigations on the mechanism of action are ongoing and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03148.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andre_pichette@uqac.ca. Tel: +1-418-545-5011, ext. 5081. Fax: +1-418-545-5012.

ORCID

Alexis St-Gelais: 0000-0003-1091-8301
Jérôme Alsarraf: 0000-0003-4641-2599
Charles Gauthier: 0000-0002-2475-2050

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) St-Gelais, A.; Legault, J.; Mshvildadze, V.; Pichette, A. J. *J. Nat. Prod.* **2015**, *78* (8), 1904–1909.
(2) Santos, C. M. M.; Silva, A. M. S. A. *Eur. J. Org. Chem.* **2017**, *2017* (22), 3115–3133.
(3) Kristanti, A. N.; Tanjung, M.; Aminah, N. S. *Mini-Rev. Org. Chem.* **2018**, *15* (1), 36–55.
(4) Huo, H. X.; Gu, Y. F.; Sun, H.; Zhang, Y. F.; Liu, W. J.; Zhu, Z. X.; Shi, S. P.; Song, Y. L.; Jin, H. W.; Zhao, Y. F.; Tu, P.-F.; Li, J. *Fitoterapia* **2017**, *118* (2016), 49–55.
(5) Chen, D.; Xu, Z.; Chai, X.; Zeng, K.; Jia, Y.; Bi, D.; Ma, Z.; Tu, P. *Eur. J. Org. Chem.* **2012**, *2012* (27), 5389–5397.
(6) Williams, D. A.; Smith, C.; Zhang, Y. *Tetrahedron Lett.* **2013**, *54* (32), 4292–4295.
(7) Jain, P. K.; Makrandi, J. K.; Grover, S. K. *Synthesis* **1982**, *3*, 221–222.
(8) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **2007**, *13*, 1–115.
(9) Zhao, D.; Beiring, B.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52* (32), 8454–8458.
(10) Lim, D.; Fang; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9* (21), 4139–4142.
(11) Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, *3*, 478–482.
(12) Ameen, D.; Snape, T. J. *Synthesis* **2015**, *47* (2), 141–158.
(13) Xing, H.; Chen, L.; Jia, Y.; Jiang, Z.; Yang, Z. *Tetrahedron Lett.* **2017**, *58* (23), 2199–2202.
(14) Wang, S. J.; Bao, L.; Han, J. J.; Wang, Q. X.; Yang, X. L.; Wen, H. A.; Guo, L. D.; Li, S. J.; Zhao, F.; Liu, H. W. *J. Nat. Prod.* **2013**, *76*, 45–50.
(15) Yu, D.; Chen, C. H.; Brossi, A.; Lee, K. H. *J. Med. Chem.* **2004**, *47* (16), 4072–4082.
(16) Gray, C. A.; Kaye, P. T.; Nchinda, A. T. *J. Nat. Prod.* **2003**, *66* (8), 1144–1146.
(17) Lim, D.; Zhou, G.; Livanos, A. E.; Fang, F.; Coltart, D. M. *Synthesis* **2008**, *2008* (13), 2148–2152.
(18) Rioz-Martínez, A.; Kopacz, M.; de Gonzalo, G.; Torres Pazmiño, D. E.; Gotor, V.; Fraaije, M. W. *Org. Biomol. Chem.* **2011**, *9* (5), 1337.
(19) Roe, R. M.; Kallapur, V.; Linderman, R. J.; Viviani, F. *Pestic. Biochem. Physiol.* **2005**, *83* (2–3), 140–154.
(20) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X. Q.; Noyori, R. *Tetrahedron* **2001**, *57* (13), 2469–2476.
(21) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104* (5), 2401–2432.
(22) Smith, L. H. S.; Coote, S. C.; Sneddon, H. E.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49* (34), 5832–5844.
(23) Horiguchi, Y.; Saitoh, T.; Terakado, S.; Honda, K.; Kimura, T.; Toda, J.; Sano, T. *Heterocycles* **2000**, *54* (2), 967–984.
(24) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6* (26), 5005–5008.
(25) Desideri, N.; Conti, C.; Mastromarino, P.; Mastropaolo, F. *Antivir. Chem. Chemother.* **2000**, *11*, 373–381.
(26) Charvin, D.; Pomel, V.; Ortiz, M.; Frauli, M.; Scheffler, S.; Steinberg, E.; Baron, L.; Deshons, L.; Rudigier, R.; Thiarc, D.; Morice, C.; Manteau, B.; Mayer, S.; Graham, D.; Giethlen, B.; Brugger, N.; Hédou, G.; Conquet, F.; Schann, S. *J. Med. Chem.* **2017**, *60* (20), 8515–8537.

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