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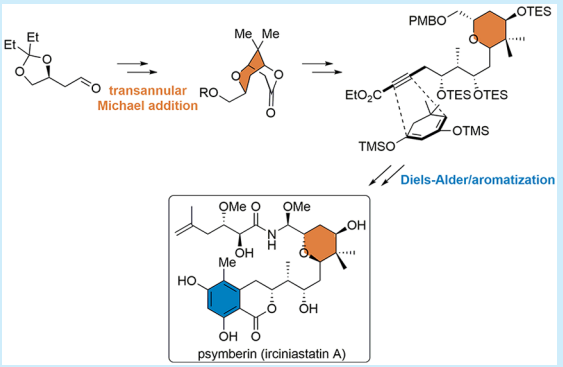
Total Synthesis of Psymberin (Irciniastatin A)

Jie Yu, Mingze Yang, Yian Guo,* and Tao Ye*

State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, Xili, Nanshan District, Shenzhen 518055, China

Supporting Information

ABSTRACT: A convergent, stereocontrolled total synthesis of psymberin, an architecturally complex marine antitumor agent, has been achieved in 27 steps from the known aldehyde **8**. Highlights of this synthesis include a novel and efficient transannular Michael addition/lactone reduction sequence to construct the highly substituted 2,6-*trans*-tetrahydropyran, a diastereoselective IBr-induced iodocarbonate cyclization to introduce the C17 stereogenic center, and a Diels−Alder/aromatization reaction to install the highly substituted aromatic ring.



In 2004, Crews and co-workers reported the isolation of psymberin (**1**) (Figure 1) from the marine sponge *Psammocinia* sp. collected from the waters of Papua New Guinea.[1] Independently, Pettit et al. reported the isolation of a novel cytotoxic polyketide, irciniastatin A, from the extract of Indo-Pacific marine sponge *Ircinia ramosa*.[2] The first total synthesis of psymberin, reported by De Brabander et al., not only fully elucidated the structure but also confirmed psymberin and irciniastatin A were structurally identical.[3]

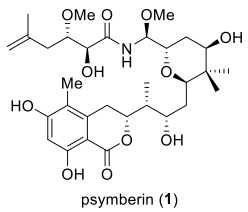
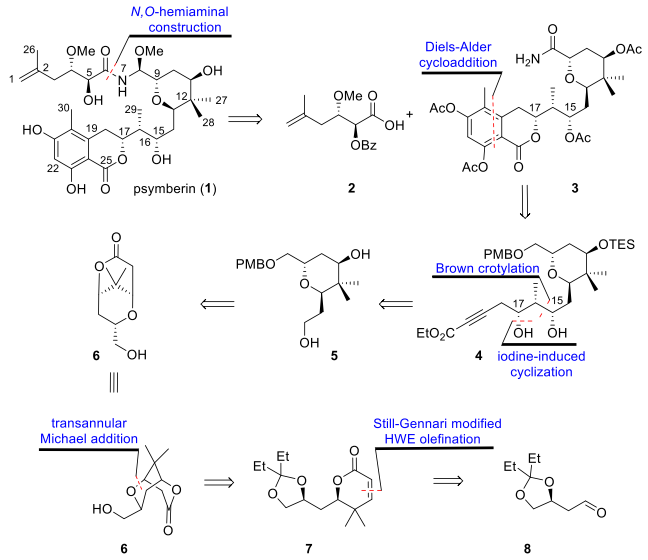


Figure 1. Structure of psymberin (irciniastatin A) (**1**).

The architecturally intriguing and biologically potent yet naturally scarce cytotoxin has spurred interest in the synthetic community. To date, strategies for accomplishing the total,[4] formal,[5] or partial[6] syntheses of psymberin have been reported by several groups, and a comprehensive review[7] of the current state of this area was published by Bielitza et al. In connection with our continuing interest in the synthesis of complex natural products with promising biological activities,[8] we embarked on the development of an asymmetric total synthesis of psymberin.

Structurally, psymberin is composed of a psymberic acid side chain, a dihydroisocoumarin unit (DHIC), an *N*,*O*-hemiaminal subunit, and a densely functionalized 2,6-*trans*-tetrahydropyran (2,6-*trans*-THP) core. Retrosynthetic analysis of **1** (Scheme 1)

Scheme 1. Retrosynthetic Analysis of Psymberin



led us to an initial disconnection of the *N*,*O*-hemiaminal that could be prepared from acid **2** and amide **3**. The dihydroisocoumarin motif was envisioned to be constructed through Diels−Alder cyclization from a dienophilic alkyne **4**, which in turn would arise from **5**, exploiting Brown asymmetric crotylation followed by Bartlett iodine-induced carbonate cyclization. Furthermore, it was envisaged that 2,6-*trans*-tetrahydropyran moiety **5** could be derived from lactone **7** via a pivotal transannular oxa-Michael addition.

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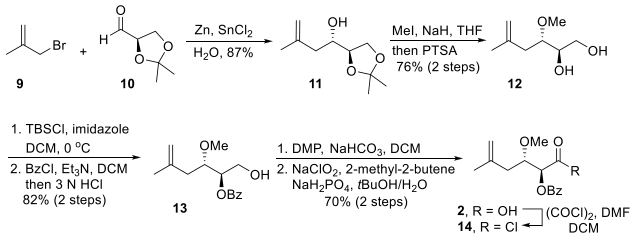
Our synthetic efforts commenced with the preparation of psymberic acid (**2**) as outlined in Scheme 2. An organozinc

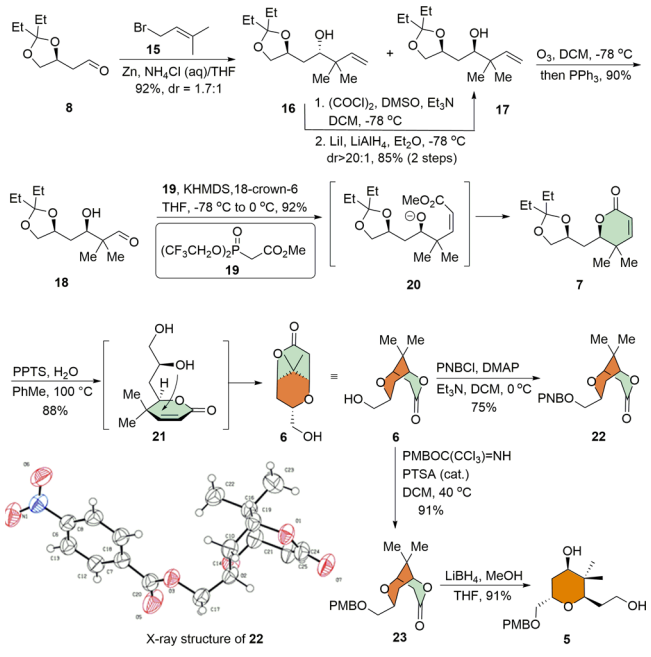
Scheme 2. Synthesis of Psymberic Acid 2



agent derived from 3-bromo-2-methylpropene underwent chelation-controlled addition[9] to commercially available aldehyde **10** in the presence of $SnCl_2$ to give rise to the corresponding homoallylic alcohol **11** as a sole isomer in 87% yield. Methylation of the homoallylic alcohol and subsequent treatment of the methyl ether with *p*-toluenesulfonic acid in methanol cleaved the acetonide moiety to afford diol **12** in 76% yield. This diol was subsequently converted into monobenzoate **13** through a two-step sequence involving (1) temporary protection of the primary alcohol as its TBS ether and (2) benzoylation of the secondary hydroxyl group followed by deprotection of the primary TBS ether under acidic conditions. Alcohol **13** was converted into the corresponding acid **2** in 70% overall yield by sequential oxidation of the primary alcohol with Dess–Martin periodinane, followed by Pinnick oxidation. The resulting carboxylic acid (**2**) was then converted into the corresponding acid chloride (**14**) that was sufficiently clean and could be used directly in the coupling with fragment **3** (*vide infra*).

The synthesis of 2,6-*trans*-tetrahydropyran commenced with the known aldehyde **8**[10] as shown in Scheme 3. Thus, treatment of **8** with prenyl bromide and freshly activated zinc powder under ultrasound sonication delivered a separable

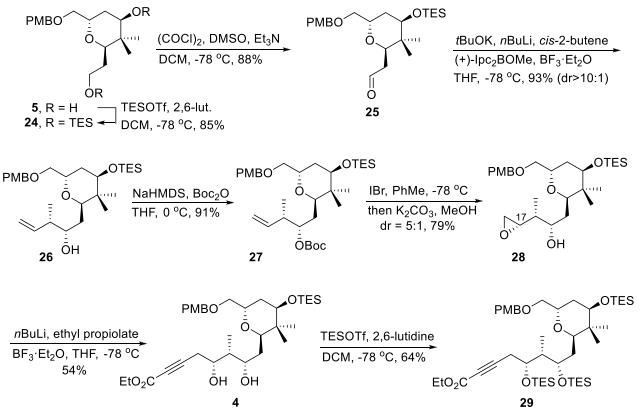
Scheme 3. Synthesis of 2,6-*trans*-THP Derivative 5



mixture (1.7:1) of **16** and **17**[11] in 92% yield. Undesired epimer **16** was readily converted into desired alcohol **17** in 85% yield via a two-step sequence involving Swern oxidation[12] and a chelation-controlled reduction.[13] Ozonolytic cleavage of the terminal alkene in **17** gave rise to desired aldehyde **18** in 90% yield, which was subsequently submitted to a Still–Gennari modified HWE olefination[14] with phosphonate **19**. By employing KHMDS as the base in combination with 18-crown-6, the resultant *cis*-α,β-unsaturated ester underwent concomitant transesterification to furnish unsaturated lactone **7** in 92% yield. It was hypothesized that acidic hydrolysis of the pentylidene ketal protecting group afforded the corresponding diol that could subsequently undergo an *in situ* transannular oxa-Michael addition to give rise to cycloadduct **6**. In the event, treatment of lactone **7** with catalytic pyridinium *p*-toluenesulfonate (PPTS) and water in toluene at 100 °C provided **6** in 88% yield. As anticipated, careful examination of NMR spectra of cycloadduct **6** allowed us to confirm the stereochemistry. Furthermore, the facial selectivity of the transannular oxa-Michael addition and the absolute and relative configuration of cycloadduct **6** were confirmed by X-ray crystallography of the corresponding *p*-nitrobenzoate derivative. Carbinol **6** was then transformed into PMB ether **23** under acidic conditions, followed by reductive ring opening with $LiBH_4$ that furnished 2,6-*trans*-tetrahydropyranyl diol **5**.

After successful construction of 2,6-*trans*-tetrahydropyran (**5**) with the requisite stereochemistry, the stage was set for the incorporation of the all-*syn*-oriented stereogenic centers at C15–C17 (Scheme 4). Thus, treatment of diol **5** with

Scheme 4. Synthesis of Dienophile 29



triethylsilyl triflate and 2,6-lutidine led to the bis-silyl ether (**24**) in 85% yield. Regioselective Swern oxidation[15] of **24** proceeded without incident to afford aldehyde **25**, which was then subjected to Brown asymmetric crotylation,[16] to furnish the desired homoallylic alcohol **26** in 93% yield with excellent diastereoselectivity. Next, we turned our attention to the Bartlett iodine-induced carbonate cyclization[17] as a means of 1,3-stereoinduction. Thus, treatment of homoallylic alcohol **26** with sodium bis(trimethylsilyl)amide followed by quenching with Boc anhydride afforded the corresponding *tert*-butyl carbonate **27** in 91% yield. *tert*-Butyl carbonate **27** was treated with iodine monobromide in toluene at −78 °C, upon workup with potassium carbonate in methanol to give rise to separable diastereomers in a 5:1 ratio, with the desired epoxide (**28**) isolated in 79% yield. Regioselective ring opening of epoxide **28** with lithium ethyl propiolate (THF, −78 °C) mediated by

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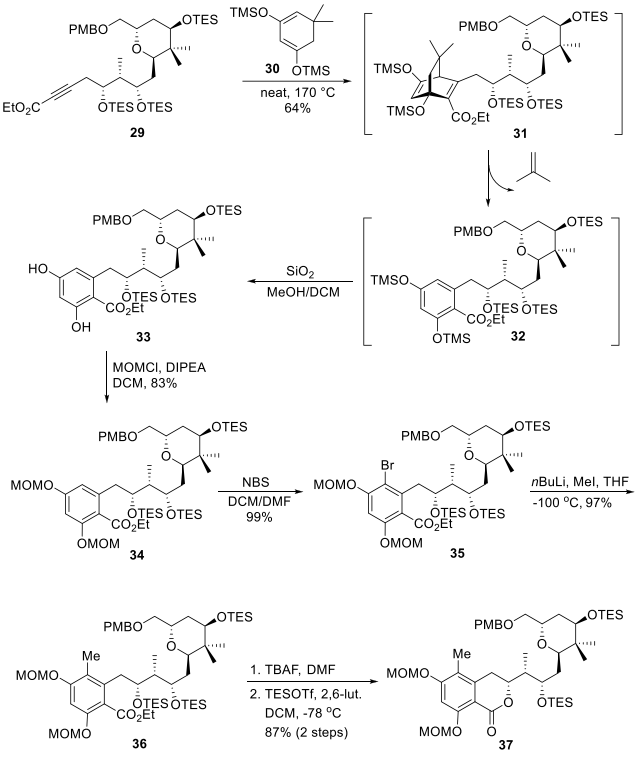
$BF_3{\cdot}Et_2O$ led to alkynoate **4** in 54% yield. Subsequent bis-silylation of **4** with triethylsilyl triflate and 2,6-lutidine furnished silyl ether **29** in 67% yield.

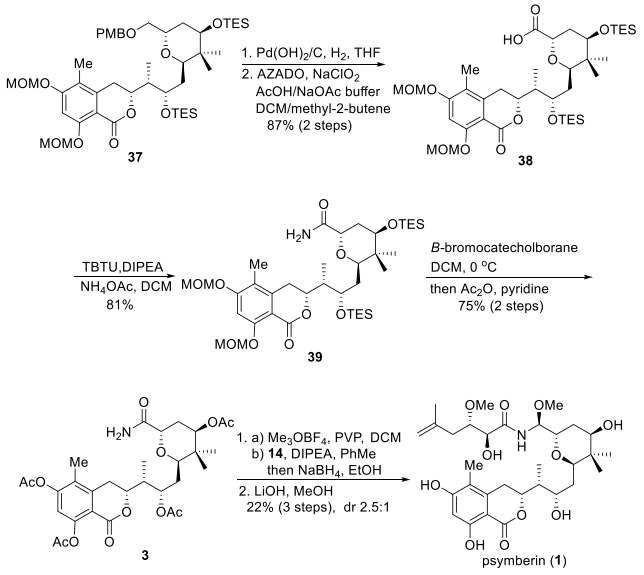
Considering the requirement of stability to the harsh conditions that would be required for the proposed Diels–Alder reaction, cyclic diene **30**, derived from dimedone,[18] served as an effective diene in Diels–Alder reaction with dienophilic alkyne **4** or **29**. In the event, attempted Diels–Alder reaction[19] of alkyne **4** with diene **30** led to complex mixtures. To our surprise and delight, heating dienophilic alkyne **29** and diene **30** at 170 °C in a sealed tube for 3 days resulted in the formation of the desired product **33** as a single isomer in 64% yield (74% yield based on consumed **29**). Apparently, the transformation follows the designed cycloaddition with spontaneous fragmentation of the presumed bicyclic intermediate **31** and extrusion of isobutylene and subsequent cleavage of TMS ethers. Both phenolic groups in **33** were protected as their corresponding MOM ethers to give rise to **34** in 83% yield. Next, regioselective bromination[20] of **34** was effected with NBS in DCM/DMF to deliver **35** in excellent yield. Lithium–bromide exchange of aryl bromide **35** upon treatment with *n*-BuLi at −100 °C followed by quenching of the carbanion with methyl iodide furnished the desired product **36** in 97% yield. TBAF-mediated removal of the three triethylsilyl (TES) groups in **36** led to a facile intramolecular transesterification with the ethyl ester to give rise to the corresponding lactone ring of the dihydroisocoumarin; reprotection of the two remaining free hydroxyl groups as their TES ethers afforded **37** in 87% overall yield (Scheme 5).

With the two key fragments **14** and **37** in hand, the stage was set for their union and elaboration into psymberin. In the event, hydrogenolytic removal of the PMB group on compound **37** provided the primary alcohol, which was then oxidized under Iwabuchi conditions,[21] to afford acid **38** in 87% yield over two steps. Treatment of acid **38** with ammonium acetate and TBTU according to the protocol reported by Pietruszka[5b] provided primary amide **39** in 81% yield. At this stage, all of the protective groups in amide **39** were removed upon exposure to *B*-bromocatechol borane in DCM. Treatment of the crude product mixture with acetic anhydride gave the corresponding peracetate **3** in 75% yield. This advanced intermediate displayed spectral properties identical in all respects to those previously reported by De Brabander.[3,4h,5a] Employing a procedure developed by De Brabander,[3,4h] tetraacetate **3** was eventually converted into psymberin (**1**). Thus, **3** was treated with Meerwein's reagent and poly(4-vinylpyridine) (PVP) to provide an extremely moisture sensitive imidate that was filtered, concentrated, condensed with acid chloride **14**, and subsequently subjected to reduction with an ethanolic sodium borohydride solution to give rise to peracetylated psymberin. Global deprotection of the acetyl groups produced the crude product in a 2.5:1 diastereomeric ratio, and psymberin (**1**) was isolated as the major product in 22% overall yield from **3** (Scheme 6).[3,4h] The specific rotation and ^1H and ^{13}C NMR spectra of the synthetic sample of **1** are in excellent agreement with the values reported for natural psymberin.[2,3,4h]

Scheme 5. Synthesis of Dihydroisocoumarin 37



Scheme 6. Completion of the Total Synthesis



In summary, the execution of a highly convergent strategy has led to completion of the total synthesis of psymberin. Key features of this synthesis include high levels of stereoselectivity in a number of reactions, including a novel transannular Michael addition/lactone reduction sequence for the construction of the 2,6-*trans*-tetrahydropyran derivative, a diastereoselective IBr-induced iodocarbonate cyclization, and a Diels–Alder/aromatization reaction to install the highly substituted aromatic system. As well as providing an avenue for the preparation of the natural product, the synthesis would provide access to analogues for further chemical biology studies.

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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.9b01113.

Experimental details and data (PDF)

Accession Codes

CCDC 1899049 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yet@pkusz.edu.cn.
*E-mail: bryan_pku@qq.com.

ORCID

Yian Guo: 0000-0002-0341-6816
Tao Ye: 0000-0002-2780-9761

Notes

The authors declare no competing financial interest.

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