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Synthetic studies toward the pyran core and the amide side chain of psymberin

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ABSTRACT

A synthetic approach to the polysubstituted pyran core and amide side chain of psymberin (irciniastatin A) using stereoselective organoboron methodology is described. An advanced oxyranyl pyran intermediate was prepared using a catalytic enantioselective and diastereoselective three-component reaction involving first an inverse electron-demand hetero [4+2] cycloaddition between 3-boronoacrolein pinacolate and 1-ethoxy-2-methylpropene, followed by an allylboration of ethyl glyoxylate. The amide side chain was prepared highly efficiently using the first example of a doubly diastereoselective allylboration of a chiral α-alkoxy aldehyde under the Lewis acid-catalyzed reaction manifold.

1. Introduction

The isolation of natural products from marine organisms has provided organic chemists with numerous challenges and opportunities to develop new cures for diseases of great consequences, such as cancer.[1] In this regard, psymberin (**1**, Fig. 1) is a naturally occurring and highly potent polyketide recently isolated independently by two research groups. Crews and co-workers reported in 2004 the isolation of psymberin from a sea sponge from the waters of Papua New Guinea, *Psammocinia* sp.[2] At about the same time, a group led by Pettit also reported the isolation of the same compound, named irciniastatin A, from the Indo-Pacific marine sponge *Ircinia ramose*.[3] In the same publication, Pettit and co-workers also described the isolation of a related structure, irciniastatin B, **2** (Fig. 1). Psymberin (irciniastatin A) is a complex pyran-containing natural product that embeds nine stereogenic centers. It is related with its central pyran core to the pederin family (e.g., **3**, Fig. 1), which includes over 35 related structures known to display a range of anticancer activities.[4] Psymberin was tested in the NIH-60 human cancer cell line screen, and displayed an unusual profile.[3] It was found to be specific toward solid tumor cell lines, with a high level of selectivity for melanoma cells characterized by a LC_{50} in the low nanomolar range. It also showed activity against some breast and colon cancer cell lines. The promising biological properties and novel structure of psymberin have attracted the attention of the synthetic chemistry community, and thus far two total syntheses have been achieved by the groups of De Brabander and Buevich,[5,6] as well as one formal synthesis.[7] A few other synthetic studies toward advanced fragments have been realized.[8]

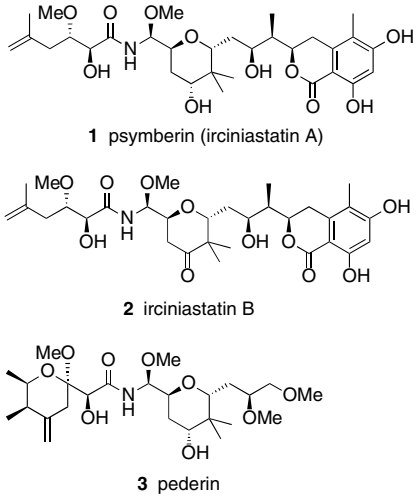

Figure. 1. Psymberin (irciniastatin A), irciniastatin B, and pederin.

We aimed to develop a convergent route to psymberin and its subunits that would allow a structure–activity study of its anticancer activity that could lead to the design of a simplified analogue. In this preliminary Letter, we describe our results focusing on the central pyran core and the left-hand amide side chain (Fig. 2), which altogether comprise six of the nine stereogenic centers of psymberin. As shown in Figure 2, we anticipated that two of our group's organoboron-based methodologies could be put to use.

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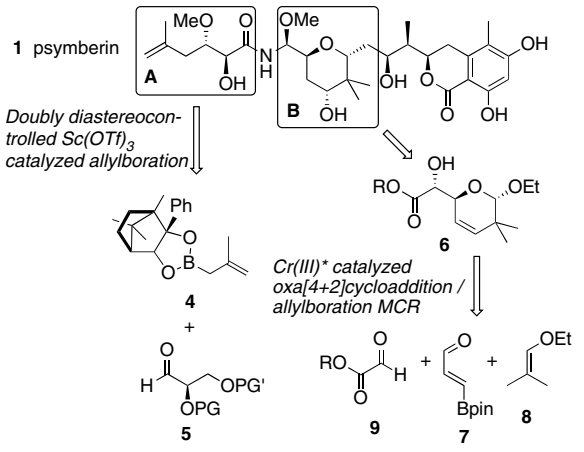


Figure. 2. Retrosynthetic plan for fragments A and B of psymberin (**1**).

First, our scandium-catalyzed allylboration with the methallyl camphordiol boronate **4**[9] could be exploited in the context of a doubly diastereoselective addition to provide fragment A from a protected, chiral α,β-dihydroxy aldehyde **5**. This transformation will provide the first ever test of the stereodirecting ability of this Lewis acid-catalyzed allylboration procedure. Then, to assemble the polysubstituted pyran unit, our tandem three-component oxa[4+2] cycloaddition/allylboration[10] between boronoacrolein pinacolate (**7**), enol ethers, and aldehydes would be employed under catalysis with Jacobsen's Cr(III) chiral complex.[11] To access fragment B, the hindered 2,2-disubstituted enol ether **8**[12] will be employed for the first time in this three-component reaction, which was foreseen as an additional element of difficulty.[11c,13] A reactive glyoxylate **9** will be used for the carbonyl allylboration step leading to **6**. It was further envisaged that a Lewis acid-catalyzed reaction between allylSnBu$_3$ and the acetal functionality in the multicomponent reaction product, **6**, would be performed in order to extend the right-hand side chain of psymberin. Ultimately, fragments A and B would be coupled using a known Curtius rearrangement/amidation sequence described in synthetic studies on pederin.[4b]

2. Results and discussion

The doubly diastereoselective methallylation of known aldehyde **10** was tested with both antipodes of chiral camphordiol boronate reagent **4** (Fig. 3). To this end, the intrinsic diastereofacial selectivity of this system was first tested with achiral pinacol methallylboronate **13** under both thermal (uncatalyzed) conditions and under Sc(OTf)$_3$ catalysis. The uncatalyzed reaction required room temperature to proceed with an appreciable rate, and led to almost no selectivity in the products **11** and **12**. The low-temperature Sc(III)-catalyzed variant led to an improvement, but the modest diastereoselectivity of 5-to-1 in favor of the desired product **11** emphasized the need for a double diastereoselection strategy that would circumvent the need for separating diastereomeric products. To our great satisfaction, the use of chiral boronate (+)-**4** led to the exclusive formation of allylic alcohol **11** in good yield.[14] To confirm the powerful stereodirecting power of this reagent, the (−) antipode was reacted with the same aldehyde (**10**) under identical conditions, only to observe a 1:2 ratio of products **11** and **12**, respectively. Thus, even in a mismatched case, reagent **4** was capable of inverting the intrinsic diastereofacial bias of this allylation reaction. The high selectivity obtained in the preparation of **11** compares favorably to the use of Brown's chiral methallylboration method.[5] It is noteworthy that the methallylation of **10**

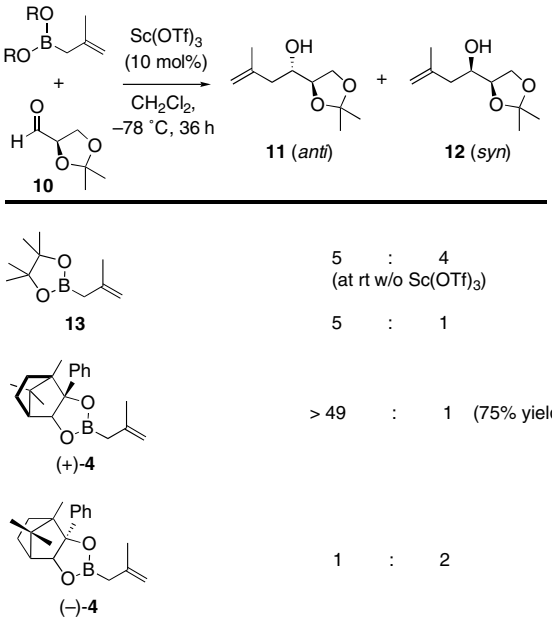
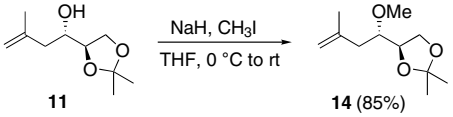


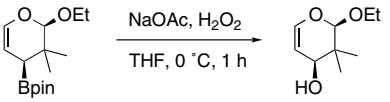
Figure. 3. Doubly diastereocontrolled allylboration toward fragment A.

with reagent (+)-**4** was accomplished in multigram quantities. Homoallylic alcohol **11** was methylated with ease to afford the desired ether **14** (Eq. 1).[14] The latter could be transformed to the requisite carboxylic acid precursor of fragment A using the same straightforward sequence described by De Brabander and co-workers.[5]



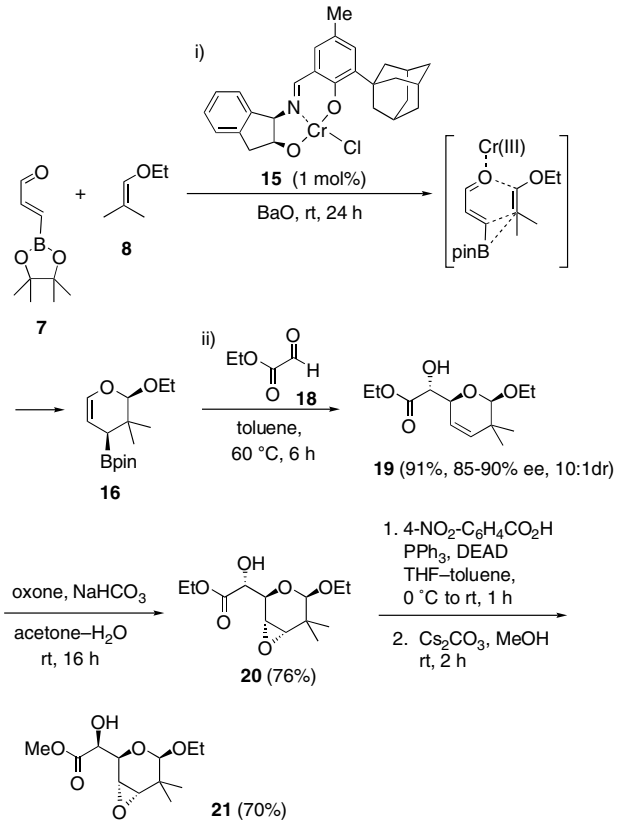
(1)

The preparation of the pyran core, fragment B, required a challenging extension of our previously reported inverse electron-demand hetero Diels–Alder cycloaddition of enal **7** catalyzed by Jacobsen's chiral chromium catalyst[11] (**15**, Scheme 1).[10] Whereas vinyl ethyl ether reacts with 3-boronoacrolein pinacolate (**7**) in less than 1 h at room temperature to afford the expected cycloadduct in 96% ee, the 2,2-dimethylated analogue **8**[12] required about 24 h to provide cycloadduct **16** (Scheme 1). The latter was obtained at best in 90% ee, as measured on the corresponding alcohol **17** according to Eq. 2. Enol ether **8** needs to be freshly distilled for the cycloaddition to proceed most efficiently. It was possible but not beneficial to realize the allylboration in 'one-pot' as it led to lower yields and the formation of unidentified decomposition products. To avoid these problems, the Cr(III) catalyst was removed by quickly passing the crude product through a pad of silica.



(2)

The second stage of this three-component reaction between **16** and the glyoxylate **18** was straightforward, and led to the desired α-hydroxyalkylated pyran **19** in 91% yield and 10:1 diastereoselectivity (85–90% ee for the major diastereomer shown, **19**).[14] Having proven the feasibility of the key step for fragment B, several methods were envisaged to functionalize the alkene of product **19**. Toward this end, a stereoselective epoxidation with dimethyldioxirane proved very efficient in affording **20** in good yield (Scheme 1).[14]



Scheme 1.

The formation of the desired stereoisomer **20** was confirmed by X-ray crystallographic evidence on the *p*-iodobenzoate derivative **22** (Fig. 4).[15] The facial selectivity can be explained by electrophilic attack of the dioxirane on the least hindered alpha face of the most favored half-chair conformation of **19** (Fig. 5). We were delighted with this successful approach to an advanced precursor of fragment B, and a few more transformations were explored in a

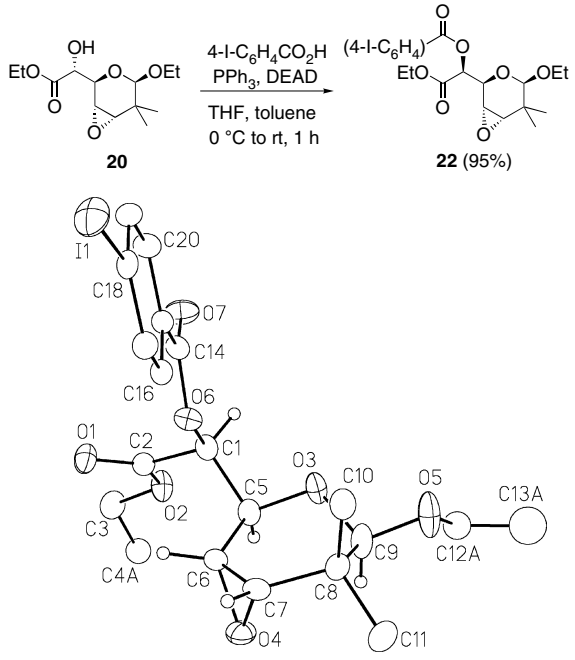


Figure. 4. Preparation and ORTEP of crystalline derivative **22**.

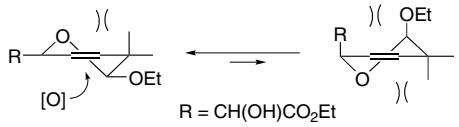


Figure. 5. Rationale for the stereoselective epoxidation of **19**.

preliminary way. To this end, the secondary hydroxyl group of **20** was easily inverted under Mitsunobu conditions to afford intermediate **21** with the requisite stereochemistry for psymberin. Initial efforts to reductively open the epoxide of **21** and to allylate the acetal functionality are underway, and should provide an advanced precursor of the unit B of psymberin ready for fragment coupling.

3. Conclusion

This preliminary Letter demonstrates the feasibility of a synthetic approach to the polysubstituted pyran core and amide side chain of psymberin (irciniastatin A) using stereoselective organoboron methodology. An advanced oxyranyl pyran intermediate was prepared using a catalytic enantioselective and diastereoselective three-component reaction involving first an inverse electron-demand hetero [4+2] cycloaddition between 3-boronoacrolein and 1-ethoxy-2-methylpropene, followed by an allylboration of ethyl glyoxylate. The cycloaddition step was realized highly enantioselectively for the first time with such a hindered enol ether as the dienophilic component. Furthermore, the amide side chain of psymberin was prepared highly efficiently using the first example of a doubly diastereoselective allylboration under the Lewis acid-catalyzed reaction manifold.

Acknowledgments

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14. Procedures and characterization data for key synthetic intermediates:
Preparation of **11** *by methallylation of* **10** *with reagent* (+)-**4**:
This reaction was performed as described in Ref. 9b, except for the use of 2 equiv of aldehyde **10**, and reaction mixture was stirred for 36 h at −78 °C. The resulting product **11** is known and the spectroscopic data matched the reported values.[5] Ether **14** is also known.[5]
Preparation of **19** *by oxa[4+2]cycloaddition/allylboration*: In a flame-dried round-bottomed flask equipped with a teflon stirbar was placed a mixture of 3-boronoacrolein pinacolate **7** (1.5 g, 8.24 mmol, freshly distilled by Kugelrohr) and 1-ethoxy-2-methylpropene (**8**) (2.23 g, 22.3 mmol). To this stirred solution was added the (1*R*,2*S*) Jacobsen catalyst **15** and powdered barium oxide (2.4 g). The reaction mixture was allowed to stir at room temperature for 48 h. The mixture was then passed through a short pad of Et_3N-deactivated silica gel (4:1 pentane–ether) to remove the catalyst. The crude product was concentrated and used directly in the next step. This crude material was mixed with ethyl glyoxylate (**18**) (1.50 g, 14.7 mmol, 50% in toluene, 3.3 mL) and stirred in a sealed tube at 60 °C for 12 h. The vessel was allowed to cool to room temperature and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added with subsequent stirring for 30 min. The resulting mixture was extracted twice with ether (2 × 60 mL) and the ethereal layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by a short column chromatography on Et_3N-deactivated silica gel (pentane–ether 4:1) to afford the desired product **19** (1.90 g, 7.5 mmol, 91% yield, 10:1 dr). The ee of the major diastereomer **19** was determined to be 90% by chiral HPLC of the phenylcarbamate derivative of alcohol **17**).
Compound **19** was obtained as a colorless oil: $[\alpha]_D^{23} - 33.70$ (*c* 2.5, $CHCl_3$) check; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.69 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.54 (dd, *J* = 10.2, 1.8, 1H), 4.68 (dd, *J* = 2.3, 2.0 Hz, 1H), 4.34 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.15 (dd, *J* = 9.7, 2.7 Hz, 1H), 3.90 (dddd, *J* = 16.9, 9.8, 9.8, 7.1 Hz, 1H), 3.61 (d, *J* = 9.7 Hz, 1H), 3.50 (dddd, *J* = 16.9, 9.8, 7.1, 7.1 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.1, 136.9, 122.4, 104.2, 75.2, 72.8, 65.3, 61.4, 35.2, 25.7, 22.3, 14.4, 14.2; IR (neat): 3502, 2977, 1750 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{22}O_5Na$: 281.1359; found 281.1359 [MNa−H]$^+$.
Preparation of **20** *by dimethyldioxirane epoxidation of* **19**:
In a round-bottomed flask open to air and equipped with a teflon stirbar was added the dihydropyran **19** (1.25 g, 4.84 mmol) and sodium bicarbonate (2.2 g) in water (5 mL) and acetone (15 mL). To the stirred mixture at room temperature were added oxone (5.0 g, 12.9 mmol) in one portion. The resulting mixture was stirred at room temperature for 12 h, then extracted three times with ethyl acetate. The combined organic layers were washed once with a saturated aqueous solution of sodium metabisulfite, once with water, and once with brine. The resulting organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on Et_3N-deactivated silica gel (pentane–ether 3:2) to give the epoxide **20** in 76% yield (1.01 g, 3.7 mmol).
Compound **20** was obtained as a white solid. Mp 56–58 °C (uncorrected); $[\alpha]_D^{23} - 51.81$ (*c* 2.8, $CHCl_3$) check; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.35–4.22 (m, 3H), 4.21 (s, 1H), 3.68 (dddd, *J* = 14.2, 9.2, 7.1, 7.1 Hz, 1H), 3.38 (dddd, *J* = 14.2, 9.8, 7.1, 7.1 Hz, 1H), 3.36 (d, *J* = 7.0 Hz, 1H), 3.14 (d, *J* = 8.8 Hz, 1H), 3.02 (dd, *J* = 4.1, 0.6 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 101.6, 75.4, 72.1, 65.1, 62.1, 61.8, 54.0, 34.8, 21.1, 16.5, 14.9, 14.1; IR (neat): 3477, 2977, 2933, 2874, 1748 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{22}O_6Na$: 297.1307; found 297.1309 [MNa−H]$^+$.
15. Crystallographic data (excluding structure factors) for the structure of compound **22** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-690426. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif).