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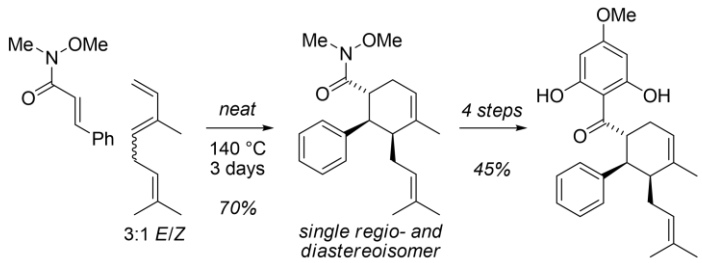

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Total synthesis of (±)-nicolaioidesin B via a highly regio- and diastereoselective Diels–Alder reaction

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ABSTRACT

The total synthesis of (±)-nicolaioidesin B, a natural product that shows preferential cytotoxicity against pancreatic cancer cells under nutrient starvation conditions, is achieved. The key step is a thermally-induced, highly regio- and diastereoselective Diels–Alder reaction between (*E*)-*N*-methoxy-*N*-methylcinnamide and ocimene under solvent-free conditions.

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Pancreatic cancer is the most deadly of human malignancies, with 5-year survival rates in developed countries of *ca*. 6%.[1] Cells within pancreatic tumors demonstrate a remarkable ability to survive in a hypoxic and nutrient deficient microenvironment. This clinical observation has been reproduced in vitro by Esumi and coworkers, who demonstrated the remarkable tolerance of pancreatic cancer cell lines towards nutrient deprivation, and proposed this as a possible target for new anti-cancer agents.[2] Since then, numerous compounds, the majority being natural products, have been discovered to have preferential cytotoxicity against pancreatic cancer cells under nutrient deprivation, while showing no toxicity under nutrient sufficient conditions.[3] These "anti-austerity" compounds are potential new leads in the fight against pancreatic cancer and could, more generally, lead to a greater understanding of cancer cell metabolism and austerity mechanisms.

We have chosen to target several anti-austerity natural products for total synthesis, e.g., (+)-angelmarin (**1**),[4–8] (–)-3,8-dihydroxy-9-methoxypterocarpan (DMPC, **2**),[9] and (±)-nicolaioidesin B (**3**),[10] with an aim of developing flexible synthetic strategies that are amenable to analogue generation, the elucidation of structure–activity relationships (SAR) and the generation of biological probe molecules with applications to mechanism of action studies and target identification. Herein we report the concise and flexible total synthesis of (±)-nicolaioidesin B (**3**), utilizing a highly regio- and diastereoselective Diels–Alder reaction as a key step.

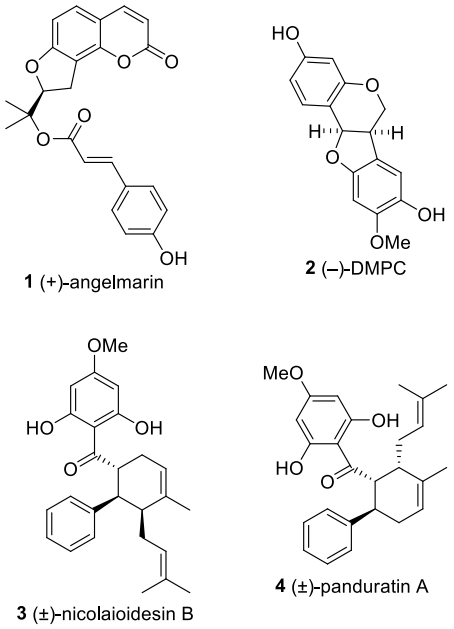


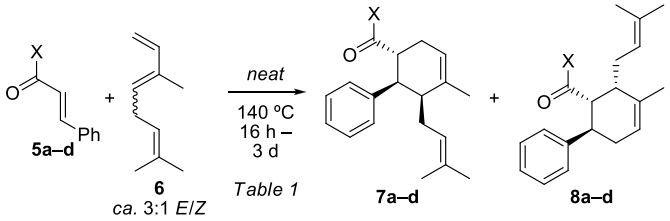
Figure 1. Anti-austerity natural products.

In 2007, Kadota and coworkers reported the isolation of several anti-austerity natural products from the rhizomes of *Boesenbergia pandurata*.[10] Amongst these, the most potent were the regioisomeric cyclohexenes nicolaioidesin B (**3**) and panduratin A (**4**), each with 100% preferential cyctotoxicity (PC_{100}) against PANC-1 cells in nutrient-deprived medium (NDM) at 2.5 μM. (±)-Nicolaioidesin B had previously been isolated from *Renealmia nicolaioides* in a search for novel cancer chemopreventive agents,[11] and (±)-panduratin A was first isolated from *Boesenbergia pandurata* in 1984.[12] Both of these plant sources are of the Zingiberaceae family, and have been associated with traditional medicine uses.[10–12] Panduratin A has been reported to have cytotoxic,[13–16] anti-angiogenic,[17] anti-inflammatory,[18–20] anti-HIV-1 protease[21] and anti-microbial activities.[22,23] It has also been reported to inhibit the dengue 2 virus NS3 protease competitively,[24] although a recent NMR-based investigation failed to show binding of synthetic **4** to this enzyme.[25]

The cyclohexenyl natural products **3** and **4**, and related panduratins and nicolaioidesins, are formally the products of Diels–Alder reactions between substituted chalcones and 1,3-dienes, and reactions of this type are likely key steps in their biogenesis.[11] Nicolaioidesin B (**3**) and panduratin A (**4**) were first synthesised as a mixture of regioisomers, via a high temperature Diels–Alder reaction between a substituted chalcone and ocimene, however the regioisomer ratio was not reported, nor were the isomers separated.[26] A highly selective silver nanoparticle promoted Diels–Alder reaction of a substituted chalcone with (*E*)-β-ocimene was used by Porco and co-workers in their total synthesis of **4**.[27] The key cycloaddition step is general for 2′-hydroxychalcones and gave complete selectivity for the panduratin A-type regioisomer and *ca*. 95:5 *endo*/*exo* selectivity. Recently, and during the course of our work, McLeod and co-workers reported a more modular approach to these natural products, utilising as the key step, a high pressure Diels–Alder reaction of (*E*)-β-ocimene with cinnamate-type dienophiles.[25]

In order to allow flexible access to the natural product **3** and analogues for SAR studies, we examined the Diels–Alder reaction of cinnamate analogues **5a–d** with *trans*-β-ocimene (**6**) under thermal conditions (Table 1). We envisioned the formation of **3** and **4,** and analogues thereof, via nucleophilic addition reactions at the product carbonyl, utilising appropriate aryllithium reagents. Commercially available β-ocimene, supplied as a *ca.* 3:1 mixture of (*E*)- and (*Z*)- isomers, respectively, was used without further purification. Previous work by Chee and coworkers demonstrated that (*Z*)-**6** undergoes polymerisation, rather than a Diels–Alder reaction, when heated with a chalcone dienophile.[26]

Table 1. Diels–Alder reaction between cinnamate derivatives and ocimene.



Entry	X	Ratio **7**/**8**[a]	Yield[b]
a	OMe	75:25	97%
b	OC_6F_5	67:33	96%
c	N(Me)OMe	>98:<2	70%
d	H	n.d.	trace[c]

[a]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.
[b]Combined isolated yield of the regioisomers.
[c]Compound **9** was isolated in 45% yield; trace quantities of the Diels–Alder products **7d**/**8d** were observed.

Initial attempts to engage cinnamate derivatives in cycloaddition reactions with β-ocimene (**6**) under standard conditions (PhMe, reflux) failed to deliver the desired products. However, heating the dienophiles in neat β-ocimene (2.25 equivalents of the (*E*)-isomer) at 140 °C for 16 hours to 3 days promoted the desired cycloaddition reactions. Methyl (*E*)-cinnamate provided a *ca*. 75:25 mixture of panduratins I (**7a**) and

H (**8a**),[28] corresponding to the nicolaioidesin B and panduratin A-type regioisomers, respectively. The selectivity we observe for this cycloaddition reaction is comparable to that observed by McLeod for this reaction under high pressure (19 kbar) conditions (74:26).[25]

The Diels–Alder reaction using the more electrophilic pentafluorophenyl ester (**5b**) reduced the regioselectivity to *ca*. 67:33. The diminished selectivity for the nicolaioidesin B-type regioisomer is consistent with the observations of McLeod and coworkers, who report a drop from 76:24 to 71:29 ratio in the high pressure reaction in going from an ethyl to 2,2,2-trifluoroethyl ester.[25] However, the role of steric interactions in this reaction is also likely to be important and cannot be accounted for without detailed computational analysis.

To our delight, the Weinreb amide[29] **5c** reacted with **6** with complete regio- and diastereoselectivity, to give the nicolaioidesin B-type isomer **7c**. The highest nicolaioidesin B-type selectivity reported by McLeod and coworkers was for the Diels–Alder reaction of (*E*)-cinnamonitrile (90:10). The McLeod group rationalised the regiochemical outcome of the Diels–Alder reaction of methyl cinnamate with ocimene on the basis of frontier molecular orbital interactions, however, the selectivity trend with differing cinnamate derivatives was not accounted for.[25] Nevertheless, the high selectivity achieved with the Weinreb amide **5c** provides a synthetically attractive route to nicolaioidesin B (**3**) and analogues.

In the case of (*E*)-cinnamaldehyde (**5d**), the expected Diels–Alder products, **7d** and **8d**, were observed in only trace quantities, along with a number of other unidentified products, however, alcohol **9** was isolated in 45% yield. The gross structure of this compound was readily deduced through the application of standard 1D and 2D NMR techniques, however, the relative configuration was assigned by X-ray crystallography (Figure 2).[30]

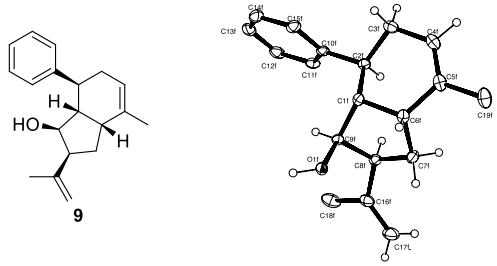
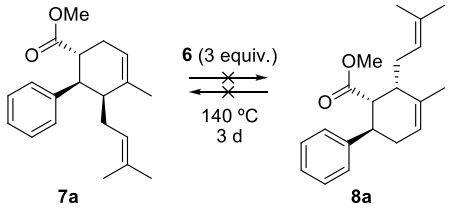


Figure 2. ORTEP representation of the X-ray crystal structure of **9**.

Compound **9** could conceivably arise from an intramolecular carbonyl-ene reaction of an initially formed panduratin A-type Diels–Alder product **8d**. Given the selectivities we have observed for nicolaioidesin B-type products, and considering the 7.2:1 ratio of **7d**/**8d** observed in the high pressure Diels–Alder reaction of **5d** with **6**,[25] the yield of **9** is surprisingly high. Although, in principle, **9** could be formed by initial carbonyl-ene reaction, followed by intramolecular Diels–Alder reaction, aliphatic and aromatic aldehydes do not generally undergo intermolecular carbonyl-ene reactions under thermal conditions.[31] Alternatively, the Diels–Alder reaction of **5d** with **6** may be reversible under the high temperature employed.

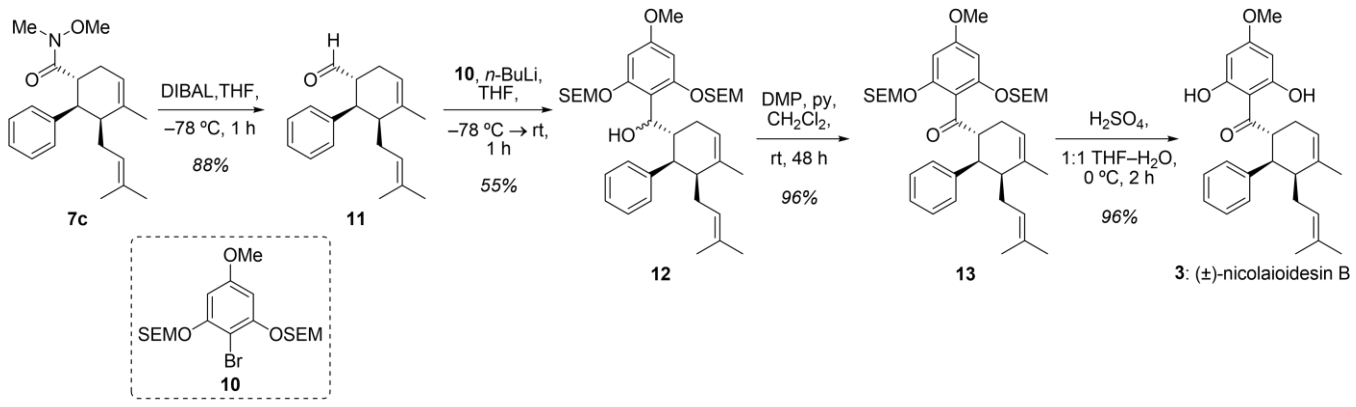
In order to investigate the potential reversibility of these Diels–Alder reactions, **7a** and **8a** were separately subjected to heating with **6** at 140 °C for 3 days (Scheme 1). In each case, ^{1}H NMR analysis of the crude product showed no sign of the other regioisomer, demonstrating that, for this substrate at least, the Diels–Alder reaction is not reversible. Nevertheless, it is still conceivable that the reaction of **5d** is reversible under these conditions.



Scheme 1. Investigation of Diels–Alder reaction reversibility.

With significant quantities of Weinreb amide **7c** at hand, its conversion into nicolaioidesin B (**3**) was investigated (Scheme 2). All attempts to react **7c** with the aryllithium reagent derived from 2-(trimethylsilyl)ethoxymethyl (SEM)-protected aryl bromide **10** were unsuccessful, presumably due to significant steric interactions between the two bulky reaction partners. Reduction of **7c** provided the more reactive aldehyde **11**, which underwent organolithium addition to give an inconsequential *ca*. 60:40 mixture of diastereomeric alcohols **12**. Oxidation with the Dess–Martin periodinane (DMP) reagent afforded ketone **13**, which efficiently underwent deprotection with H_2SO_4 in 1:1 THF–MeOH to give (±)-nicolaioidesin B (**3**). All spectroscopic data for synthetic **3** agreed with that previously reported.[10,11]

In summary, we have completed the total synthesis of nicolaioidesin B (**3**) in five steps from Weinreb amide **5c**, employing a highly regio- and diastereoselective Diels–Alder



Scheme 2. Completion of the total synthesis of (±)-nicolaioidesin B (**3**).

reaction as the key step. The route developed is highly flexible, particularly with respect to modification of the aryl ketone subunit, thereby expediting the synthesis of analogues for SAR studies. Further work of this nature will be reported in due course.

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Supplementary Material

Supplementary data (experimental procedures and characterisation data for all new compounds; X-ray crystallography procedures for **9**; ^{1}H and ^{13}C NMR spectra for **3**) associated with this article can be found, in the online version, at doi: XX.XXXX/X.