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# Towards the total synthesis of colletofragarones: constructing the macrocyclic lactone by high pressure-mediated intramolecular Diels–Alder reaction

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ABSTRACT

We report herein an intramolecular Diels–Alder approach towards the construction of the macrocyclic lactone ring and the perhydrobenzofuran system of the colletofragarones, novel metabolites produced by fungi of the genus *Colletotrichum* that are responsible for inhibition of germination of the conidia in these species.



We have previously reported[1] that methyl 2-methyl-5-vinyl-3-furoate acts as a diene, reacting solely by extra-annular cycloaddition under high-pressure conditions with a variety of doubly activated dienophiles without concomitant rearomatisation of the cycloadducts. This outcome presented us with a potential means of constructing the tricyclic core of the colletofragarones, (Fig. 1), a closely related pair of structures that inhibit germination of the conidia of the fungus *Colletotrichum fragariae*.[2] Although their gross structures have been elucidated, the configurations at the three stereogenic centres on the macrocyclic lactone have not yet been determined.[3]

The dictyosphaeric acids (Fig. 2) are related structures isolated from the fungus F01V25 found upon the alga *Dictyosphaeria versluyii*.[4] Colletofragarones A1 and A2 differ from dictyosphaeric acids A and B in that they do not contain the carboxylic acid group and also display a different hydroxylation pattern.

The colletofragarones and dictyosphaeric acids thus represent novel, as yet incompletely defined, structures in some cases, demonstrating antifungal activity and a total synthesis would provide a means of establishing their complete structures as well as giving access to analogues.

The key step in our synthetic strategy involves construction of the tricyclic system **2** from the 2-vinylfuran precursor **3** by an intramolecular Diels–Alder (IMDA) reaction to build both the macrocyclic lactone and the cyclohexenone (Scheme 1). The dienophile could be introduced by a Horner–Wadsworth–Emmons reaction with aldehyde **4**. The approach has the twofold requirements of being able to react selectively with the diene comprising the exocyclic vinylic substituent as opposed to the furan diene and avoiding subsequent rearomatisation of the initial cycloadduct to regenerate the furan. Subsequent conjugation of the cyclohexene

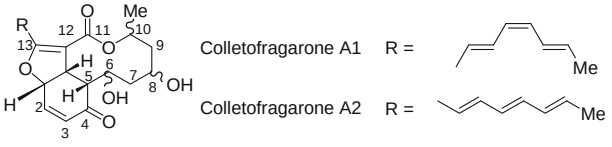


**Figure 1.** Structures of colletofragarones A1 and A2.

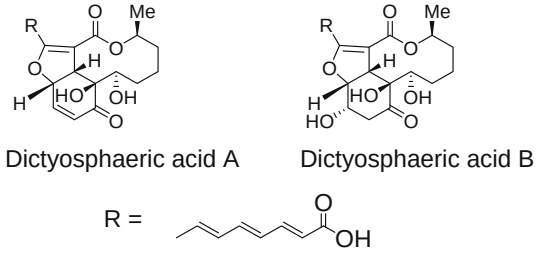


**Figure 2.** Structures of dictyosphaeric acids A and B.

double bond with the ketone sets up the final system although clearly there are stereochemical considerations in obtaining the correct relative stereochemistry.

In this approach, X and Y must be groups that activate the dienophile while providing the potential to be converted to a ketone without destruction of other sensitive functionality.

Esterification of 2-methyl-5-vinyl-3-furoic[1] acid **5** with monoprotected alcohol **6**[5] using EDCI coupling,[6] produced the corresponding ester **7** in 96% yield. Deprotection of the silyl ether with tetrabutylammonium fluoride furnished the corresponding primary alcohol **8** in 80% yield. Finally, the alcohol **8** was oxidised under Swern oxidation conditions, to provide aldehyde **4** in 85% yield (Scheme 2).

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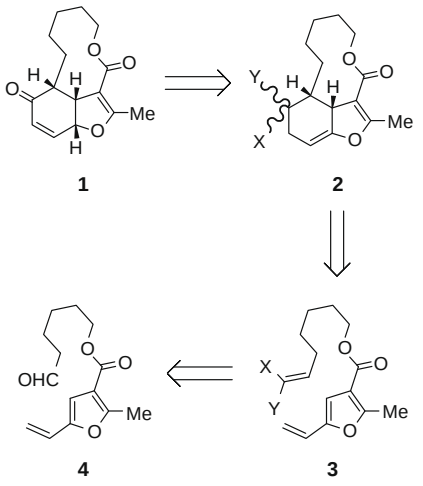
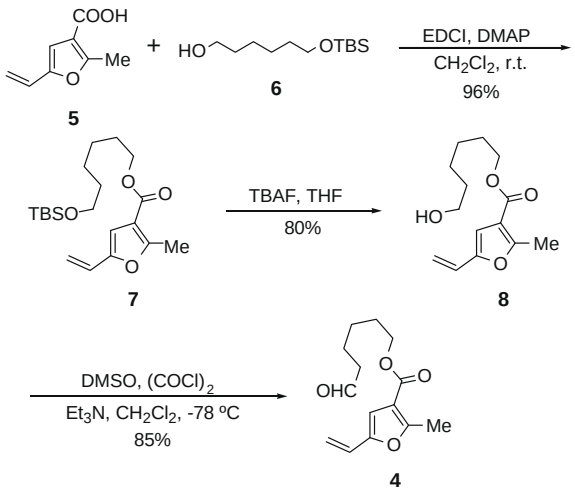


**Scheme 1.** Retrosynthetic analysis of the tricyclic skeleton of the colletofragarones.

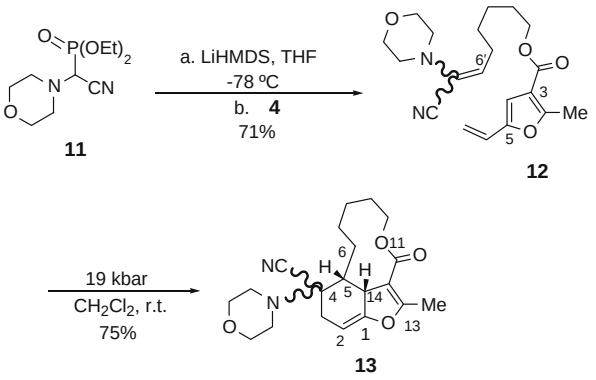


**Scheme 2.** Synthesis of aldehyde **4**.

The next step was the synthesis of the Horner–Wadsworth–Emmons reagent, required to introduce the α-morpholineacrylonitrile functionality.[7] Reaction of chloroacetonitrile **9** with morpholine and triethylamine in acetone[8] with stirring at room temperature overnight, furnished α-morpholineacrylonitrile **10** in 49% yield. Subsequent treatment of **10**, first with lithium hexamethyldisilazide (LHMDS) and then with diethyl chlorophosphite, afforded the phosphonate **11**, which was used without purification (Scheme 3).

Horner–Wadsworth–Emmons olefination of aldehyde **4** using the anion generated from phosphonate **11** with LHMDS[9] led to α-morpholinoacrylonitrile **12**[10] as a 3:1 mixture of alkene geometric isomers. This material was unreactive under a range of conditions surveyed for promoting Diels–Alder reaction but underwent cycloaddition under ultra-high pressure ($CH_2Cl_2$, 20 °C, 19 kbar) to yield the desired tricyclic adduct **13**[11] as a 7:2 mixture of C-4 epimers possessing the basic carbon skeleton of the colletofragarones (Scheme 4), resulting from the desired extra-annular cycloaddition, without subsequent double bond migration.

**Scheme 3.** Synthesis of phosphonate **11**.



**Scheme 4.** Synthesis of tricyclic compound **13**.

In the $^1$H NMR spectrum of the product **13**, the signals of the exocyclic double bond (δ 5.13 and 5.60) and the vinylic proton of carbon **6′** (δ 5.22 and 5.91) of precursor **12** had been replaced by resonances corresponding to a vinylic methine (δ 5.26 and 5.95) and the methine at the 6–5 ring junction (δ 5.11). In the $^{13}$C NMR the signals for the double bond (δ 108.8 and 113.1) and the vinylic carbon at C-**6′** (δ 141.5) of the starting material had disappeared while signals corresponding to carbons in the endocyclic double bond (δ 121.9 and 126.1) and a new methine group (δ 45.5) were present. The relative stereochemistry of **13** was tentatively assigned on the basis of the 3.4 Hz coupling constant between H5 and H14. This coupling constant is consistent with an axial–equatorial coupling indicating a cis junction.

In summary, we have developed a synthetic route to the tricyclic system of colletofragarones, efficiently generating the macrocyclic lactone via an IMDA reaction of a 2-vinylfuran substrate with a dienophile tethered at C-4 of the furan, avoiding a subsequent aromatising double bond migration to reform the furan.

## Acknowledgements

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10. *Construction of Diels–Alder precursor* **12**: To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.6 mL, 3.0 mmol, 3.1 equiv) in THF (20 mL) was added dropwise *n*-butyllithium (2.5 M in hexanes, 1.2 mL, 3 mmol, 3.1 equiv) at −78 °C under nitrogen. The solution was stirred for 15 min, and a solution of

diethyl [cyano(morpholino)methyl]phosphonate (814.2 mg, 3.1 equiv) in THF (3 mL) was added. The mixture was stirred for a further 1 h, then 6-oxohexyl 2-methyl-5-vinyl-3-furoate (243.6 mg, 1.0 mmol) in THF (3 mL) was added dropwise at −78 °C. After 1 h at this temperature, the reaction mixture was quenched with 5% HCl (2 mL). The aqueous layer was extracted with ether (3 × 25 mL), the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel, eluting with light petroleum–diethyl ether (2:1), furnished **12** as an inseparable 3:1 mixture of alkene geometric isomers (249.1 mg, 71%). $^1$H NMR ($\delta$, ppm, 250 MHz, $CDCl_3$): 1.38–1.44 (5H, m), 1.66–1.68 (2H, m), 2.28–2.30 (2H, m), 2.53 (3H, s), 2.64–2.66 (2H, m), 2.80–2.85 (3H, m), 3.65–3.72 (4H, m), 4.14–4.20 (2H, m), 5.13 (1H, d, *J* 11.3), 5.22 (0.75H, t, *J* 7.9), 5.60 (1H, d, *J* 17.5), 5.91 (0.25H, t, *J* 7.9), 6.35–6.42 (1H, m), 6.42 (1H, s). $^{13}$C NMR ($\delta$, ppm, 100.4 MHz, $CDCl_3$): 14.2 ($CH_3$), 25.7 ($CH_2$), 26.0 ($CH_2$), 27.2 ($CH_2$), 28.3 ($CH_2$), 28.8 ($CH_2$), 29.7 ($CH_2$), 49.6 ($CH_2$), 51.7 ($CH_2$), 64.2 ($CH_2$), 66.5 ($CH_2$), 66.9 ($CH_2$), 108.8 (CH), 113.1 ($CH_2$), 114.8 (4 °C), 115.2 (C≡N), 121.8 (CH), 124.7 (CH), 126.1 (4 °C), 141.5 (CH), 151.2 (4 °C), 159.1 (4 °C), 164.2 (C=O, ester). I. R. $\nu_{max}$ (film, $cm^{-1}$): 2835, 2227, 1725, 1624, 1153. MS (*m*/*z*, %, E. I.): 358 ([M]$^+$, 32), 281 (11), 231 (13), 223 (62), 181 (24), 169 (23), 151 (55), 135 (76), 119 (35), 69 (100), 57 (16). HRMS: $C_{20}H_{26}N_2O_4$, calcd: 358.1893, found: 358.1904.

11. *High pressure reaction procedure*: A solution of **12** (201.3 mg, 0.6 mmol) in dichloromethane (8 mL) was subjected to high pressure (19 kbar) for 24 h at 25 °C. On depressurisation, the solution was filtered through a plug of cotton wool, and the solvent removed under reduced pressure to afford the crude product. Purification by flash column chromatography on silica gel, eluting with light petroleum–diethyl ether (2:1) furnished the desired compound **13** as a 7:2 mixture of C-4 epimers (151 mg, 75%). $^1$H NMR ($\delta$, ppm, 250 MHz, $CDCl_3$): 1.43 (3H, s), 1.70 (2H, q, *J* 7.0 Hz), 2.23–2.33 (3H, m), 2.45 (3H, s), 2.71 (2H, t, *J* 4.6 Hz), 2.88–2.91 (4H, m), 3.75 (4H, t, *J* 4.5 Hz), 4.18 (2H, m), 5.11 (1H, d, *J* 3.4 Hz), 5.26 (0.7H, m), 5.95 (0.3H, m). $^{13}$C NMR ($\delta$, ppm, 100.4 MHz, $CDCl_3$): 14.3 ($CH_3$), 25.8 ($CH_2$), 28.4 ($CH_2$), 28.9 ($CH_2$), 30.7 ($CH_2$), 33.8 (CH), 45.5 (CH), 49.5 ($CH_2$), 51.7 ($CH_2$), 64.1 ($CH_2$), 66.3 ($CH_2$), 64.2 ($CH_2$), 66.7 ($CH_2$), 98.4 (CH), 106.3 (4 °C), 107.4 (4 °C), 114.9 (C≡N), 121.9 (4 °C), 126.1 (CH), 153.6 (4 °C), 165.5 (4 °C), 167.2 (C=O, ester). I. R. $\nu_{max}$ (film, $cm^{-1}$): 2820, 2250, 1735, 1644, 1203. MS (*m*/*z*, %, E. I.): 358 ([M]$^+$, 44), 343 (8), 252 (23), 223 (42), 175 (16), 159 (9), 145 (55), 130 (87), 102 (19), 69 (100), 57 (16). HRMS: $C_{20}H_{26}N_2O_4$, calcd: 358.1893, found: 358.1945.