## Natural Product Synthesis

## Total Synthesis and Structural Reassignment of (+)-Dictyosphaeric Acid A: A Tandem Intramolecular Michael Addition/Alkene Migration Approach\*\*

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Given the recent increase in bacterial resistance, the search for new and more effective antibiotics is an ever-pressing concern. The polyketide-derived natural products (+)-dictyosphaeric acid A (1) and (+)-dictyosphaeric acid B (2) were isolated by Ireland and co-workers in 2004 from a fungal isolate (F01V25) obtained from the green alga Dictyosphaeria versluyii.<sup>[1]</sup> Interestingly, when screened for biological activity, (+)-dictyosphaeric acid A (1) exhibited antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus faecium, and Candida albicans. In marked contrast, (+)-dictyosphaeric acid B (2) did not exhibit any significant antibacterial activity, which presumably indicates the importance of the  $\alpha$ , $\beta$ -unsaturated ketone in the pharmacophore of dictyosphaeric acid A(1). As shown in Scheme 1, both natural products are based on a highly oxygenated decalactone core and triene carboxylic acid side-chain, with the only difference being that the enone double bond of 1 is hydrated in 2. Dictyosphaeric acid A (1) has five stereocentres, four of which are contiguous, whereas dictyosphaeric acid B (2) has six stereocentres, five of which are contiguous. The relative stereochemical configuration of both molecules was determined by extensive 1D and twodimensional (2D) NMR studies<sup>[1]</sup> [key nOe and rotatingframe Overhauser effect (rOe)<sup>[2]</sup> correlations shown in Scheme 1]. However, assignment of the relative configuration at C6 relied on a single correlation (not conclusive in a conformationally mobile system) and the absolute configu-

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**Scheme 1.** Dictyosphaeric acid A (1) and B (2), colletofragarones A1 (3) and A2 (4), and key nOe and rOe correlations supporting the assignment of the relative configuration of 1.

ration was not elucidated.<sup>[1]</sup> These natural products pose a significant synthetic challenge, not only due to their structural complexity, but also due to the need for a flexible and convergent route, which would give easy access to analogues for biological screening and SAR (structure–activity relation-ship) studies.

The only other natural products isolated to date, which have the same tricyclic decalactone-based carbon skeleton as the dictyosphaeric acids, are the fungal metabolites colleto-fragarone A1 (3) and colletofragarone A2 (4).<sup>[3]</sup> To date, there have been no total syntheses reported for either pair of natural products, although our group published a route to novel dictyosphaeric acid analogues in 2008,<sup>[4]</sup> and Harwood et al. recently disclosed model studies in the colletofragarone area.<sup>[5,6]</sup> Herein, we report the first total synthesis of dictyosphaeric acid A (1) which also serves to clarify the uncertainties of relative and absolute configuration referred to above.

The retrosynthetic analysis adopted in the current study is shown in Scheme 2. Initial disconnection would give the activated enol **5** and an organometallic triene such as stannane **6**, with a view to utilising a Pd-mediated crosscoupling approach. Then, we envisaged introducing the 1,2diol portion of the decalactone ring through dihydroxylation or epoxidation/hydrolysis of exocyclic enone **7**. We proposed to form conjugated alkene **7** by isomerisation of alkene **8** which, in turn, would be accessed from  $\beta$ -keto ester **9** using a doubly tethered intramolecular Michael addition (IMA) of the type developed in earlier model studies.<sup>[4]</sup> We anticipated preparing macrocyclic alkene **9** by a ring-closing metathesis



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Scheme 2. Retrosynthetic analysis.

(RCM) reaction from precursor diene **10**, which could be further simplified to functionalized cyclohexenone **11**, propenyl organometallic reagent **12** and carboxylic acid **13**.

The starting point in the synthesis was the known enantiometrically enriched (>99% ee) iodide (-)-11.<sup>[4,7]</sup> This was expediently functionalized using a Suzuki-Miyaura coupling with the commercially available propenvl MIDA boronate 14<sup>[8]</sup> and *trans*-bromo[*N*-succinimidyl-*bis*(triphenylphosphine)]palladium(II) (15), developed within our own group,<sup>[9]</sup> as catalyst. Notably, the corresponding vinyl derivative (as opposed to the propenyl variant) could also be prepared, but proved to be prone to decomposition, even when stored at -20 °C. Straightforward elaboration to RCM precursor 10 was achieved by desilylation and esterification with carboxylic acid 13,<sup>[10]</sup> utilizing T3P as the coupling reagent (Scheme 3).<sup>[11,12]</sup> Treating substrate 10 with the Hoveyda-Grubbs second generation catalyst<sup>[13]</sup> furnished the 13-membered macrocycle 9 in excellent yield (82%) and, interestingly, with the exclusive formation of the (Z)alkene ( ${}^{3}J = 11.5 \text{ Hz}$ ).

The stage was then set for one of the key reaction sequences of the synthesis: IMA of 9 and then alkene isomerization to give the exocyclic enone 17. Initially, the IMA was achieved with either NaH or Et<sub>3</sub>N/Bu<sub>4</sub>NCl (see Table in Scheme 3, entries 1 and 2), and then the resulting alkene 8 was isomerized using DBU to give the conjugated alkene. However, the isomerization step was particularly lowyielding (ca. 30%). Therefore, as both the Michael addition and the alkene isomerization reaction could be performed with an amine base, a tandem "two-step, one-pot" process was investigated (entries 3 and 4). Pleasingly, and after extensive optimization, treatment of enone 9 with sub-stoichiometric piperidine (0.5 equiv) and tetra-butylammonium hydrogensulfate (0.1 equiv) in acetonitrile facilitated the tandem IMA/ alkene isomerization reaction to furnish the exocyclic alkene 17 (65%), along with the un-reacted Michael addition adduct



**Scheme 3.** Conversion of iodide 11 into exocyclic enone 17. Reagents and conditions: a) 14 (1 equiv),  $[(NBS)Pd(PPh_3)_2]$  (15) (3.4 mol%), 3 M K<sub>3</sub>PO<sub>4</sub> (aq.), THF, 60°C, 16 h, 82%; b) TBAF (1.1 equiv), THF, 0°C, 2.5 h; c) 13 (1 equiv), T3P (1.3 equiv), DIPEA (1.95 equiv), PhMe, 0°C to RT, 5 h, 73% (over 2 steps); d) Hoveyda–Grubbs catalyst, 2nd generation (8 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 40°C, 24 h, 82%; e) (optimum conditions) piperidine (0.5 equiv), Bu<sub>4</sub>NHSO<sub>4</sub> (0.1 equiv), MeCN, 85°C, 24 h, 65% 9 + 23% 8; f) piperidine (0.5 equiv), THF, 70°C, 24 h, 62% 17, 26% 8. NBS = N-bromosuccinimide, TBAF = *tetra*-butylammonium fluoride, DIPEA = N,N-di-isopropyl(ethyl)amine, T3P = propane phosphonic acid anhydride.

**8** (23%) which was readily converted into **17** using piperidine in THF. The requirement for a phase transfer catalyst in the IMA using organic amines is fascinating (no IMA occurs in its absence) but not yet fully understood.

Interestingly, the isomerized enone product was formed as a single diastereomer and as a single alkene geometric isomer; X-ray crystallography<sup>[14]</sup> confirmed that this was the (E)-enone **17**, as depicted in Scheme 4, and not as the (Z)-enone **7** as proposed in the retrosynthetic analysis (Scheme 2).



**Scheme 4.** X-ray crystal structure<sup>[14]</sup> of (*E*)-enone **17** depicted using Mercury 2.2.

Clearly, this observation concerning the 5,6-alkene configuration had implications with respect to the strategy for installing the 5*S*,6*S*-diol of dictyosphaeric acid A (1). Dihydroxylation of compound 17 from the more accessible top face of the olefin would produce the 5*S*,6*R*-diastereomer whereas nucleophilic epoxidation followed by a regioselective epoxide opening with H<sub>2</sub>O would lead to the correct 5*S*,6*S*-

## Communications

diol configuration with respect to the proposed structures of the natural products.

Frustratingly, various attempts at nucleophilic epoxidation of the exocyclic enone **17** failed. Given the uncertainty concerning the C6 configuration referred to earlier, we therefore turned our attention to dihydroxylation procedures. To our delight, utilising the mildly acidic osmylation conditions developed by Sharpless et al.,<sup>[15]</sup> dihydroxylation of enone **17** proceeded in high yield and with complete diastereoselectivity to produce diol **18** (Scheme 5). Protection of the diol group proved to be far from trivial (e.g. PMBacetal, acetate, TBS- and TMS-ether formation all failed). Ultimately, acetonide protection was successful giving adduct **19**, albeit with the unavoidable formation of the mixed acetal **20**. However, compound **20** could be hydrolysed back to diol **18** (98%) with 2M HCl and thus recycled with reasonable efficiency.

With the acetonide **19** in hand, a triflation/Stille sequence was carried out using trienylstannane **6** (readily prepared



Scheme 5. The elaboration of enone 17. Reagents and conditions: a)  $K_2[OsO_2(OH)_4]$  (1 mol%), NMO (1.1 equiv), citric acid (2 equiv), MeCN/tBuOH/H<sub>2</sub>O (1:1:1), RT, 7 d, 95%; b) 2,2-dimethoxypropane (10 equiv), acetone (20 equiv), ( $\pm$ )-CSA (0.1 equiv), PhMe, 80°C, 18 h, 63% 19 + 30% 20; c) KHMDS (2.0 equiv), Tf<sub>2</sub>O (1.2 equiv), 1,2-DME, -40°C to RT, 1.5 h; d) stannane 6 (1.2 equiv), [Pd<sub>2</sub>dba<sub>3</sub>] (10 mol%), LiCl (3 equiv), (2-furyl)<sub>3</sub>P (0.3 equiv), 1,2-DME, 85°C, 1 h, 50°C 16 h, 60% (2 steps); e) LiHMDS (2 equiv), Et<sub>3</sub>N (3 equiv), TMSCI (3 equiv), THF, -78°C, 1.5 h; f) Pd(OAc)<sub>2</sub> (4.4 equiv), MeCN, RT, 4 d, 59% (2 steps, 83% brsm); g) 80% TFA (aq), CH<sub>2</sub>Cl<sub>2</sub>, RT, 28 h, 100%. CSA = camphorsulfonic acid, dba = dibenzylideneacetone, DME = dimethoxyethane, HMDS = hexamethyldisilazide, NMO = *N*-methylmorpholine-*N*-oxide, TfO = trifluoromethylsulfonate, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

using tandem oxidation chemistry<sup>[16]</sup>). This Pd<sup>0</sup>-catalyzed coupling delivered adduct **22** in a 60% yield over the twostep process. Saegusa–Ito oxidation<sup>[17]</sup> of ketone **22**, through the corresponding silyl enol ether, then proceeded as expected to give enone **23**.

Finally, treatment of compound **23** with aqueous TFA removed both the *tert*-butyl ester and acetonide groups to generate the acid **24**. We were now in a position to determine whether natural dictyosphaeric acid possessed the 5S,6S-diol configuration (as reported in the literature)<sup>[1]</sup> or the 5S,6R-diol configuration, which also seemed compatible with the published 2D NMR experiments. Interestingly, the NMR data for acid **24** was essentially identical to the published<sup>[1]</sup> NMR data, with key comparisons being shown in Table 1 (see the

**Table 1:** Comparison of key <sup>1</sup>H and <sup>13</sup>C NMR data for synthetic (+)-24 and natural (+)-dictyosphaeric acid A (1).<sup>[a,b]</sup>

|          |                                | Synthetic (+)- <b>24</b> |               |                                | Lit. (+)-1 <sup>[1]</sup> |               |
|----------|--------------------------------|--------------------------|---------------|--------------------------------|---------------------------|---------------|
| Position | <sup>13</sup> C <sup>[c]</sup> | $^{1}H^{[d]}$            | mult.,        | <sup>13</sup> C <sup>[c]</sup> | ${}^{1}H^{[d]}$           | mult.,        |
|          |                                |                          | <i>J</i> [Hz] |                                |                           | J [Hz]        |
| 2        | 141.3                          | 6.59–6.57                | m             | 141.2                          | 6.58                      | dd, 10.5, 3.3 |
| 3        | 129.1                          | 6.09                     | dd, 10.2, 1.0 | 129.1                          | 6.09                      | dd, 10.5, 0.8 |
| 4        | 202.9                          | _                        |               | 202.9                          | -                         |               |
| 5        | 78.1                           | -                        |               | 78.0                           | -                         |               |
| 6        | 74.1                           | 3.79                     | d, 8.8        | 74.1                           | 3.80                      | d, 8.9        |
| 10       | 75.3                           | 4.86-4.82                | m             | 75.3                           | 4.84                      | m             |
| 14       | 52.3                           | 4.22                     | d, 8.8        | 52.2                           | 4.23                      | d, 8.7        |

[a] For a full comparison, as well as copies of spectra, see the Supporting Information. [b] Solvent: CDCl<sub>3</sub>/CD<sub>3</sub>OD. [c] 125 MHz. [d] 500 MHz.

Supporting Information for a full comparison). In addition, the optical rotation of acid **24** ( $[\alpha]_D = +116.9, c=0.12$ , MeOH) was very close to the published value for dictyosphaeric acid A (lit.<sup>[1]</sup> + 126, c = 0.22, MeOH). We therefore concluded that (+)-dictyosphaeric acid A actually possesses the 5S,6R-**24** structure and not that with the 5S,6S-diol configuration originally reported.<sup>[18]</sup>

In summary, we have developed a concise and convergent synthesis of the antibacterial natural product (+)-dictyosphaeric acid A (24), which proceeds in twelve steps from known iodide (-)-11 in an overall yield of 10%. Through synthesis, we were able to correct the published (minor) structural mis-assignment, and to confirm the absolute configuration of dictyosphaeric acid A (+)-24. We are currently extending this route to prepare dictyosphaeric acid B and the colletofragarones. We are also exploiting the efficiency and diversification potential of the synthetic route to prepare a small library of dictyosphaeric acid analogues for biological screening. These results, along with a full account of this work, will be published in due course.

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- [18] After the preparation of this manuscript, a pre-print was sent to Professor C. M. Ireland, University of Utah, who replied (email correspondence dated April 21, 2010) stating that "The hydroxy at C6 is up and the stereochemistry *R*. It would appear that there was an error made in translating the stereoview to a flat drawing."