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A Convergent Synthesis of the Tricyclic Core of the Dictyosphaeric Acids

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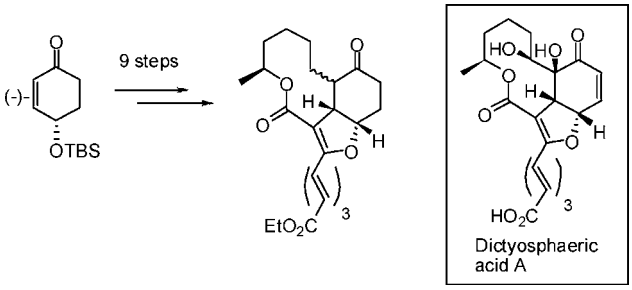
ABSTRACT



The first synthetic route to the tricyclic core of the dictyosphaeric acids has been established starting from readily available (*S*)-(−)-4-(*tert*-butyldimethylsilyloxy)cyclohexenone and involving 9 steps, including a ring-closing metathesis to produce a 13-membered macrolactone, and a doubly tethered intramolecular Michael addition.

Dictyosphaeric acids A (**1**) and B (**2**) were isolated by Ireland and co-workers in 2004[1] from the fermentation of a previously undescribed *Penicillium* sp. F01V25, itself obtained from the marine algae *Dictyosphaeria versluyii*. The dictyosphaeric acids are polyketide-derived natural products containing a highly oxygenated tricyclic core comprising decalactone, dihydrofuran, and cyclohexanone components (Figure 1). Dictyosphaeric acid A has 5 stereogenic centers, 4 of which are contiguous, and dictyosphaeric acid B has 6 stereogenic centers, 5 of which are contiguous, and both contain an unusual polyene carboxylic acid side chain. The relative stereochemistry of the dictyosphaeric acids was determined by extensive 1D and 2D NMR studies[1] but, as yet, the absolute stereochemistry is unknown.

When subjected to biological screening, dictyosphaeric acid A exhibited antibacterial activity toward Gram-positive bacteria and inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA).[1] On the other hand, dictyosphaeric acid B did not exhibit any significant biological activity,[1] which presumably indicates the importance of the α,β-unsaturated ketone in the antibacterial pharmacophore of dictyosphaeric acid A.

The only other structurally related natural products are the colletofragarones A1 (**3**) and A2 (**4**), isolated by Ueno and co-workers in 1996[2] from the fungus *Colletotrichum fragariae* and shown to act as germination inhibitors. The colletofragarones have the same carbon skeleton as the dictyo-

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(1) Bugni, T. S.; Janso, J. E.; Williamson, R. T.; Feng, X.; Bernan, V. S.; Greenstein, M.; Carter, G. T.; Maiese, W. M.; Ireland, C. M. *J. Nat. Prod.* **2004**, *67*, 1396−1399.

(2) Inoue, M.; Takenaka, H.; Tsurushima, T.; Ueno, T. *Tetrahedron Lett.* **1996**, *37*, 5731−5734.

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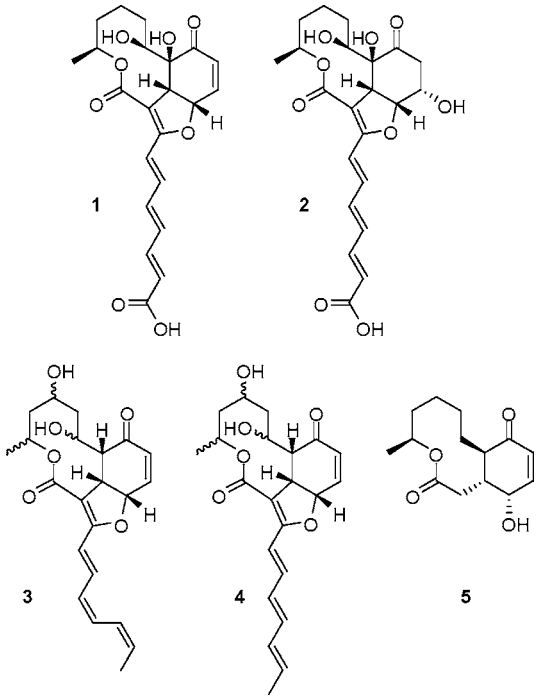


Figure 1. Dictyosphaeric acids, colletofragarones, and Sch 642305.

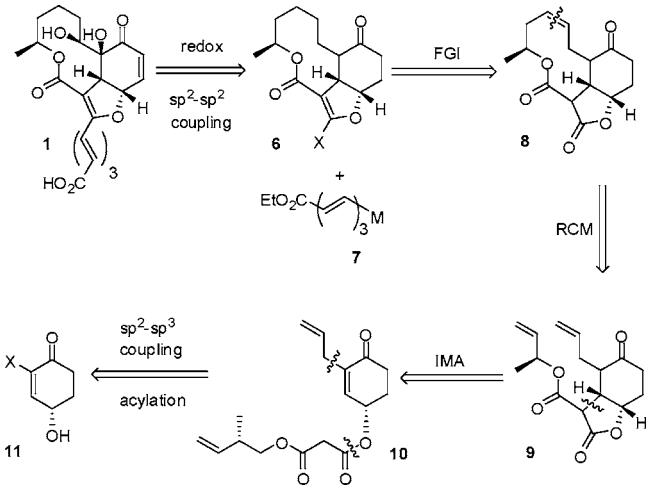
sphaeric acids, although they differ in terms of the oxygenation pattern of the 10-membered ring and also lack the carboxylic acid moiety at the terminus of the triene side chain. The relative and absolute stereochemistry of the colletofragarones has yet to be fully assigned.

To date, there have been no reported syntheses of the dictyosphaeric acids (or the colletofragarones[3]) although there have been several publications on the synthesis of the related bicyclic bacterial DNA primase inhibitor, (+)-Sch 642305 (**5**).[4]

Herein, we report the first synthesis of the tricyclic core of the dictyosphaeric acids by a convergent route that should also allow access to the dictyosphaeric acid and colletofragarone natural products, as well as novel synthetic analogues of both natural product families, to probe further the biological activity. The retrosynthetic analysis adopted in this research is illustrated in Scheme 1.

Thus, redox simplification and a cross-coupling disconnection leads from dictyosphaeric acid **1** to precursors **6** and **7**. Compound **6** should be available from γ-lactone **8**, and by also introducing unsaturation into the decalactone portion of **8**, ring-closing metathesis (RCM) can be employed to construct the tricyclic ring system. The metathesis precursor

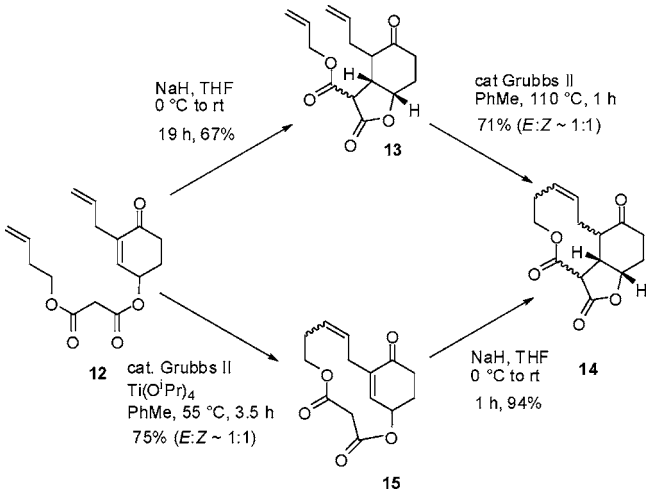
Scheme 1. Retrosynthetic Analysis



9 appeared to be accessible using the intramolecular Michael addition (IMA)[5] of β-keto ester **10**, which in turn should be available by straightforward elaboration of functionalized cyclohexenone **11**.[6,7]

Before commencing on the synthesis outlined in Scheme 1, model studies were carried out to validate this approach to the tricyclic decalactone core (Scheme 2).

Scheme 2. Model Studies to the Tricyclic Decalactone Core



The readily available divinyl precursor **12**[8] was first subjected to IMA using sodium hydride in THF. The bicyclic lactone **13** was obtained with the expected *syn*-ring junction

(3) For colletofragarone analogues see: Drew, M. G. B.; Jahans, A.; Harwood, L. M.; Apoux, S. A. B. H. *Eur. J. Org. Chem.* **2002**, 3589−3594.

(4) (a) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2005**, *46*, 6633−6636. (b) Ishigimi, K.; Katsuta, R.; Watanabe, H. *Tetrahedron* **2006**, *8*, 2224−2230. (c) Snider, B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283−1286. (d) Trauner, D.; Wilson, E. M. *Org. Lett.* **2007**, *7*, 1327−1329. (e) Fujioka, H.; Ohba, Y.; Nakahara, K.; Takatsuji, M.; Murai, K.; Ito, M.; Kita, Y. *Org. Lett.* **2007**, *9*, 5605−5608.

(5) Little, R. D.; Masjedizadeh, M. R. *Org. React.* **1995**, *47*, 315−552.

(6) Danishefsky, S. J.; Simoneau, B. J. *J. Am. Chem. Soc.* **1989**, *111*, 2599−2604.

(7) (a) Morgan, B. S.; Hoenner, D.; Evans, P.; Roberts, S. M. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2807−2809. (b) Bickley, J. F.; Evans, P.; Morgan, B. S.; Roberts, S. M. *Tetrahedron*: *Asymmetry* **2006**, *17*, 355−362.

(8) Divinyl compound **12** was readily prepared in racemic form following a similar sequence to that shown in Scheme 3.

(NOE) but the reaction was slow and gave mixtures of products, and the yield was disappointing. Generally, intramolecular reactions have advantages over the equivalent intermolecular reactions due to gains in reaction rates. We reasoned that, by having a double tether, the cyclization process would be further facilitated. We therefore decided to first prepare the 13-membered compound **15** and then look at the "doubly tethered intramolecular Michael addition" (DTIMA) to install the γ-lactone and the decalactone systems at the same time.

As can be seen (Scheme 2), RCM on the divinyl compound **12** produced the required macrolactone **15** and on treatment with NaH/THF the DTIMA proceeded cleanly and in 1 h (rather than overnight) to give the required product **14** in an excellent 94% yield. The RCM-DTIMA sequence shown therefore showed great promise as a rapid and efficient entry to the tricyclic macrolide core of the dictyosphaeric acids.

A short study to determine the optimum conditions for the RCM reaction was then undertaken. As shown in Table 1, performing the reaction at high temperature caused

Table 1. RCM of **12** To Form **15**

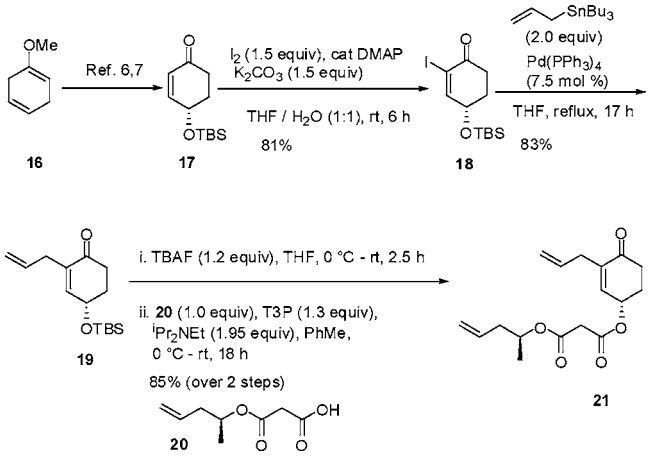
entry	catalyst (mol %)	additive (mol %)	solvent, temp (°C)	yield (%)
1	Grubbs II (10)		PhMe, 110	65[a,b]
2	Grubbs II (10)		CH_2Cl_2, 40	30[c]
3	Grubbs II (10)	$Ti(O^iPr)_4$ (30)	CH_2Cl_2, 40	51
4	Grubbs II (10)	$Ti(O^iPr)_4$ (30)	PhMe, 55	69
5	Grubbs II (20)	$Ti(O^iPr)_4$ (30)	PhMe, 55	75
6	Hoveyda−Grubbs (10)		CH_2Cl_2, 40	69

[a] Unwanted isomerization of product occurred, with the double bond formed through RCM partially moving into conjugtion with the enone system. [b] Analogous conditions with Grubbs I gave only 50% yield, although without significant isomerization. [c] Incomplete conversion of starting material.

unwanted isomerization of the product (entry 1). Lowering the temperature by changing solvent led to incomplete conversion of the starting material and poor yield (entry 2). However, the addition of $Ti(O^iPr)_4$ to the reaction, to break up any chelation between the starting material and Ru-catalyst,[9] resulted in improved yields, with toluene proving to be the best solvent for the reaction (entries 3, 4, and 5). Ultimately though, utilizing the Hoveyda−Grubbs catalyst (10 mol %) in refluxing dichloromethane gave the best and most consistent results (entry 6).

We then went on to apply this RCM-DTIMA sequence to prepare the complete carbon skeleton of the dictyosphaeric acids in enantiomerically pure form; the preparation of the RCM precursor **21** is shown in Scheme 3. The (*S*)-TBS-protected γ-hydroxy enone **17** was readily prepared from commercially available 1-methoxycyclohexa-1,4-diene (**16**) via literature methods {$[\alpha]^{21}_D$ −106.5 (*c* 1.43, CH_2Cl_2; lit.[7]

Scheme 3. Synthesis of RCM Precursor

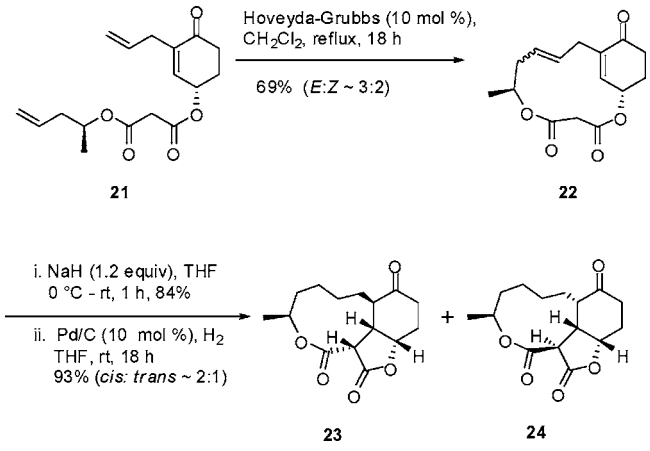


[α]$^{22}_D$ −109.6 (*c* 1.45, CH_2Cl_2)}.[6,7] Enone **17** was then α-iodinated using the procedure developed by Krafft et al.[10] to afford iodo-enone **18** in excellent yield.

Stille coupling of **18** with allyltributylstannane gave allylated adduct **19** (83%), which was subsequently deprotected with TBAF and coupled with acid **20**[11] to give RCM precursor **21** in excellent yield using T3P[12] (conventional coupling agents, such as DCC, EDC, and HATU, were less efficient).

With substrate **21** in hand, we proceeded to study the key RCM step for formation of the 13-membered ring in bicycle **22** (Scheme 4). The optimum conditons involved performing

Scheme 4. Synthesis of Fully Saturated Tricyclic Intermediates



the reaction with 10 mol % of the Hoveyda−Grubbs catalyst in refluxing dichloromethane, as described in Table 1, giving

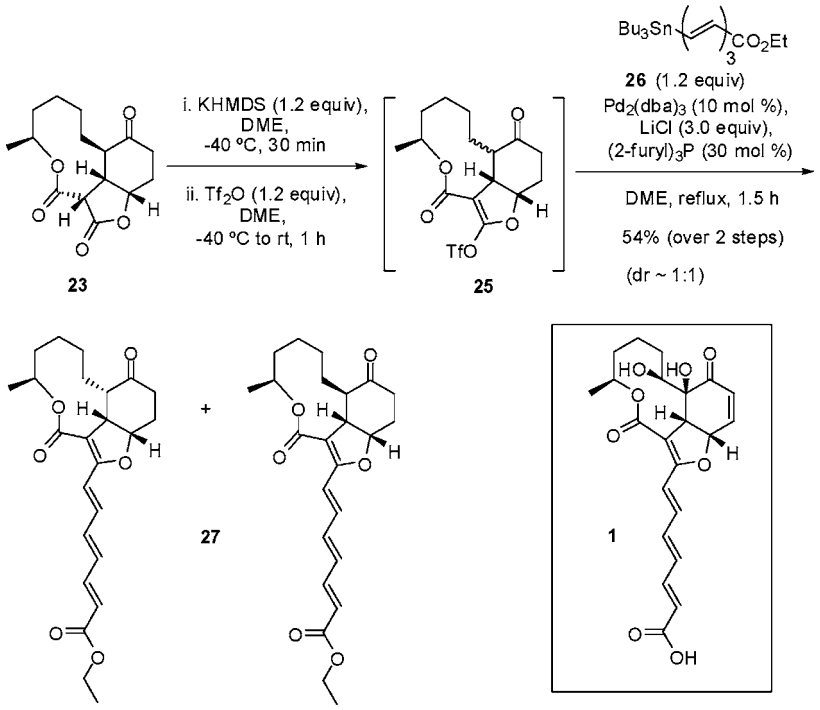
(9) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

(10) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, *8*, 1263−1266.

(11) Acid **20** was prepared in 99% yield from the DCC coupling of the commercially available (*S*)-(+)-4-pentene-2-ol and malonic acid.

(12) Wissmann, H.; Kleiner, H. J. *Angew. Chem., Int. Ed.* **1980**, *19*, 133−134.

Scheme 5. Introduction of Triene Side Chain



the desired bicycle **22** in 69% yield, as a separable 3:2 ratio of *E*/*Z* isomers.[13]

Next, we investigated the DTIMA process on mixture **22** and were delighted to observe that with NaH/THF, cyclization proceeded in high yield (84%); hydrogenation to remove the alkene isomers provided the fully saturated tricyclic intermediates **23** and **24** (Scheme 4), the relative stereochemistry being determined by extensive NOE studies.

To complete the synthesis of the carbon skeleton of the dictyosphaeric acids, what remained was to introduce the triene side chain, and this was achieved through organometallic cross coupling (Scheme 5). Thus, dicarbonyl compound **23**[14] was deprotonated and converted into the vinyl triflate **25**.[15] Without isolation, triflate **25** was successfully coupled to trienylstannane **26**[16] using palladium catalysis giving the target system **27** as an inseparable mixture of two diastereomers (and as compound **23** was the single diastereomer shown, this observation indicates the ease of epimerization adjacent to the cyclohexanone group in these compounds).

In conclusion, we have developed a highly convergent and concise synthesis of the carbon skeleton of the dictyosphaeric acids. The route involves nine linear steps from the readily available (*S*)-(−)-4-(*tert*-butyldimethylsilyloxy)cyclohexenone and incorporates a ring-closing metathesis to produce a 13-membered macrolactone and a doubly tethered intramolecular Michael addition. We are currently optimizing and diversifing this synthetic route to allow the total synthesis of the natural products, and access to novel analogues, and these studies will be reported in due course.

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Supporting Information Available: Full experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) These alkene isomers could be separated by column chromatography on $AgNO_3$-doped silica gel, which allowed for full structural characterization (see: Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145−3152).

(14) Single diastereomer **23** was utilized initially in an attempt to avoid mixtures of products and to simplify the data analysis. However, the reaction can also be performed on the mixture of **23** and **24** with similar results.

(15) NMR spectroscopy indicated formation of a single triflate. Such regioselectivity is amply precedented; see, for example: Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323−11334.

(16) Prepared by Stille coupling of the known ethyl *E*,*E*-5-bromopenta-2,4-dienoate (Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616−620) with (*E*)-1,2-di(tributylstannyl)ethene.