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

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Current Literature

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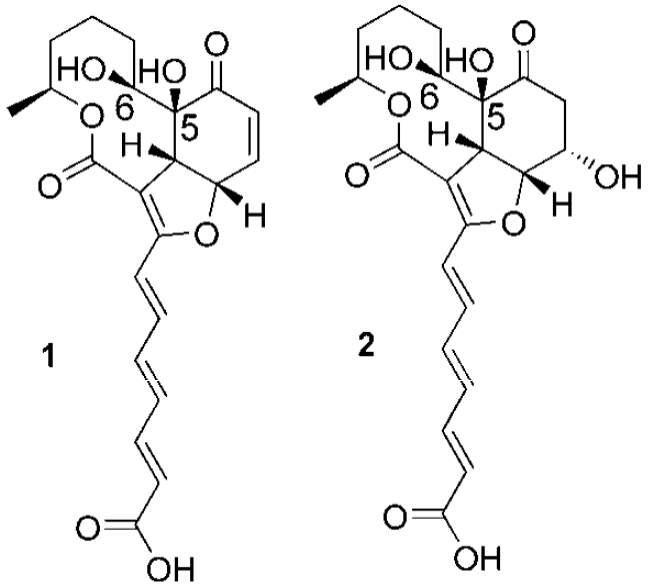
- Polyketide-derived natural products (+)-dictyosphaeric acid A (**1**) and (+)-dictyosphaeric acid B (**2**) were isolated from a fungal isolate obtained from the green alga *Dictyosphaeria versluyii*

Ireland et al. *J. Nat. Prod.* **2004**, *67*, 1396

- Activity:
  - (+)-Dictyosphaeric acid A showed antibacterial activity at 50 *μ*g/well against methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus faecium* and *Candida albicans*
  - (+)-Dictyosphaeric acid B did not exhibit antimicrobial activity at 50 and 200 *μ*g/well

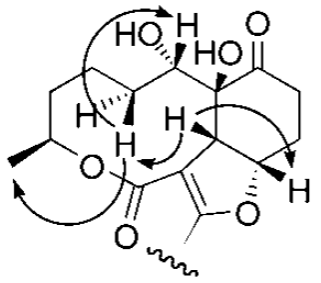


- SAR: α,β-unsaturated ketone required for activity

- Mechanism of action not known

- Key structural features of (+)-dictyosphaeric acid A:
  - 5 stereocenters (4 contiguous)
  - Higly oxygenated decalactone
  - Triene carboxylic acid

- Relative stereochemical configuration in (+)-dictyosphaeric acid A at C6 relied on a single correlation



key nOe and rOe correlations

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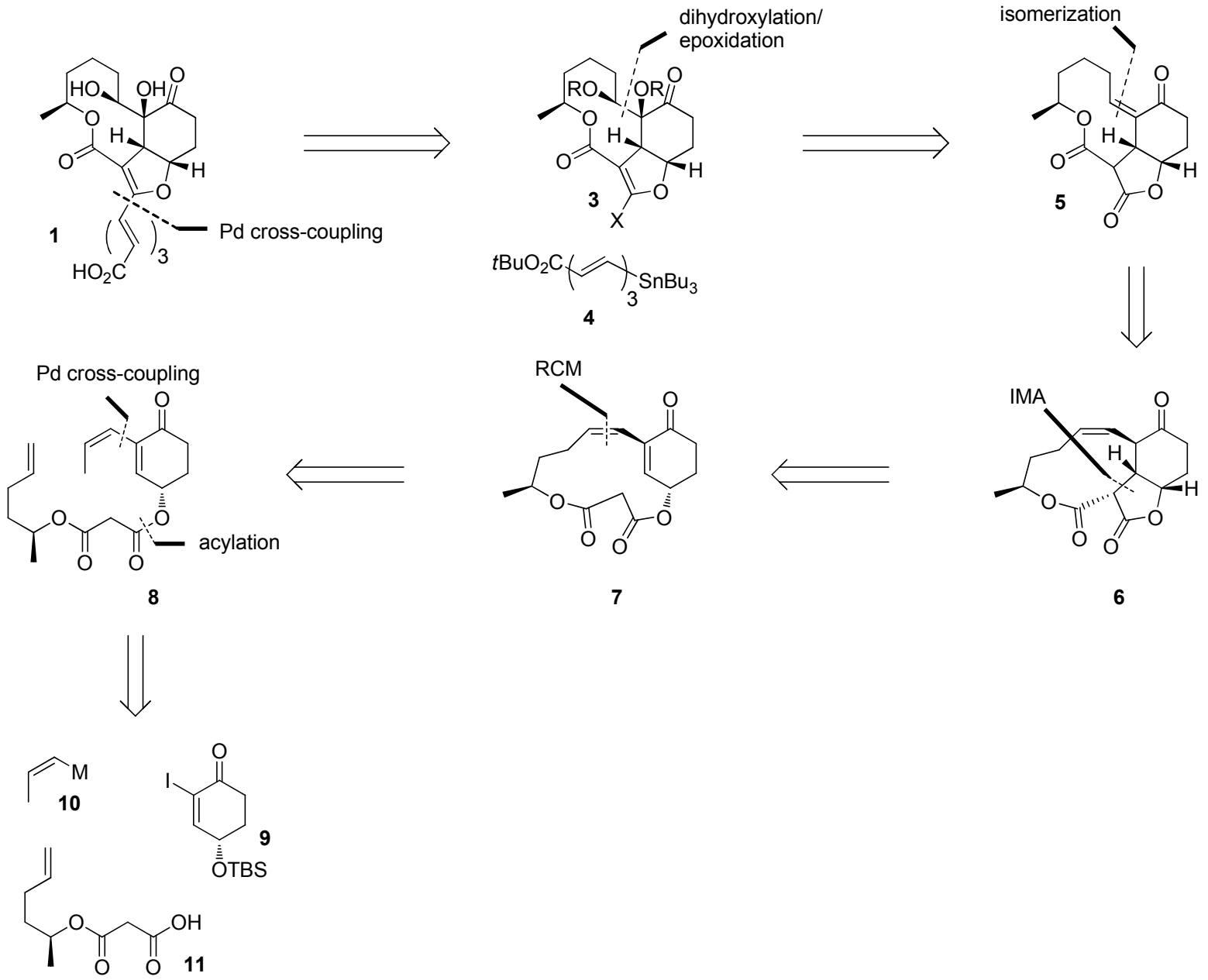
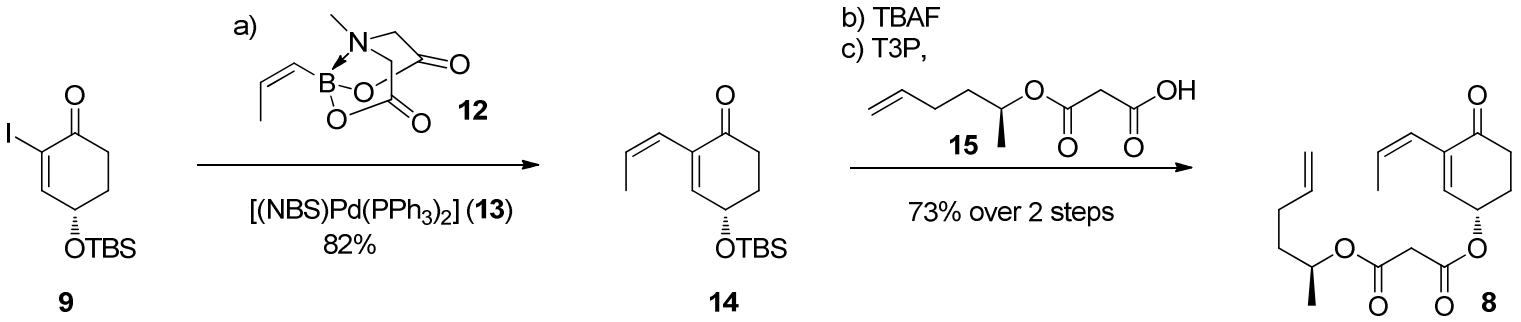
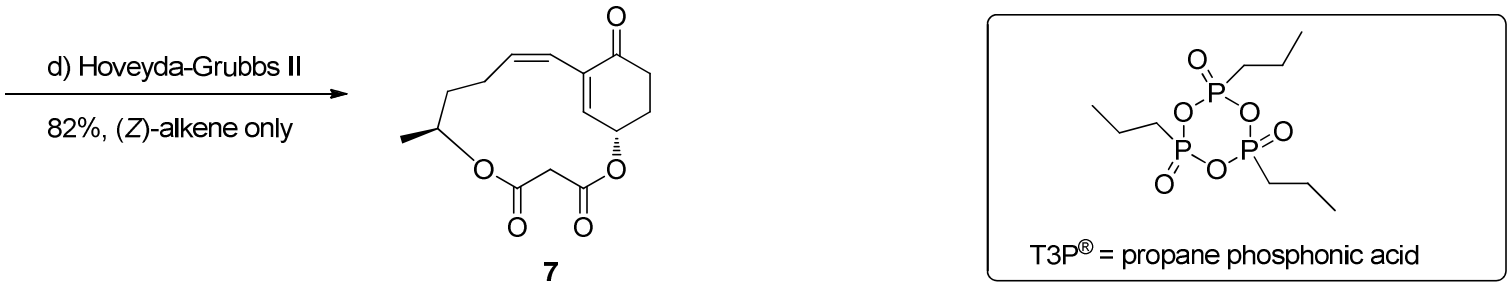

dihydroxylation/
epoxidation
isomerization
Pd cross-coupling
1
3
4
5
6
7
8
9
10
11
RCM
IMA
acylation
Pd cross-coupling



Taylor et al. *Org. Lett.*
2008, *10*, 353-356



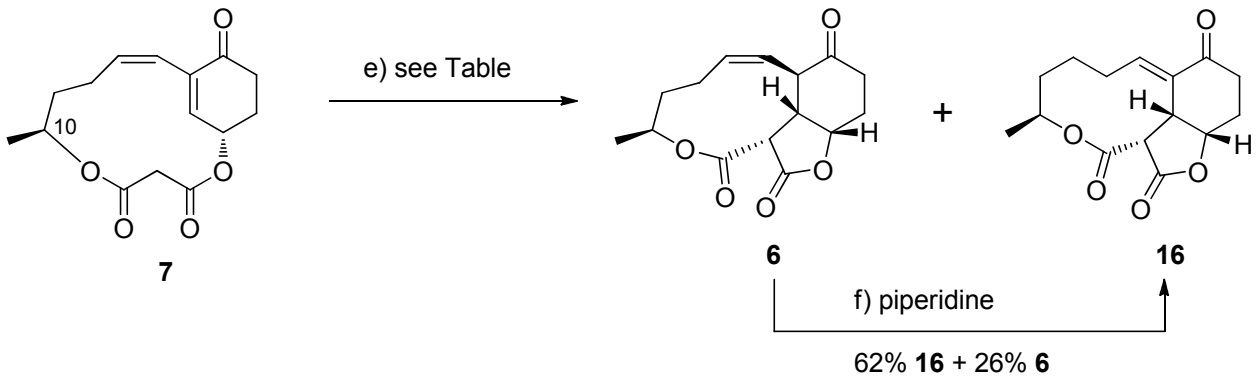
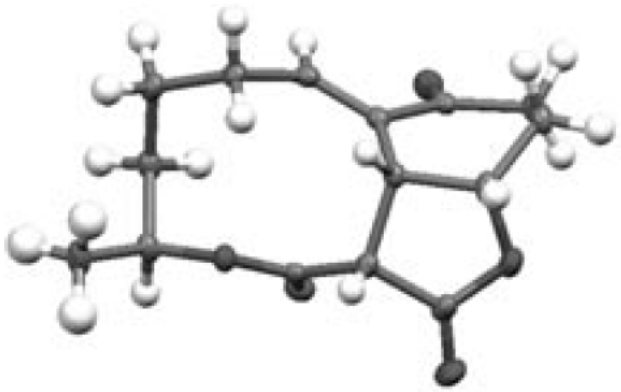


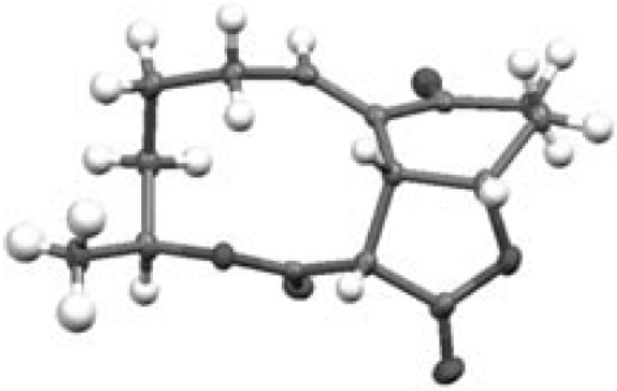
Table: IMA of compound **7**

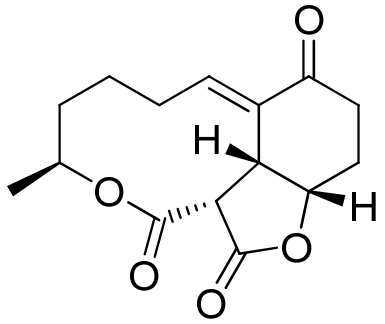
1.	NaH/THF	**6**, 90%
2.	Et_3N, Bu_4NCl, MeCN, RT[a,b]	**6**, 91%
3.	Et_3N, Bu_4NCl, MeCN, Δ [a]	**6**, 40% **16**, 34%
4.	Piperidine, Bu_4NHSO_4, MeCN, Δ	**6**, 23% **16**, 65%

[a] Carried out on 10-desmethyl analogue
[b] Only recovered **7** was obtained in the absence of Bu_4NCl

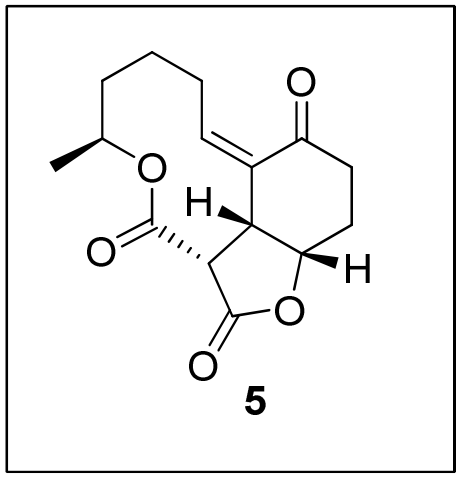


X-ray crystal structure of **16**





16



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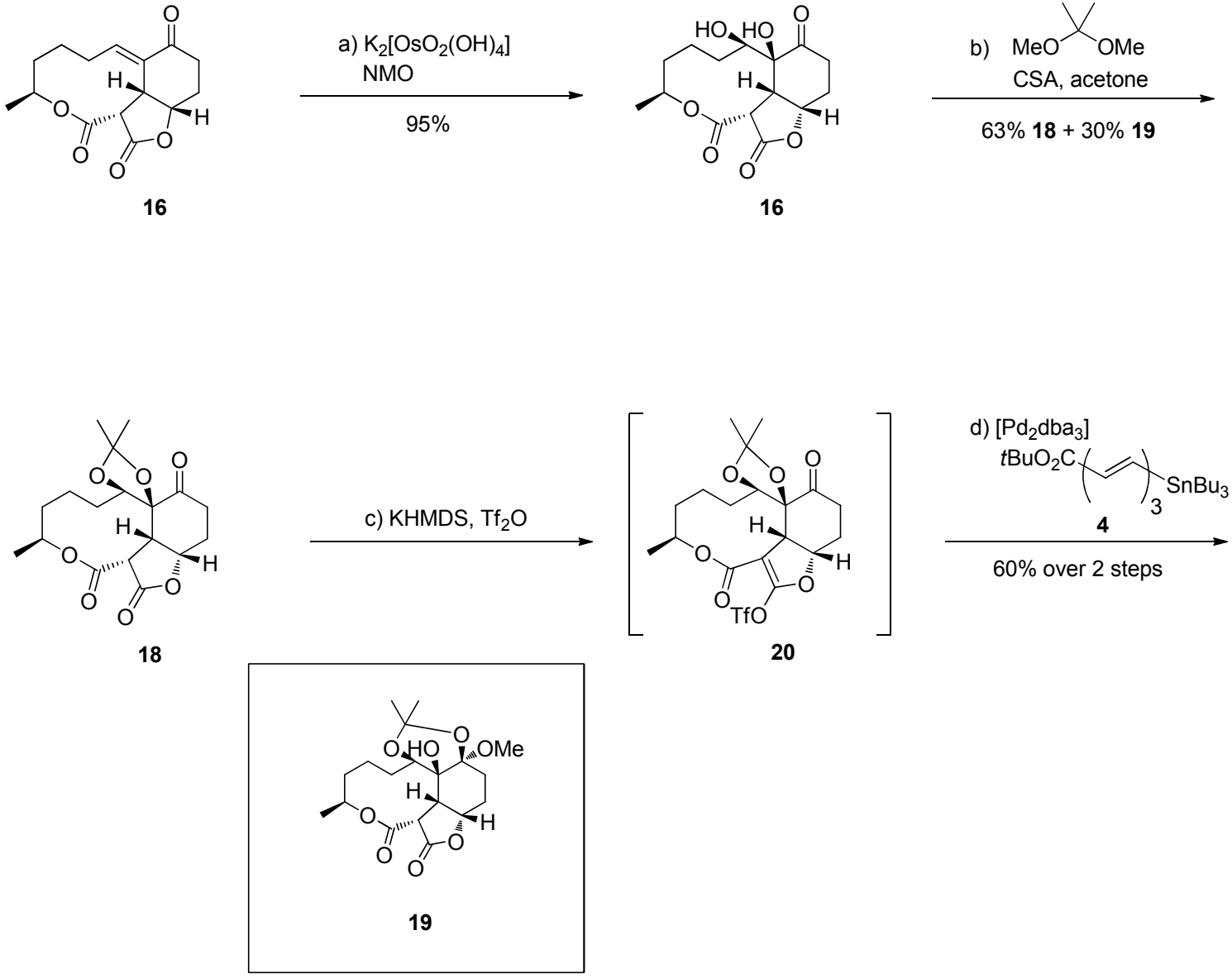
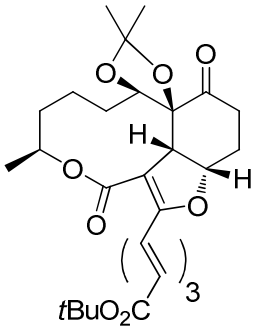
- The isomerized enone product was formed as a single diastereomer and as a single alkene geometric isomer

- X-ray crystallography confirmed that the (*E*)-enone **16** was formed, and not the (*Z*)-enone **5** as proposed in the retrosynthetic analysis


a) $K_2[OsO_2(OH)_4]$
NMO
95%
b) MeO OMe
CSA, acetone
63% **18** + 30% **19**
c) KHMDS, Tf_2O
d) $[Pd_2dba_3]$
$tBuO_2C$
$SnBu_3$
3
4
60% over 2 steps
16
16
18
20
19



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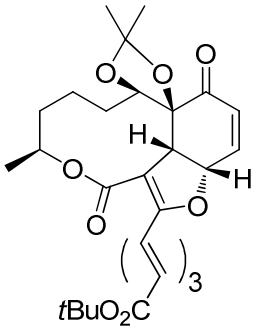
e) LHMDS, TMSCl

f) $Pd(OAc)_2$

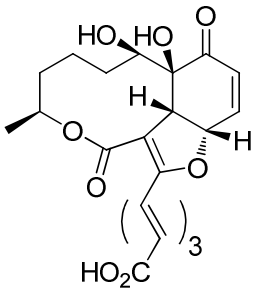
59% over 2 steps
(83% brsm)



22

g) 80% TFA

100%



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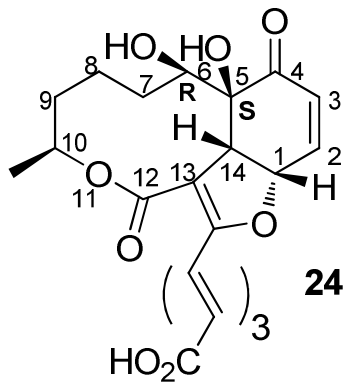
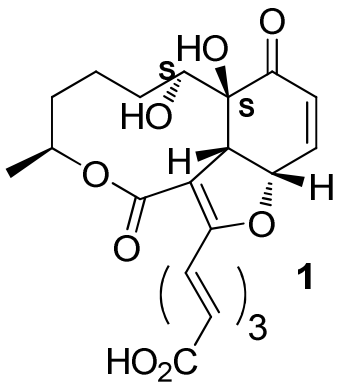
Total synthesis completed in
twelve steps from known intermediate
in 10% overall yield

Synthetic



$[\alpha]_D$ = + 116.9, *c* = 0.12, MeOH

Natural
with
Proposed
Assignment

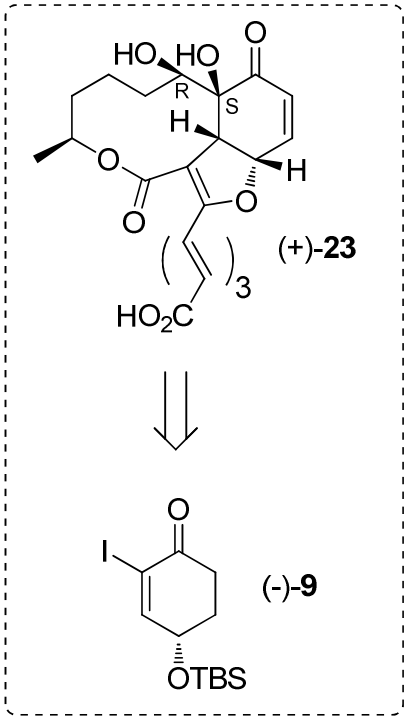


$[\alpha]_D$ = + 126, *c* = 0.21, MeOH

Position	Synthetic (+) [23] ^{13}C	^{1}H	mult., *J* [Hz]	Lit. (+)-[1] ^{13}C	^{1}H	mult., *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

Conclusion

- Total synthesis of (+)-dictyosphaeric acid A achieved from known (-)-**9** in
  - Twelve steps
  - 10% overall yield
- Convergent synthetic scheme developed
- Through synthesis, previously published structural mis-assignment at C6 of (+)-dictyosphaeric acid A was corrected and absolute configuration determined



A preprint of the manuscript was sent to Prof. Ireland (Isolation group), who replied by e-mail 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."