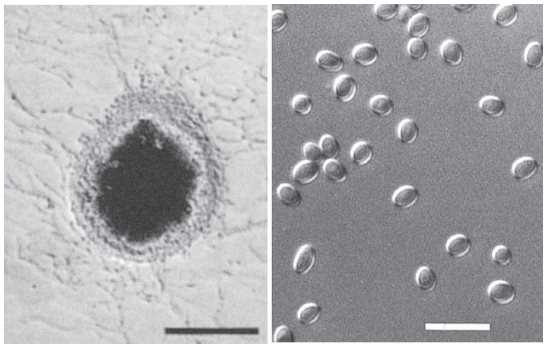
Macrosphelide ©

1. Discovery, producing organism and structures

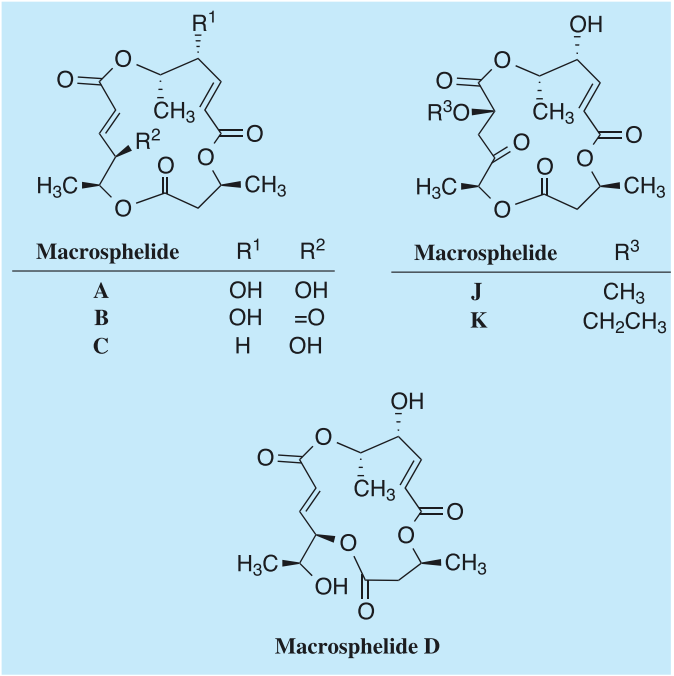
Macrosphelides A-D, J and K were isolated from the culture broth of *Paraconiothyrium sporulosum* FO-5050 and recognized as cell-adhesion inhibitors[1-6]. It was reported by Numata *et al* that macrosphelides E-I, L were isolated from another fungal strain[7-9]. Recently, the structure of macrosphelide D was revised and determined by using NMR spectroscopy and by synthesizing its stereoisomers in Curran's group.[11]



pycnidium
Bar: 100 μm

conidia
Bar: 20 μm

Microsphaeropsis sp. FO-5050
(*Paraconiothyrium sporulosum* FO-5050)



Macrosphelide	R^1	R^2
A	OH	OH
B	OH	=O
C	H	OH

Macrosphelide	R^3
J	CH_3
K	CH_2CH_3

Macrosphelide D

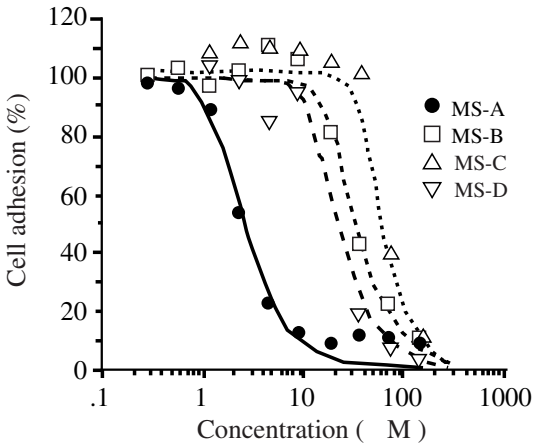
2. Physical data (Macrosphelide A)[1-5]

Colorless needles.$C_{16}H_{22}O_8$; mol wt 342.13. Sol. in $CHCl_3$, MeOH, EtOAc. Insol. in hexane.

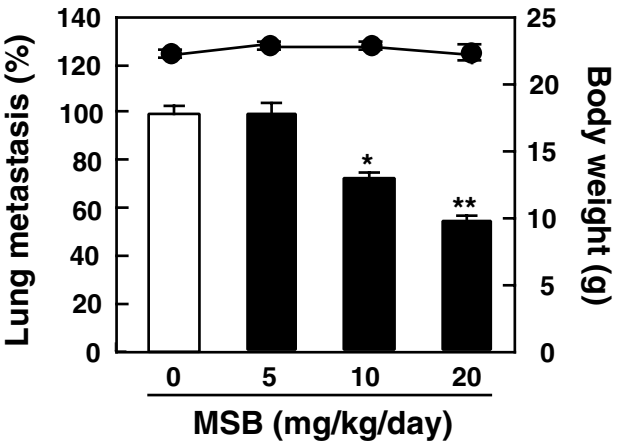
3. Biological activity

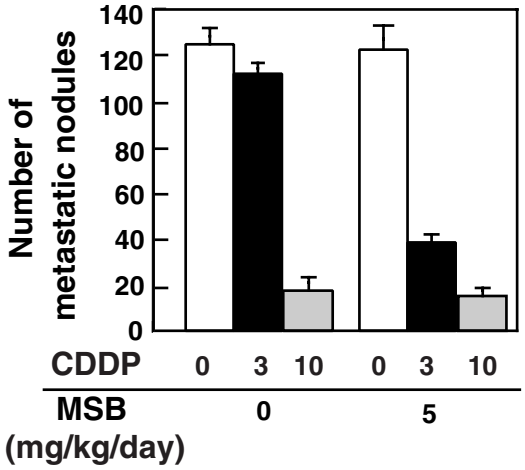
1) Inhibition of cell adhesion[1,3]

Macrosphelide (MS) A showed potent inhibitory activity against cell adhesion of human leukemia cell (HL-60) to LPS-activated human umbilical vein endothelial cell (HUVEC), with an IC_{50} value of 3.5 μM. The IC_{50} values of macrosphelides B, C and D were 36, 67.5 and 25 μM, respectively. The IC_{50} values of both macrosphelides J and K were greater than 100 μg/ml. Macrosphelide A and B did not show any cytocidal activities at a concentration of 100 μg/ml.



2) MSB suppressed metastasis through inhibition of adhesion of sLe^x/E-selectin molecules[9]. MSB inhibits adhesion of sialyl Lewisx (sLe^x)-expressing HL-60 cells to LSP-activated (E-selectin-expressing) HUVECs *in vitro*. When MSB was administered to B16/BL6 mice at 20 mg/kg/day, lung metastatic nodules of B16/BL6 mouse melanoma cells (B16/BL6 cells) were significantly decreased (T/C = 45%). Flow cytometry analysis showed that B16/BL6 cells expressed high levels of sLe^x antigens. Under in vitro conditions, B16/BL6 cells demonstrated a greater degree of adhesion to LSP-activated HUVECs, but adhesion was significantly inhibited by MSB and sLe^x antibodies. Combined therapy of MSB and cisplatin (CDDP) induced remarkable lung metastasis inhibition without the adverse effects of CDDP to the host.

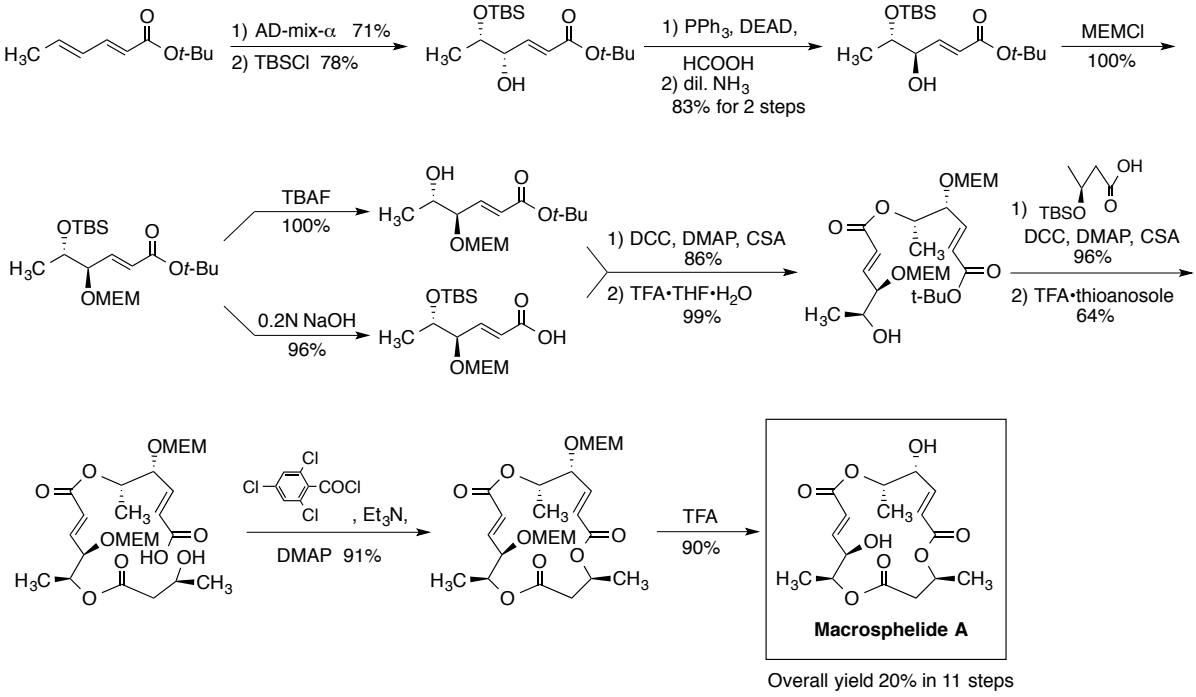




3) Macrosphelide A inhibited growth of some ascomycetes, basidiomycetes, oomycetes and Gram-positive bacteria. Minimum inhibitory concentration of this compound against Staphylococcus aureus was <500 μg/ml. No inhibitory activities were observed against yeasts and Gram-negative bacteria at 700 mg/μl of macrosphelide A.[12]

4. Total synthesis[4,5]

The total syntheses of macrosphelides have been reported by several groups. The following scheme is Ōmura's approach (See Appendix-I).



Overall yield 20% in 11 steps

5. References

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