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Synthesis of (+)-Lasonolide A: (−)-Lasonolide A is the Biologically Active Enantiomer

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Abstract—(+)-Lasonolide A was synthesized following the established procedure. (−)-Lasonolide A was found to be the biologically active enantiomer.

Lasonolide A is a novel macrolide isolated from the shallow water Caribbean marine sponge, *Forcepia* sp. It is a potent cytotoxin against the A-549 human lung carcinoma and P388 murine leukemia cell lines, and inhibits cell adhesion in the EL-4.IL-2 cell line.[1] In the previous communication,[2] we reported synthesis of the compounds **1** and **2** (the proposed structures), neither of which corresponded with the structure of the natural product. Compounds **3**, **4**, **5**, and **6** were also prepared (Fig. 1), and we were able to show that compound **6** exhibited identical spectroscopic data (except the optical rotation) as reported for the natural product. Since the naturally occurring (and presumably biologically active) enantiomer was reported to be dextrorotatory ($[\alpha]_D$ $+24.4$ (*c* 0.045, $CDCl_3$)),[1] and compound **6** was found to be levorotatory ($[\alpha]_D^{20}$ -24.1 (*c* 0.055, $CDCl_3$)), we concluded that the natural product should be represented by the structure **7**, which is the (+)-enantiomer of **6**. Compound **7** was duly synthesized following the established synthetic procedure (Scheme 1), and the samples were subjected to biological assay. Surprisingly, it was found that the (−)-enantiomer **6** was the most potent compound tested (Table 1). On the contrary, the (+)-enantiomer **7** was found to possess much lower activities.[3] Accordingly, it was concluded that the active (and natural) enantiomer of lasonolide A is the (−)-enantiomer **6**, and the original report[1] on the optical rotation data for natural lasonolide A is in error.

Inspection of the data on Table 1 reveals that the (*R*)-configuration at C28 enhances the activity. The *cis* double bond at C25-26 is important, and the *trans* double bond at C17-18 is essential, for the compound **1** is almost devoid of activity. The correct structure of

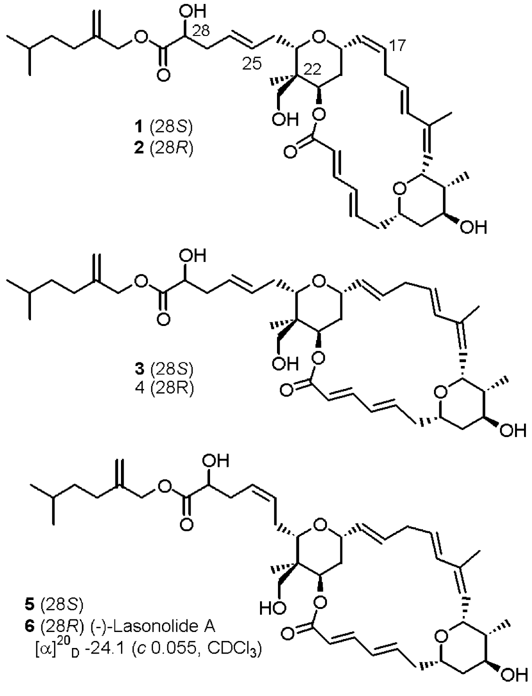

Figure 1. (−)-Lasonolide A and related compounds.

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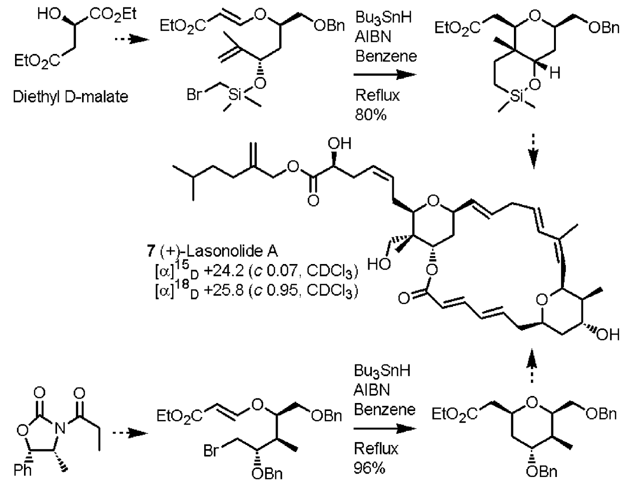

Scheme 1. Synthesis of (+)-lasonolide A (7).

Table 1. GI_{50} (μM) values of lasonolide A and related compounds[4,5]

Compd	A549	HCT-116	NCI-H460
1	>10	5	5
3	3.2	0.1	0.04
4	2	0.04	0.02
5	0.05	0.009	<0.003
6	0.02	<0.003	<0.003
7	6	3	2

lasonolide A is finally identified, and the search for more useful analogues may now begin.

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References and Notes

1. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.
2. Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384.
3. The IC_{50} value of the natural lasonolide A against the A-549 human lung carcinoma cell line was reported to be 40 ng/mL (~0.06 μM).
4. Wu, L.; Smythe, A. M.; Stinson, S. F.; Mullendore, L. A.; Monks, A.; Scudiero, D. A.; Paull, K. D.; Koutsoukos, A. D.; Rubinstein, L. V.; Boyd, M. R.; Shoemaker, R. H. *Cancer Res.* **1992**, *52*, 3029.
5. **Cell Culture.** All tumor cell lines including A549 and NCI-H460, human small cell lung carcinoma cell lines, and HCT-116, a human colon cancer cell line, were maintained in RPMI1640 plus 5% (v/v) heat-inactivated fetal bovine serum (FBS). All the media were supplemented with additional 100 units/mL penicillin G, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin B and 2 mM L-glutamine. Cells were maintained at 37 °C in a humidified incubator containing 5% CO_2.

Cell proliferation assay. Cellular response to drugs was determined using sulforhodamine B (SRB) method described in ref 3 with minor modifications. Briefly, cells were seeded at 3000 cells/100 μL/well in 96-well plates, and on the next day treated with 100 μL of medium containing test compounds at the serial concentrations for another 48 h incubation. To fix the cells, 100 μL of 4% formaldehyde was added to each well and kept at room temperature for at least 30 min. The wells were washed with distilled water three times and air dried. Subsequently, 100 μL of SRB at 0.4% (w/v) (Sigma Chemical Co., St. Louis, MO) was added to each well for >10 min at room temperature before washing five times with 1% acetic acid. Bound stain in the dried wells was solubilized with 10 mM Tris buffer, and the absorbances were read at 530 nm on an automated plate reader. Percentage growth inhibition (GI) was calculated to be (Ti-Tz)/(C-Tz)×100, where Ti is the OD_{540} value at 48 h at the concentration i, Tz at 0 h, and C is the OD_{540} value at 48 h at zero concentration.