STEREOCONTROLLED SYNTHESES OF C_{18}-C_{24} FRAGMENTS OF ISOLASALOCID A AND LASALOCID A. AN APPLICATION OF THE ACID ASSISTED SYNTHESIS OF FUNCTIONALIZED TETRAHYDROFURANS AND TETRAHYDROPYRANS

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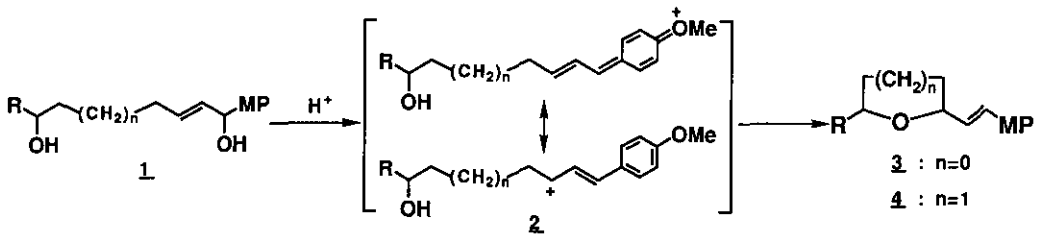
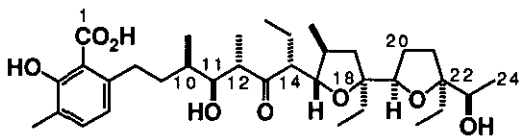
Abstract - The allyl alcohol (9) derived from D-glucose was easily cyclized by acid treatment and then converted to the C_{18}-C_{24} fragment (13) of isolasalocid A (5). Similarly, the allyl alcohol (15) derived from ethyl L-lactate was converted to the C_{18}-C_{24} fragment (20) of lasalocid A (6) via the tetrahydropyran derivative (16), which was kinetically formed by a chelation-controlled reaction.

In the course of our synthetic study of the complex natural products, such as polyether and macrolide antibiotics, we recently reported some successful results.[1, 2] In order to establish a common synthetic methodology of the polyether antibiotics, we developed a new synthetic method of functionalized tetrahydrofurans (THF) and tetrahydropyrans (THP)[3] which are the most typical structural units of the polyether antibiotics. Our synthetic method is shown in Scheme 1.[3b] The THF (3) and THP (4) derivatives were easily and stereoselectively prepared from allyl alcohols bearing p-methoxyphenyl (MP) group (1) via the intermediates (2) by treatment with an acid.

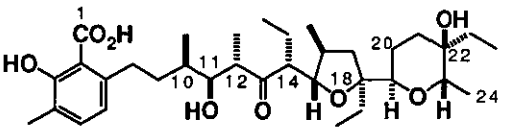


Scheme 1

Isolasalocid A (5)[4] and lasalocid A (6)[5], produced from *Streptomyces lasaliensis* are members of the class of naturally occurring ionophores known as polyether antibiotics. Total syntheses of 6 were achieved by Kishi[6] and Ireland[7], but 5 has not been synthesized yet. In this communication we describe stereocontrolled syntheses of the C_{18}-C_{24} fragments, 13 and 20 of 5 and 6, respectively, by using our method[3b] as the first application toward complex natural product synthesis.



Isolasalocid A 5

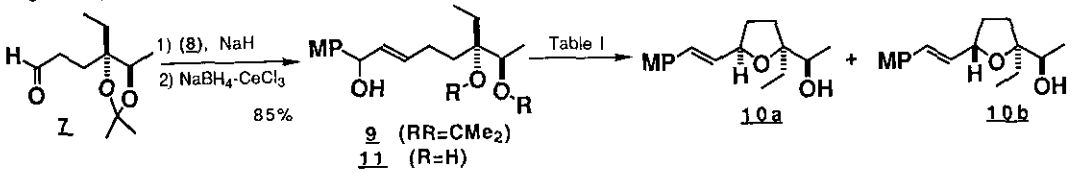


lasalocid A 6

Synthesis of C_{18}-C_{24} fragment of isolasalocid A

At first the aldehyde (7),[8] derived from D-glucose in 43% overall yield (19 steps), was converted to the allyl alcohol (9) via two conventional reactions [Wittig-Horner reaction with β-ketophosphonate (8) and $NaBH_4$-$CeCl_3$ reduction[9] of the *resulting α,β-unsaturated ketone*] in 85% overall yield. When 9 was treated with CSA in CH_2Cl_2 at room temperature for a short time, an intramolecular cyclization proceeded smoothly and stereoselectively to give the 2,5-cis-THF (10a) and the 2,5-trans-THF (10b) in a 1 : 99 ratio (Table I, entry 1). This stereoselectivity fell *sharply by prolonging the reaction* time (entry 2) or by using $ZnBr_2$ in stead of CSA (entry 3). Furthermore, a non-stereoselective cyclization proceeded in the case of the triol (11) under the same conditions as described in entry 1. Therefore, it is evident that the cyclization of 9 in entry 1 was kinetically controlled by the *steric effect* between the isopropylidene group and the p-methoxy styryl group as shown in Scheme 3. Although 10b had the undesired configuration at the C_{19} position, this problem was easily solved by epimerization. After oxidative cleavage of the double bond [osmilation and $NaIO_4$ oxidation], treatment with KOH of the resulting aldehyde gave the desired lactol (12) in 60% overall yield.

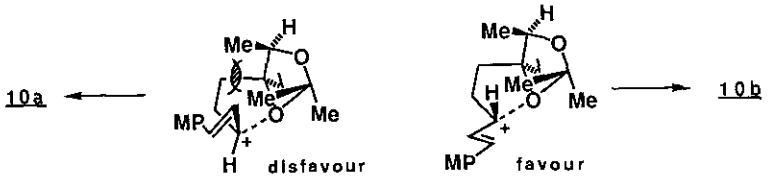
Finally five-step conversion of 12 [$LiAlH_4$ reduction, TBDMS protection of the primary hydroxy group, BOM protection of the *secondary hydroxy group*, removal of the TBDMS group, Swern oxidation[10]] gave the C_{18}-C_{24} fragment (13) of 5 in 72% overall yield.



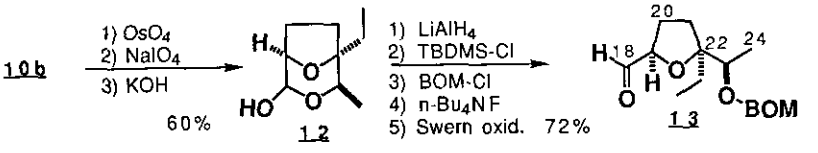
Scheme 2

Table I Cyclization reaction of 9

entry	conditions		yield	10a : 10b
1	CSA, CH_2Cl_2, rt	20 min	96%	1 : 99
2	CSA, CH_2Cl_2, rt	1 h	89%	1 : 2.2
3	$ZnBr_2$, CH_2Cl_2, rt	3 h	96%	1 : 1.7



Scheme 3



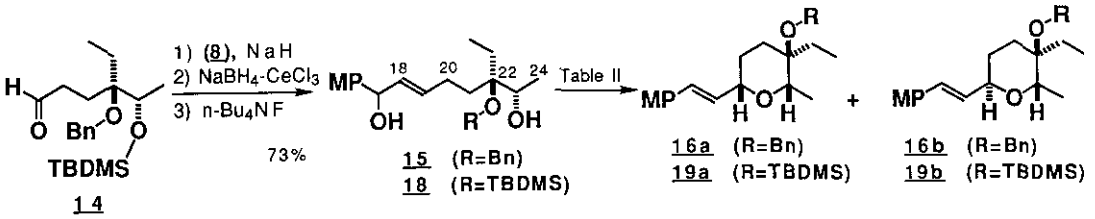
Scheme 4

Synthesis of C_{18}-C_{24} fragment of lasalocid A

The aldehyde (14),[11] derived from ethyl L-lactate in 25% overall yield (11 steps), was converted to the allyl alcohol (15) via three-step reactions [Wittig-Horner reaction, $NaBH_4$-$CeCl_3$ reduction, deprotection of the TBDMS group] in 73% overall yield. Treatment of 15 with CSA in CH_2Cl_2 at room temperature for 3 min gave mainly the 2,6-trans-THP (16b) as a kinetic product (stereoselectivity 4.4 : 1). When the acid-treatment was prolonged, 16b was gradually converted to the thermodynamically stable 2,6-cis-THP (16a), and after 48 h, the ratio of 16b and 16a was 1 : 4.3 (entry 1). Therefore, it was difficult to obtain 16b with high selectivity by the treatment with CSA. However, when 15 was treated with $ZnBr_2$ in CH_2Cl_2 at -20°C, the expected product (16b) was obtained with high selectivity (14 : 1)(entry 3). This result shows that the cyclization proceeded kinetically via an intermediate (17b) arising from a chelating ability of zinc cation as shown in Scheme 6. This mechanism was supported by a reaction of 18, which has no chelating ability. When 18 was treated with $ZnBr_2$ under the same conditions as described in entry 3, the 2,6-cis-THP (19a), a non-chelating product, was obtained with 24 : 1 selectivity.

Finally, the synthesis of the C_{18}-C_{24} fragment (20) of 6 was easily achieved by oxidative cleavage of the double bond of 16b [osmilation and $NaIO_4$ oxidation].

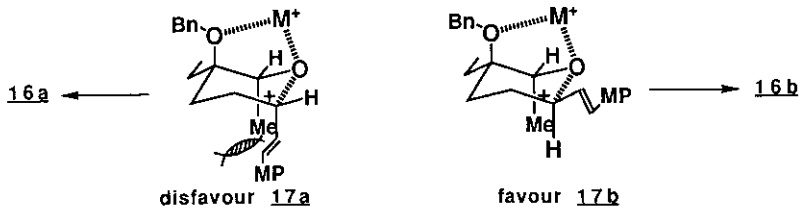
The total synthesis of isolasalocid A and lasalocid A will be reported in the near future.



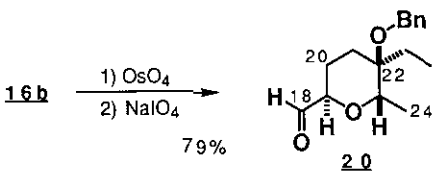
Scheme 5

Table II Cyclization of 15

entry	conditions		yield	16a : 16b
1	CSA, CH_2Cl_2, rt	48 h	60%	4.3 : 1
2	CSA, CH_2Cl_2, rt	3 min	56%	1 : 4.4
3	$ZnBr_2$, CH_2Cl_2, -20°C	80 min	79%	1 : 14



Scheme 6



Scheme 7

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