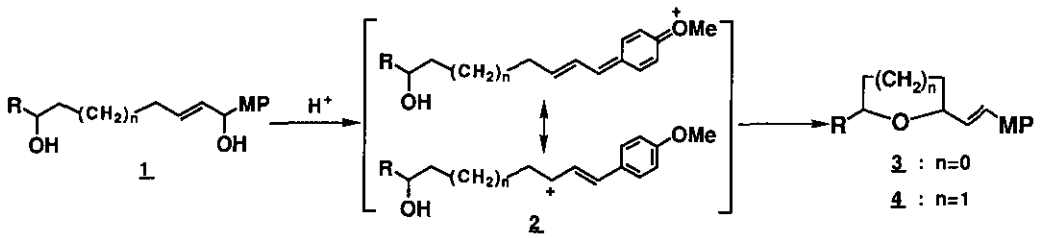
# STEREOCONTROLLED SYNTHESES OF $C_{18}$-$C_{24}$ FRAGMENTS OF ISOLASALOCID A AND LASALOCID A. AN APPLICATION OF THE ACID ASSISTED SYNTHESIS OF FUNCTIONALIZED TETRAHYDROFURANS AND TETRAHYDROPYRANS

Kiyoshi Horita*, Ichio Noda, Kazuhiro Tanaka, Tamaki Miura, and Osamu Yonemitsu*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

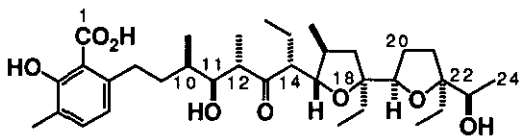
Abstract - The allyl alcohol (9) derived from D-glucose was easily cyclized by acid treatment and then converted to the $C_{18}$-$C_{24}$ fragment (13) of isolasalocid A (5). Similarly, the allyl alcohol (15) derived from ethyl L-lactate was converted to the $C_{18}$-$C_{24}$ fragment (20) of lasalocid 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.

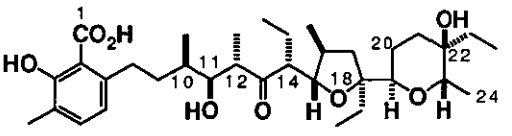



**Scheme 1**

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**

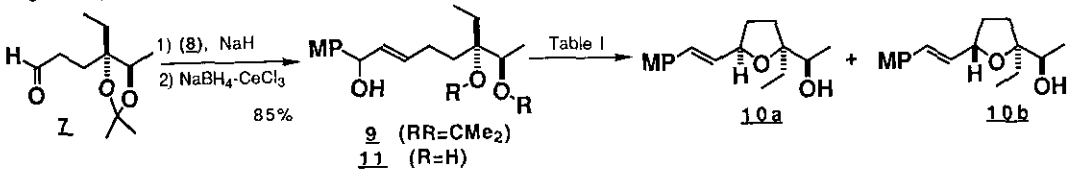



**lasalocid A 6**

**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.

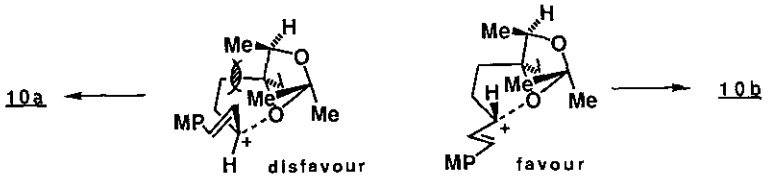
Finally five-step conversion of 12 [ $LiAlH_4$ reduction, TBDMS protection of the primary hydroxy group, BOM protection of the *secondary hydroxy group*, removal of the TBDMS group, Swern oxidation[10] ] gave the $C_{18}$-$C_{24}$ fragment (13) of 5 in 72% overall yield.



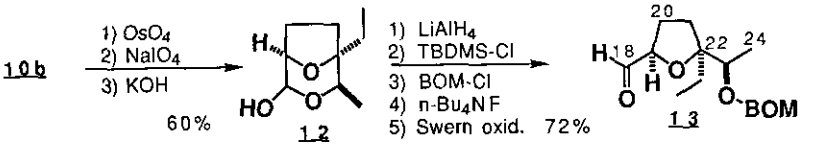

Scheme 2

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*



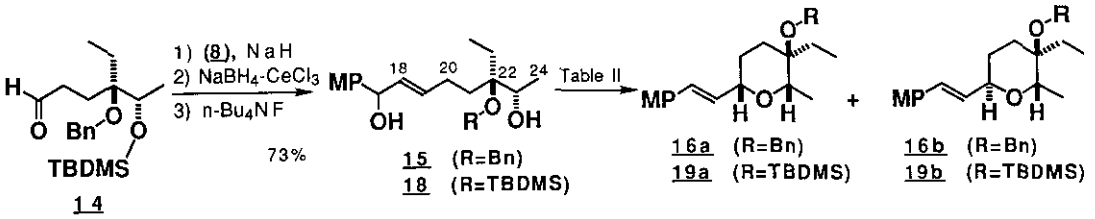

*Scheme 4*

**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 ].

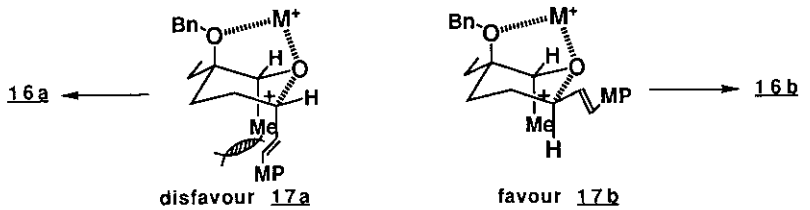
*The total synthesis of isolasalocid A and lasalocid A will be reported in the near future.*



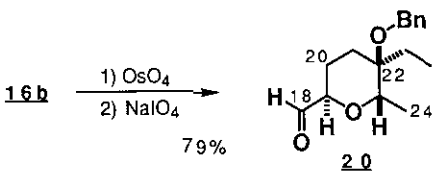

**Scheme 5**

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**

REFERENCES AND NOTES


1. Synthesis of macrolides : (a) Y. Oikawa, T. Tanaka, and O. Yonemitsu, Tetrahedron Lett., 1986, **27**, 3647. (b) Y. Oikawa, T. Tanaka, T. Hamada, and O. Yonemitsu, Chem. Pharm. Bull., 1987, **35**, 2196. (c).T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada, and O. Yonemitsu, *ibid*., 1987, **35**, 2203. (d) N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, J. Am. Chem. Soc., 1986, **108**, 4645. (e) N. Nakajima, T. Tanaka, T. Hamada, Y. Oikawa, and O. Yonemitsu, Chem. Pharm. Bull., 1987, **35**, 2228. (f) T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, Tetrahedron Lett., 1986, **27**, 3651. (g) *idem*, Chem. Pharm. Bull., 1987, **35**, 2219. (h) T. Tone, T. Nishi, Y. Oikawa, M. Hikota, and O. Yonemitsu, Tetrahedron Lett., 1987, **28**, 4569. (i) H. Tone, M. Hikota, T. Hamada, T. Nishi, Y. Oikawa, and O. Yonemitsu, Chem. Pharm. Bull., 1989, **37**, 1155. (j) H. Tone, T. Nishi, Y. Oikawa, M. Hikota, and O.Yonemitsu, Chem. Pharm. Bull., 1989, **37**, 1160. (k) *idem*, *ibid*., 1989, **37**, 1167.
2. Synthesis of polyether : (a) K. Horita, S. Nagato, Y. Oikawa, and O. Yonemitsu, Tetrahedron Lett.,1987, **28**, 3253. (b) *idem*, *ibid*., 1988, **29**, 5143. (c) *idem*, Chem. Pharm. Bull., 1989, **37**, 1698 (d) *idem*, *ibid*., 1989, **37**, 1705 (e) *idem*, *ibid*, 1989, **37**, 1717. (f) *idem*, *ibid*., 1989, **37**, 1726.
3. (a) Y. Oikawa, K. Horita, and O. Yonemitsu, Heterocycles, 1985, **23**, 553. (b) I. Noda, K. Horita, and O. Yonemitsu, Tetrahedron Lett., 1986, **27**, 1917.
4. Isolation and structure elucidation of isolasalocid A: see reference 5c.
5. (a) Isolation : J. Berger, A. Rachlin, W. E. Scott, L. H. Sternback, and M. W. Glodberg, J. Am. Chem. Soc., 1951, **73**, 5295. (b) Structure elucidation : J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, J. Chem. Soc., Chem. Comm., 1970, 71 : S. M. Johnson, J. Herrin, S. J. Liu, and I. C. Paul, J. Chem. Soc., Chem. Comm.,1970, 72. *idem*, J. Am. Chem. Soc., 1970, **92**, 4428.
   (c) J. W. Wesyley, J. F. Blount, R. H. Evans, Jr., A. Stempel, and J. Berger, J. Antibiot., 1974, **27**, 597.
6. T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, J. Am. Chem. Soc., 1978, **100**, 2933.
7. (a) R. E. Ireland, S. Thaisrivongs, and C. S. Wilcox., J. Am. Chem. Soc., 1980, **102**, 1155. (b) R. E. Ireland, R. C. Anderson, R. Bodoud, B. J. Fitzsimmons, G. J. McGarvey, S. Thaisrivongs, and C. S. Wilcox, J. Am. Chem. Soc., 1983, **105**, 1988.
8. Synthesis of 7 from D-glucose will be reported elsewhere soon.
9. J. L. Lucke, L. Rodriguez-Hahn, and P. Crabbe, J. Chem. Soc., Chem. Comm., 1978, 601.
10. A. J. Mancuso, S. L. Hung, and D. Swern, J. Org. Chem., 1978, **43**, 2480. A. J. Mancuso and D. Swern, Synthesis, 1981, 165.
11. Synthesis of 14 from ethyl L-lactate will be reported elsewhere soon.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