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STEREOSELECTIVE SYNTHESIS OF POLYETHER ANTIBIOTICS, LASALOCID A AND ISOLASALOCID A, VIA A CHELATION-CONTROLLED FORMATION OF TETRAHYDROFURAN RINGS UNDER THERMODYNAMIC CONDITIONS[1]

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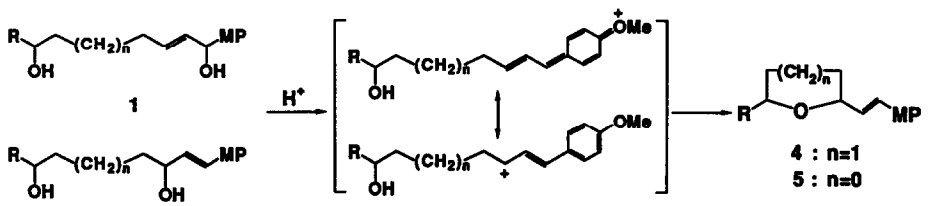
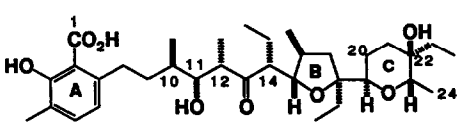
Summary: The B-rings (2,5-*trans*-tetrahydrofurans) of lasalocid A (**6**) and isolasalocid A (**7**) were stereoselectively constructed from the corresponding *p*-methoxyphenylallyl alcohols (**13a, 13b**) by treatment with $ZnBr_2$ to give C_{13}-C_{24} fragments (**14a, 14b**) via a new chelation-controlled cyclization under thermodynamic conditions. After their conversion into lasalocid ketone (**19**) and BOM-isolasalocid ketone (**20**), coupling with the C_1-C_{11} aldehyde (**22**) completed the synthesis of **6** and **7**, respectively.

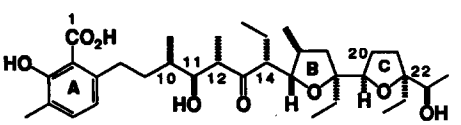
Naturally occurring polyether ionophore antibiotics with very complex structures[2] continue to provide challenging synthetic targets.[3] A remarkable structural feature of most of the polyether ionophores is the chain of substituted tetrahydropyran and tetrahydrofuran rings, whose efficient and stereoselective formation is crucial for synthesizing such complex ionophores.[4] In connection with our continuing synthetic study of polyether antibiotics,[3j,k] we recently reported a new method[5] for the synthesis of substituted tetrahydropyrans and tetrahydrofurans to establish a common synthetic methodology of polyether antibiotics. On treatment with an acid, allyl alcohols, **1** or **2**, bearing a *p*-methoxyphenyl (MP) group were converted to the corresponding tetrahydropyrans (**4**) and tetrahydrofurans (**5**) via a cation intermediate (**3**). This method was recently applied to the stereocontrolled synthesis of C_{18}-C_{24} fragments, **8** and **9**,[6,7] corresponding to the C-ring parts of lasalocid A (**6**) and isolasalocid A (**7**), respectively.



Lasalocid A (**6**)[8] and isolasalocid A (**7**),[9] isolated from *Streptomyces lasaliensis*, are representatives of a growing class of naturally occurring ionophores known as polyether antibiotics, and total syntheses of **6** were achieved by Kishi[3c] and Ireland.[3d,e] As a remarkable extention of the above cyclization, we report here the efficient and stereoselective synthesis of **6** and **7** from **8** and **9**, respectively, via a chelation-controlled



lasalocid A (6)

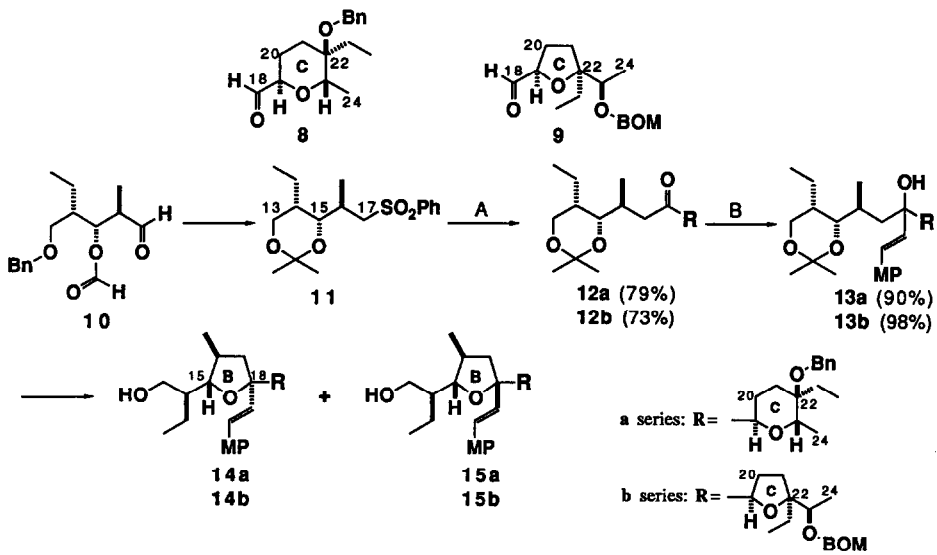


isolasalocid A (7)

cyclization of the B-rings under thermodynamic conditions.

The aldehyde (**10**)[10] was first converted to the sulfone (**11**),[11] whose anion generated with *n*-BuLi[12] was coupled with **8**, and Swern oxidation[13] of the resulting alcohol followed by Al-Hg reduction gave the ketone (**12a**). Conversion of **12** to the allyl alcohol (**13**) was carried out by addition of *p*-methoxyphenylethynyllithium and subsequent $LiAlH_4$ reduction of the triple bond.

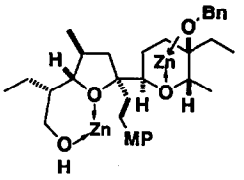
The allyl alcohols (**13a, b**) were subjected to acid cyclization in order to construct the B-rings of **6** and **7**. Some typical results are shown in Table I. When **13a** was treated with CSA in CH_2Cl_2 at room temperature for 4.0 h, mainly the undesired 2,5-*cis*-tetrahydrofuran (**15a**) (kinetic product) was obtained with 17:1 selectivity (entry 1). Prolonged treatment with the acid (entry 2) or rise in temperature (entry 3) caused a slight reversal of the selectivity. This indicates that there is almost no difference in the thermodynamical stabilities of **15a** and the desired 2,5-*trans*-tetrahydrofuran (**14a**). However, **14a** was obtained with 3:1 selectivity by treatment with excess (3~4 equiv.) $ZnBr_2$ for a short time (1 h) (entry 4). Under thermodynamic conditions (entries 5, 6) the selectivity was surprisingly improved to 29~35:1.[14,15] Similarly, **13b** gave **14b** and **15b** (entries 7-9).[16] This



(A) 1) **11**, *n*-BuLi, ether - *n*-hexane (1:1), -78°C, then **8** or **9** [a (88%), b (95%)]; 2) DMSO, $(COCl)_2$, Et_3N [a (100%), b (91%)]; 3) Al-Hg, THF, room temperature [a (90%), b (84%)]. (B) 1) MPC≡CLi, ether, -78~-30°C, [a (93%), b (99%)]; 2) $LiAlH_4$, THF, room temperature [a (97%), b (99%)].

Table I. Acid Cyclization of 13 into 14 and 15

entry	substrate	acid	solvent	temperature (°C)	time (h)	yield (%)	product ratio
1	**13a**	CSA	CH_2Cl_2	rt	4.0	71	**14a** : **15a** = 1 : 17
2	**13a**	CSA	CH_2Cl_2	rt	12	86	**14a** : **15a** = 1.4 : 1
3	**13a**	CSA	toluene	90	6.0	75	**14a** : **15a** = 1.3 : 1
4	**13a**	$ZnBr_2$	CH_2Cl_2	rt	1.0	77	**14a** : **15a** = 3 : 1
5	**13a**	$ZnBr_2$	CH_2Cl_2	rt	8.0	82	**14a** : **15a** = 29 : 1
6	**13a**	$ZnBr_2$	CH_2Cl_2	40	4.0	90	**14a** : **15a** = 35 : 1
7	**13b**	CSA	benzene	rt	3.0	76	**14b** : **15b** = 1 : 10
8	**13b**	$ZnBr_2$	CH_2Cl_2	rt	2.2	77	**14b** : **15b** = 1.5 : 1
9	**13b**	$ZnBr_2$	CH_2Cl_2	rt	8.0	79	**14b** : **15b** = 7 : 1



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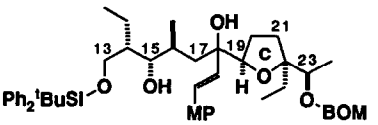

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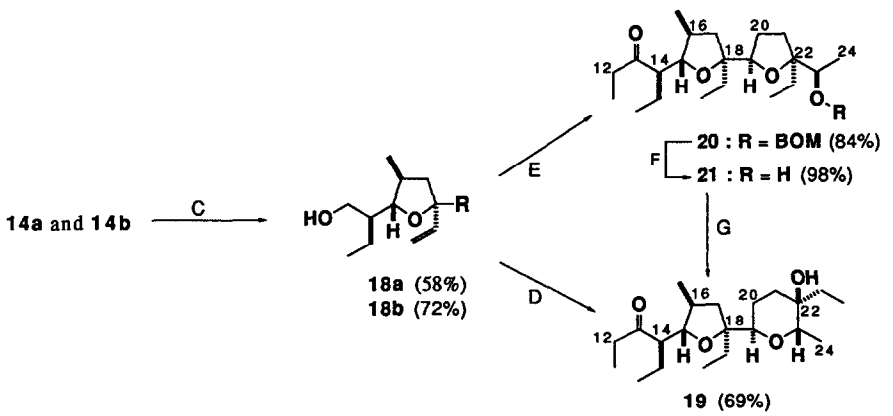
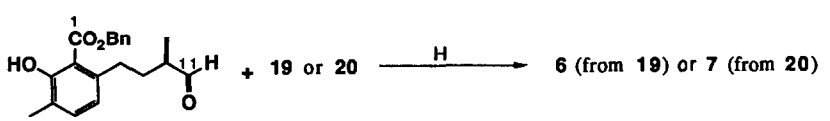
reaction required more than 2 equiv. of $ZnBr_2$, otherwise only poor results were obtained.[14] Thus, the double chelation of Zn, leading to a thermodynamically favorable intermediate, e.g. **16**, became an important factor to control the stereochemistry of tetrahydrofuran ring.[17]

Conversion of **14a** into lasalocid ketone (**19**) was carried out via **18a** by a series of conventional reactions. Similarly, **14b** was easily converted to isolasalocid ketone (**21**)[3c,18] via **18b** and **20**. To confirm its structure, **21** was converted to **19** by Kishi's method.[3c] Lasalocid ketone (**19**) was condensed with the C_1-C_{11} aldehyde (**22**)[3e] according to the published procedures[3c,e] to give lasalocid A (**6**) in 27% isolated yield. Similarly, the zinc enolate of 23-O-BOM-isolasalocid ketone (**20**) was coupled with **22** to give a diastereoisomeric mixture of four aldol adducts in 34% yield. Hydrogenation of the main adduct (isolated yield, 22%; yield based on the consumed **20**, 42%) on $Pd(OH)_2$ proceeded quite smoothly and isolasalocid A (**7**) was first isolated in quantitative yield.



(C) 1) TBSCl, imidazole, CH_2Cl_2, room temperature [**a** (100%), **b** (100%)]; 2) OsO_4-NMO, acetone-H_2O (5:2), room temperature [**a** (85%), **b** (95%)]; 3) $Pb(OAc)_4$, benzene, room temperature [**a** (98%), **b** (95%)]; 4) $Ph_3P{=}CH_2$, THF, room temperature, 1 d [**a** (70%), **b** (83%)]; 5) *n*-Bu_4NF, THF, room temperature [**a** (100%), **b** (96%)]. (D) 1) H_2, $Pd(OH)_2$, AcOEt, room temperature (97%); 2) PCC, 3A-MS, CH_2Cl_2, room temperature (84%); 3) EtMgBr, THF, 0°C; 4) PCC, 3A-MS, CH_2Cl_2, room temperature (2steps 85%). (E) 1) PCC, 3A-MS, CH_2Cl_2, room temperature (94%); 2) EtMgBr, THF, 0°C (89%); 3) PCC, 3A-MS, CH_2Cl_2, room temperature (100%); 4) H_2, 10% Pd-C, AcOEt, room temperature (100%). (F) H_2, $Pd(OH)_2$, EtOH, room temperature (98%). (G) 1) MsCl, pyridine, room temperature (82%); 2) $AgCO_3$, H_2O-acetone (1:4), reflux (66%).



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(H) 1) **19** or **20**, LDA, ether, -78°C, $ZnCl_2$, 0°C, then **22**; 2) H_2, $Pd(OH)_2$, EtOH, room temperature [2 steps **6** (27%), **7** (22%)].

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14. Treatment of **13a** with 1 equiv. of $ZnBr_2$ at room temperature for 72 h gave a mixture of **14a** and **15a** (1:5.8) in only 9.9% yield and 88.7% of **13a** was recovered.
15. On treatment with $ZnBr_2$ under the conditions of entry 5, undesired **15a** isomerized gradually to desired **14a** and after 25 h the ratio of **14a** and **15a** was 19:1.
16. The selectivity in entry 9 could be improved by prolonged treatment with $ZnBr_2$, but the yield was gradually lowered because the BOM group was not completely stable to $ZnBr_2$. Therefore, the reaction was stopped within 8 h.
17. Two Zn ions in **16** are situated in positions apart from each other. On treatment with excess $ZnBr_2$, the silyl ether (**17**) gave a 1:1 mixture of *trans* and *cis* tetrahydrofuran (B-ring) derivatives, because the C_{13}-O did not chelate with zinc cation.
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