Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1021–1025
Tetrahedron Letters

# Stereo-controlled synthesis of prelasalocid, a key precursor proposed in the biosynthesis of polyether antibiotic lasalocid A

Akira Migita, Yoshihiro Shichijo, Hiroki Oguri *, Mami Watanabe, Tetsuo Tokiwano, Hideaki Oikawa *

*Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan*

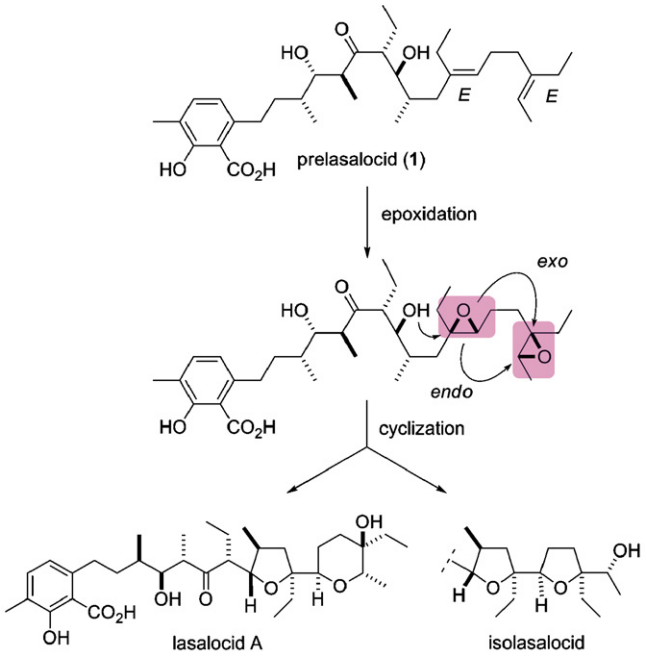
Received 9 November 2007; revised 28 November 2007; accepted 3 December 2007
Available online 5 December 2007

**Abstract**

In the biosynthesis of a polyether ionophore antibiotic, lasalocid A, the cyclic ether skeleton composed of a tetrahydrofuran linked to a tetrahydropyran could be constructed by oxidative cyclization of linear dodecaketide diene precursor. Hence, we hypothesized a prelasalocid having (*E*,*E*)-trisubstituted olefins as the dodecaketide biosynthetic precursor. A stereo-controlled synthetic route to the prelasalocid has been devised in a highly convergent manner entailing installation of a variety of substituents at the trisubstituted olefins.


*Keywords:* Lasalocid; Polyether antibiotics; Biosynthesis; Trisubstituted olefin; Aldol coupling

Polyether antibiotics exhibit a selective antimicrobial activity against Gram-positive bacteria and have been used for the control of chicken coccidiosis as well as the growth promotion in animal husbandry.[1] Lasalocid A[2] and isolasalocid,[3] isolated from the *Streptomyces lasaliensis*, are polyether ionophore antibiotics and have distinct cyclic ether skeletons on the right side of the molecules, a tetrahydrofuran linked to a tetrahydropyran and two adjacent tetrahydrofuran rings, respectively (Scheme 1). A hypothetical biosynthetic mechanism has been proposed, which involves stereoselective epoxidations of the dodecaketide linear precursor followed by sequential cyclizations with divergent modes of ring-closure leading to co-production of lasalocid A and isolasalocid.[3] This insightful hypothesis was supported by feeding experiments[4] with isotopically labeled precursors including [1-$^{13}$C,1-$^{18}$O]-short chain fatty acids, indicating that two oxygen atoms on the ether rings could be derived from molecular oxygen by the corresponding epoxidation of a (*E*,*E*)-diene precursor, prelasalocid




Scheme 1. Hypothetical biosynthetic pathway of lasalocid A.

* Corresponding authors. Tel.: +81 11 706 2622; fax: +81 11 706 3448.
*E-mail addresses:* oguri@sci.hokudai.ac.jp (H. Oguri), hoik@sci.hokudai.ac.jp (H. Oikawa).

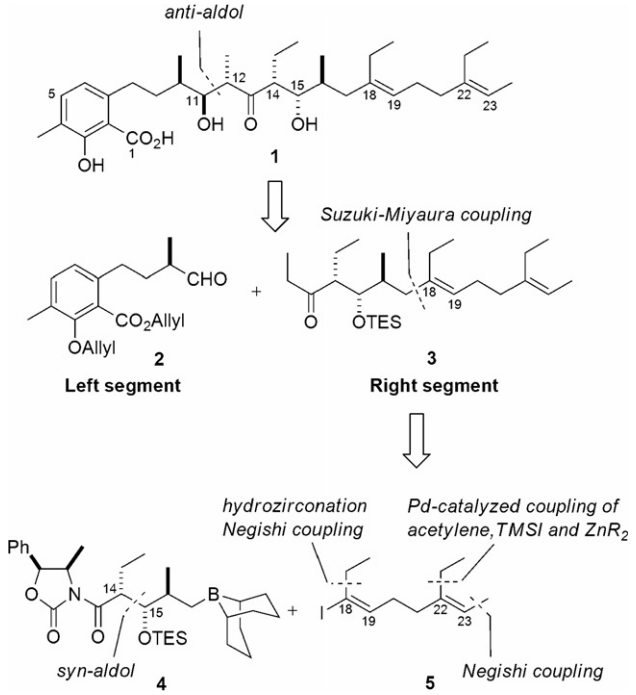
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.003

(**1**). These data and the studies on monensin biosynthesis brought a unified theory, Cane–Celmer–Westley hypothesis for polyether formation.[5] Recently, Cambridge group has identified biosynthetic gene cluster of a representative polyether antibiotic monensin[6] and succeeded isolation of a putative triene intermediate analog from gene-disruption mutant.[7] To date, however, an enzymatic conversion of triene or triepoxide has not been reported. To gain mechanistic insights into the polyether formation in lasalocid biosynthesis based on the enzymatic conversions of linear substrate possessing either dienes or epoxides, we have initiated to develop a synthetic route to prelasalocid **1**. Herein, we describe the synthesis of **1** based on a convergent strategy that features stereo-controlled constructions of trisubstituted olefins and an *anti*-selective aldol coupling.

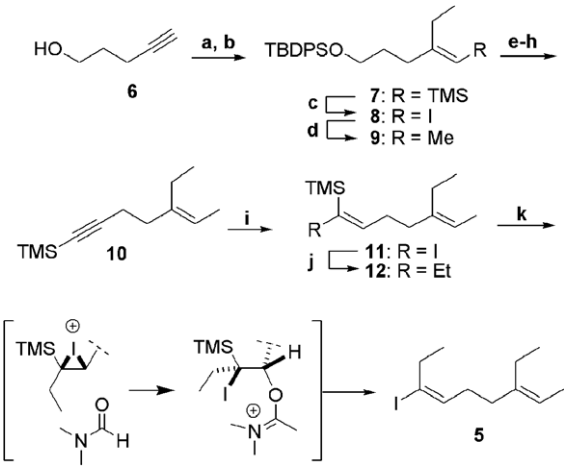
To obtain mechanistic insight between substrate specificity and enzymatic polyether formation, it is necessary to develop a flexible route for synthesizing various substrate analogs. The retrosynthetic disconnections of prelasalocid **1** are outlined in Scheme 2. Since degradation of benzyl ester of lasalocid A through the retro-aldol fragmentation at $C_{11}$–$C_{12}$ was reported to provide the optically pure aldehyde as a left segment, we employed a convergent strategy that unifies aldehyde **2**[8] and ethylketone **3** by an *anti*-selective aldol coupling. The key right segment **3** would be assembled by *B*-alkyl Suzuki–Miyaura coupling[9] of alkylborane **4** and iodoolefin **5** installing the $C_{18}$–$C_{19}$ trisubstituted olefin. The alkylborane part **4** would be synthesized by *syn*-selective aldol coupling between $C_{14}$ and $C_{15}$. For the synthesis of iodoolefin **5** having the pair of trisubstituted olefins, we devised a flexible and stereo-controlled synthetic route that entails diversification of olefin geometry as well as the introduction of variety of substituents at $C_{18}$, $C_{22}$, and $C_{23}$.

Synthesis of **5** commenced with the protection of commercially available 4-pentyn-1-ol **6** as a silyl ether (Scheme 3). The palladium-catalyzed coupling of a terminal acetylene, TMSI and $Et_2Zn$ stereoselectively produced the 2,2-disubstituted (*E*)-vinylsilane **7** in 45% yield.[10] The regio- and stereo-selectivities of the conversion are supported by a mechanistic rationale that involves regio-controlled silylpalladation of a terminal acetylene followed by coupling of the resulting alkenylpalladium(II) with $Et_2Zn$. Treatment of vinylsilane **7** with NIS in $CH_3CN$ afforded (*E*)-iodoolefin **8** in 95% yield with retention of the olefin geometry. The Negishi coupling with Grignard-derived methylzinc chloride furnished the terminal trisubstituted (*E*)-olefin **9** in 96% yield. Removal of the silyl group and subsequent Swern oxidation yielded an aldehyde, which was then converted to silylacetylene **10** under the Corey–Fuchs conditions.[11] The terminal silylacetylene **10** was then converted by hydrozirconation using $Cp_2Zr(H)Cl$, generated in situ from $Cp_2ZrCl_2$ and DIBAL,[12] followed by treatment with NIS to afford iodovinylsilane **11** in one pot as a single isomer in 69% yield. The ethyl group was installed by Negishi coupling with Grignard-derived ethylzinc chloride to give (*Z*)-vinylsilane **12** in nearly quantitative yield. Upon treatment with NIS in DMF under Tamao's conditions,[13] iodation of (*Z*)-vinylsilane **12** proceeded smoothly with complete inversion of the olefin geometry, presumably through *anti*-addition of iodide and DMF and subsequent *anti*-elimination, to afford the desired (*E*)-iodoolefin **5** in 53% yield.

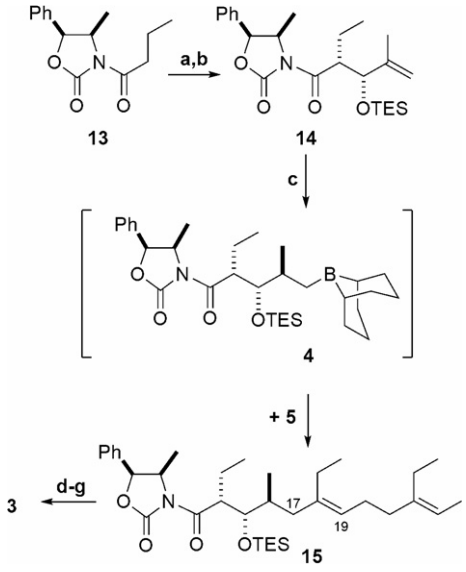
Next, we turned our attentions to the *B*-alkyl Suzuki–Miyaura coupling of alkylborane **4** and **5** leading to the



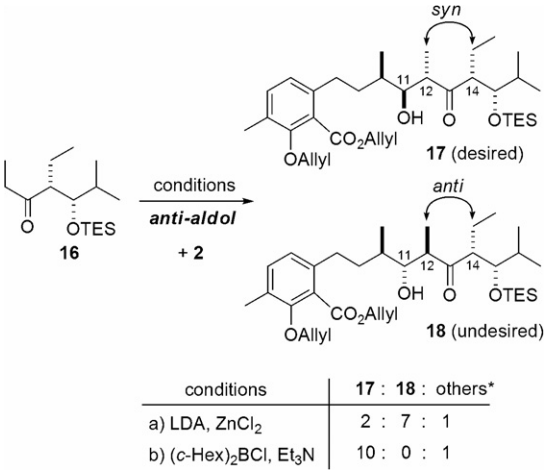

Scheme 2. Synthetic strategy for prelasalocid (**1**).




Scheme 3. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 98%; (b) $Et_2Zn$, TMSI, 5 mol % $Pd(PPh_3)_4$, 1,4-dioxane, 45%; (c) NIS (1.2 equiv), $CH_3CN$, 95%; (d) $ZnCl_2$, MeMgBr, $Pd(PPh_3)_4$, THF, 96%; (e) $Bu_4NF$, THF; (f) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 to −45 °C; (g) $CBr_4$, $PPh_3$, pyridine, $CH_2Cl_2$, 53% (three steps); (h) *n*-BuLi, TMSCl, THF, −78 °C, 95%; (i) $Cp_2ZrCl_2$ (1.5 equiv), DIBALH (1.5 equiv), then NIS (1.2 equiv), THF, 10 °C, 69%; (j) EtMgBr, $ZnCl_2$, $Pd(PPh_3)_4$, THF, 99%; (k) NIS (1.2 equiv), DMF, 53%.




Scheme 4. Reagents and conditions: (a) $Bu_2BOTf$, $(i\text{-}Pr)_2NEt$, methacrolein, $CH_2Cl_2$, −78 °C, 95%; (b)TESCl, imidazole, DMF, rt, 98%; (c) **14** (3.0 equiv), 9-BBN dimer (3.0 equiv), THF, 0 °C, then $Cs_2CO_3$ (3.0 equiv), 10 mol % $Pd(dppf)Cl_2$, **5** (1.0 equiv), THF/1,4-dioxane/$H_2O$ = 10:8:1, rt, 82%; (d) EtSH, *n*-BuLi, THF, −78 °C, 91%; (e) DIBALH, $CH_2Cl_2$, −78 °C, 92%; (f) EtMgBr, THF, −78 °C, 94%; (g) Dess–Martin periodinane, $CH_2Cl_2$, 98%.




| conditions | 17 : 18 : others* |
|---|---|
| a) LDA, $ZnCl_2$ | 2 : 7 : 1 |
| b) $(c\text{-Hex})_2BCl$, $Et_3N$ | 10 : 0 : 1 |

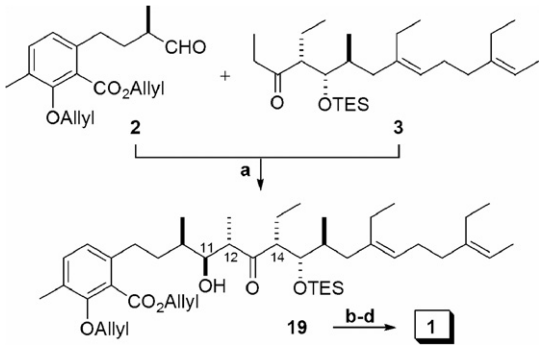
Scheme 5. Reagents and conditions: (a) (i) LDA (1.5 equiv), $Et_2O$, 0 °C, 30 min, (ii) $ZnCl_2$ (1.5 equiv), 0 °C, 30 min, (iii) **2** (1.0 equiv), $Et_2O$, 0 °C, 10 min, **17** (12%), **18** (42%), **16** (15% recovery); (b) $(c\text{-Hex})_2BCl$ (1.2 equiv), $Et_3N$ (1.2 equiv), then **2** (1 equiv), THF, −78 °C, **17** (27%), **16** (42% recovery). *Mixture of other aldol adducts.

right segment **3** (Scheme 4). Synthesis of precursor **15** of **3** began with *syn*-selective Evans aldol reaction[14] of **13** with methacrolein and subsequent silyl ether formation to give **14** in 93% yield (two steps). Diastereo-controlled hydroboration of **14** with 9-BBN generated the corresponding alkyl borane **4**,[15] which was in situ treated with **5** under the conditions [aqueous $Cs_2CO_3$, $Pd(dppf)Cl_2$, THF/1,4-dioxane/$H_2O$ = 10:8:1, rt][16] to produce **15** in 82% yield. The (*E*)-configuration of the resulting trisubstituted olefin of **15** was confirmed on the basis of NOE correlation between methylene protons at C17 and a vinyl proton at C19. Removal of the oxazolidinone group to form a thioester and stepwise installation of the ethylketone functionality yielded **3** in good yields.

With the elaborated **3** in hand, model studies for the critical *anti*-aldol reaction for the assembly of the left and right segments were examined using a readily accessible ethylketone **16** (Scheme 5). As an initial attempt, we applied the Kishi's procedure employing a zinc-enolate, which was reported to effect the *anti*-aldol reaction leading to the total synthesis of lasalocid A.[17] Deprotonation of **16** with LDA (1.5 equiv) in $Et_2O$ at 0 °C and subsequent addition of $ZnCl_2$ (1.5 equiv) generated the zinc enolate, which was treated with aldehyde **2** in one pot at 0 °C for 10 min to form a mixture of aldol adducts in 60% yield. Apart from the minor isomers, the resulting two adducts (**17**:**18** = 2:7) were *anti*-aldol adducts. However, desired **17** ($C_{11}$,$C_{12}$-*anti*, $C_{12}$,$C_{14}$-*syn*) was obtained in 12% yield as a minor product, and instead, **18** ($C_{11}$,$C_{12}$-*anti*, $C_{12}$,$C_{14}$-*anti*) predominantly formed in 42% yield. As a rationale for the different stereochemical outcomes between model **16** with $C_{14}$ silyl ether and Kishi's fully elaborated substrate **20**[17] having cyclic ether rings, the distinct modes of zinc chelation are surmised to play a pivotal role in the double asymmetric induction for the condensation with chiral aldehyde **2**. The stereochemistry of the *anti*-aldol adduct **17** was unambiguously determined based on NMR analysis after conversion into 1,3-diol acetonides **21** and **22**.[18]

To attain the desired stereoselectivity ($C_{11}$,$C_{12}$-*anti*, $C_{12}$,$C_{14}$-*syn*), we next adopted an alternative approach for the *anti*-aldol reaction using sterically demanding dialkylboron enolate reported by Paterson et al.[19] Treatment of **16** with $(c\text{-Hex})_2BCl$ (1.2 equiv) and $Et_3N$ (1.2 equiv) generated the (*E*)-boron enolate, which was then condensed with aldehyde **2** to afford the desired *anti*-aldol adduct **17** as a major product in 27% yield along with minor aldol adducts (**17**:others = 10:1) and recovered **16** (42%). Since lasalocid A is labile to the retro-aldol fragmentation at $C_{11}$–$C_{12}$ under basic conditions, equilibrium between substrates and aldol adducts is probably responsible for the low yield of this reaction. Despite several experimentations, no significant improvement has been achieved so far. Nonetheless, it is worth mentioning that the formation of undesired **18** was completely suppressed under the conditions. Taking into account for the remarkable diastereoselectivity as well as the substantial recovery of ethylketone **16** which was actually recycled, we employed the boron-aldol approach for the condensation of the elaborated **3**.

As shown in Scheme 6, the assembly of the left and right segments (**2**, **3**) was achieved by the boron enolate mediated *anti*-aldol coupling to produce desired aldol adduct **19** in 27% yield (**3**: 40% recovery) in a highly stereo-controlled manner (**19**:other aldol adducts = 10:1).[20] Finally, the protecting group manipulations were conducted in three steps: (1) silylation of $C_{11}$ hydroxyl group; (2) palladium-catalyzed cleavage of *O*-allyl groups; (3) removal of TES




Scheme 6. Reagents and conditions: (a) $(c\text{-Hex})_2BCl$ (1.2 equiv), $Et_3N$ (1.2 equiv), then **2** (1.0 equiv), THF, −78 °C, 1 h, **19** (27%), **3** (40% recovery); (b) TESCl, imidazole, DMF, rt; (c) $HCO_2H$, $Et_3N$, $Pd(PPh_3)_4$, THF, rt; (d) HF, $CH_3CN$, rt, 84% (three steps).

groups at $C_{11}$ and $C_{15}$ by treatment with HF, leading to the targeted prelasalocid **1** in 84% overall yield.[21]

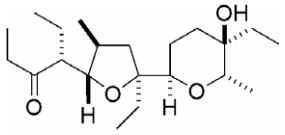
In summary, the convergent synthesis of prelasalocid **1** has been achieved in a highly stereo-controlled manner. The trisubstituted olefins ($C_{18}$–$C_{19}$ and $C_{22}$–$C_{23}$) were successfully synthesized by transition-metal mediated construction of vinyl silanes, stereo-divergent iodination by NIS, and Negishi and Suzuki–Miyaura cross-couplings. The efficient access to prelasalocid **1** and its analogues paves the way for extensive investigation for substrate specificities of epoxidase and hydrolase that effect the cyclic ether formations on the right side. Recently, we have identified a gene cluster for lasalocid biosynthesis. The enzymatic conversions of **1** and its analogues will be reported in due course.

## Acknowledgments

We are grateful to Kaken Pharmaceutical Co. Ltd for supplying generous amount of natural lasalocid A, and to High Resolution NMR Laboratory, Faculty of Science, Hokkaido University, for NMR measurements. This work was supported by the Mitsubishi Foundation, and the Grants-in-Aid for Scientific Research [(A)17208010 to H. Oikawa and 17710175 to H. Oguri] from the Japan Society for the Promotion of Science (JSPS). A fellowship to A.M. from JSPS is gratefully acknowledged.

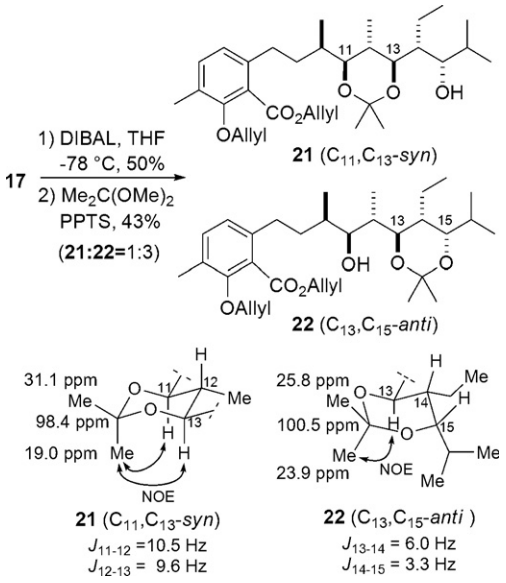
## References and notes

1. *Polyether Antibiotics: Naturally Occurring Acid Ionophores, Biology*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982.
2. Breger, J.; Rachlin, A. I.; Scott, W. E.; Sternbach, L. H.; Goldberg, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 5295.
3. Westley, J. W.; Blount, J. F.; Evans, R. H., Jr.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597.
4. (a) Hutchinson, C. R.; Sherman, M. M.; Vederas, J. C.; Nakashima, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 5953; (b) Hutchinson, C. R.; Sherman, M. M.; McInnes, A. G.; Walter, J. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 5956.
5. Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
6. Leadlay, P. F.; Staunton, J.; Oliynyk, M.; Bisang, C.; Cortes, J.; Frost, E.; Hughes-Thomas, Z. A.; Jones, M. A.; Kendrew, S. G.; Lester, J. B.; Long, P. F.; McArthur, H. A. I.; McCormick, E. L.; Oliynyk, Z.; Stark, C. B. W.; Wilkinson, C. J. *J. Ind. Microbiol. Biotechnol.* **2001**, *27*, 360.
7. Bhatt, A.; Stark, C. B. W.; Harvey, B. M.; Gallimore, A. R.; Demydchuk, Y. A.; Spencer, J. B.; Staunton, J.; Leadlay, P. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 7075.
8. The left segment **2** was readily prepared from sodium salt of lasalocid A: (1) allyl bromide, $K_2CO_3$, dioxane (92%); (2) pyrolysis (230 °C), 5 min, 65%, see: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
9. For excellent reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Chemler, S. R.; Traunar, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.
10. Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S. *J. Org. Chem.* **1995**, *60*, 1834.
11. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
12. Kiyotsuka, Y.; Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 2725.
13. Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.
14. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
15. Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.
16. Mickel, S.; Sedelmeier, G. H.; Niederee, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R. *Org. Process Res. Dev.* **2004**, *8*, 113.
17. Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. Structure of right segment **20** for the *anti*-aldol reaction for the Kishi's total synthesis of lasalocid A is shown below:




**20**

18. The stereochemistry of the aldol adduct **17** was determined as $C_{11}$,$C_{12}$-*anti* and $C_{12}$,$C_{14}$-*syn* by extensive NMR analysis ($^1H$, $^{13}C$ NMR, and NOE experiments) on the corresponding acetonides converted from **17**. The stereochemistry of **18** was also determined in a similar manner. Selected $^1H$ NMR data of **21**: $\delta$ 3.78 (br d, $J = 10.5$ Hz, $H_{11}$), 3.47 (br d, $J = 9.6$ Hz, $H_{13}$), 1.79 (ddq, $J = 10.5$, 9.6, 3.3 Hz, $H_{12}$), **22**: $\delta$ 3.55 (t, $J = 6.0$ Hz, $H_{13}$), 3.31 (dd, $J = 9.6$, 3.3 Hz, $H_{15}$), 1.40 (ddt, $J = 6.0$, 3.3, 3.3 Hz, $H_{14}$).



19. Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685.
20. The stereochemistry of the aldol adduct **19** was confirmed based on a comparison of $^{1}$H NMR data of **17**.
21. *Data for prelasalocid* **1**: $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.19 (d, $J = 7.5$ Hz, 1H), 6.63 (d, $J = 7.5$, 1H), 5.14 (q, $J = 6.9$ Hz, 1H), 5.07 (t, $J = 6.6$ Hz, 1H), 3.95 (dd, $J = 8.2$, 2.7 Hz, 1H), 3.71 (dd, $J = 9.6$, 1.5 Hz, 1H ), 3.16 (dt, $J = 10.1$, 3.9 Hz, 1H), 2.96 (qn, $J = 7.8$ Hz, 1H), 2.72 (dt, $J = 9.6$, 1.5 Hz, 1H), 2.70 (dt, $J = 10.1$, 3.9 Hz, 1H), 2.21 (s, 3H), 1.83–2.02 (m, 12H), 1.17 (m, 1H), 1.56 (d, $J = 6.6$ Hz, 3H), 1.30–1.53 (m, 3H), 1.02 (d, $J = 8.2$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 9.0$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 217.6, 171.1, 167.8, 161.4, 143.7, 141.6, 139.4, 134.9, 126.3, 124.3, 121.3, 117.6, 77.2, 76.8, 74.7, 73.9, 57.3, 67.6, 41.9, 36.9, 36.8, 34.5, 34.3, 34.0, 26.5, 23.7, 23.0, 22.8, 22.7, 13.4, 13.2, 13.1, 12.9, 12.8; IR(neat) $\nu_{max.}$ 2963, 1700, 1655, 1257, 1093, 844 cm$^{-1}$; HRMS(ESI) calcd for $C_{34}H_{54}O_6Na$ $[M+Na]^+$ 581.7787; found 581.7762.