HIGHLY STEREOSELECTIVE SYNTHESIS OF ANTITUMOR ANTIBIOTICS, (+)-ACTINOBOLIN AND (-)-BACTOBOLIN, BY ASYMMETRIC CYCLIZATION

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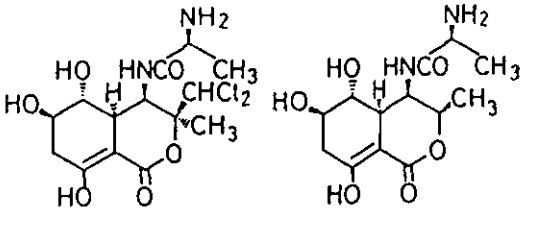
Abstract- A common skeleton of (+)-actinobolin and (-)-bactobolin was efficiently formed by an intramolecular Diels-Alder reaction of a chiral Z diene with a substituent at the pentadienylic carbon, and the following transformation completed the first total synthesis of (+)-actinobolin from L-threonine.

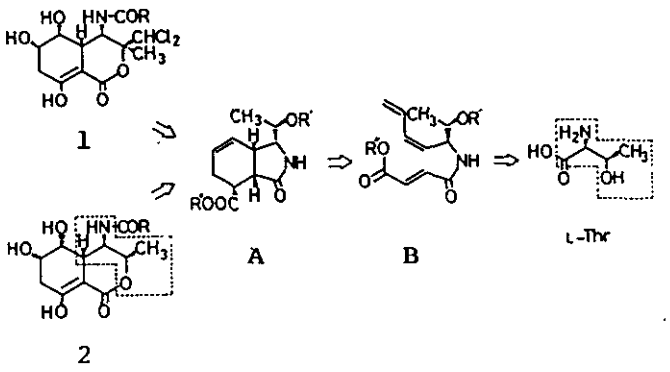
Bactobolin, recently isolated from the culture broth of a Pseudomonas, has been shown to be a structural analog of actinobolin isolated from a Streptomyces in 1959.[1,2] The antitumor and antibiotic activities of bactobolin are remarkably stronger than those of actinobolin in spite of the close structural similarity. The absolute structure was first proposed chemically[2a] to be (3S,4R,4aR,5R,6R)-4-(L)-alanylamino-3-(dichloromethyl)-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-1H-2-oxa-1-naphthalene (1) in 1979 and it was confirmed by X-ray crystallographic analysis of the hydrobromide[2b] in 1980. The unique polyfunctional structure containing five asymmetric carbons located consecutively within such a simple bicyclic system and biological activity of bactobolin (1) and



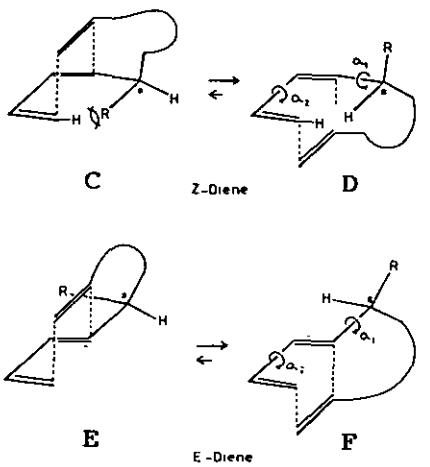
1 2

(-)-Bactobolin (+)-Actinobolin

Retrosynthesis



Scheme 1



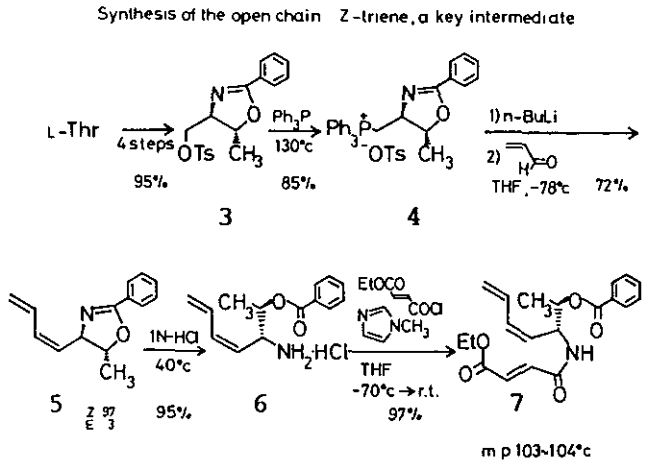
Scheme 2

actinobolin (2) distinguish these molecules as unusually interesting targets for synthesis. We report here the first total synthesis of actinobolin and also a synthetic approach to a potential intermediate of bactobolin. As shown in Scheme 1, the key features of the present strategy include: (1) use of L-threonine as a chiral synthon for the introduction of two asymmetric carbons contained in the δ-lactone moiety of 1 and 2; (2) transformation to a chiral diene (**B**) from L-threonine, possessing not only Z stereochemistry but also a

chiral substituent at the pentadienylic position;(3) the key step is the stereocontrolled formation of the bicyclic γ-lactam by the intramolecular Diels-Alder reaction of the Z-triene (**B**); (4) stereocontrolled functionalization of the cyclohexane ring; (5) conversion of γ-lactam (**A**) to δ-lactone derivatives, and complete elaboration of **1** and **2**. The intramolecular Diels-Alder reactions occupy a prominent position in contemporary organic synthesis.[3] However, only a few examples of the successful intramolecular cycloaddition of Z-dienes have thus far been reported.[4,5,6] Especially, only **Fuchs** et al. recently showed remarkable success in the chiral and stereochemical control of a potential intermediate for the synthesis of cytochalasin C by using an intramolecular Diels-Alder reaction of a Z-diene possessing a substituent at the pentadienylic center[6,7], although the total synthesis of the natural product was not completed yet. We are also independently interested in such a concept and initiated a synthetic program of **1** and **2** just after the structural determination of **1**.[2b] The reason that a diene of the Z configuration is more preferable to that of the E configuration should briefly be mentioned here. As shown in Scheme 2, an E-diene has two relatively easily accessible transition states (**E** and **F**) which afforded mixtures of cis- and trans-fused products as demonstrated by many recent examples.[7b] However, there is a considerable energy-difference between the two transition states (**C** and **D**) for a Z-diene and essentially only one transition state **D** will be preferred from the nonbonded interactions between the substituent (R) at the pentadienylic center and the Z hydrogen at the diene terminus.

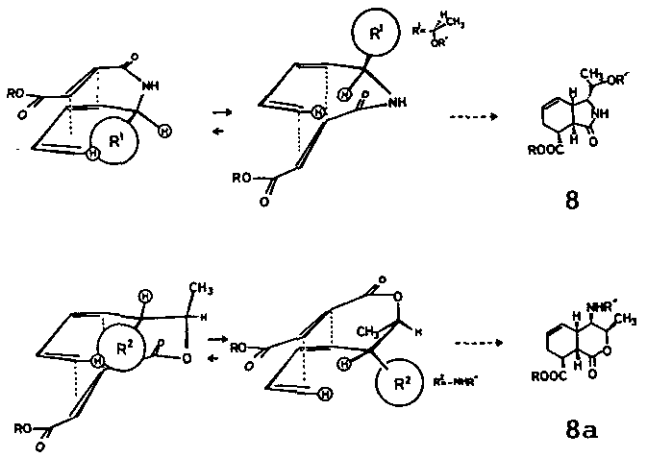
Synthesis of Chiral Z triene 7, a key intermediate (Scheme 3). L-Threonine was converted into the tosylate **3** of (4R,5R)-5-methyl-2-phenyl-Δ^2-oxazoline-4-methanol by 4 step known procedures[8] (EtOH/HCl → ethyl benzimidate → $LiAlH_4$ → TsCl, 95% overall yields). The phosphonium tosylate **4** obtained by treatment of neat **3** with Ph_3P at 130°C (85% yield) was directly subjected to Wittig reaction by treatment with n-BuLi and thence with acrolein in THF at -78°C, affording the Wittig product **5** in 70% yield[9] after chromatography on SiO_2. The ratio of Z- and E-isomers was determined to be 97 to 3 by gas chromatography, and the Z-stereochemistry of the main product was strongly supported by NMR[10], but the mixture was subjected to the following reactions without separation. Selective

hydrolysis of 5 to 6 took place smoothly with 1N HCl in EtOH-H_2O (1:1) at 40°C for 3h (95% yield). Reaction of 6 with ethyl (E)-3-chloroformylacrylate[11] in the presence of methylimidazole (4eq) afforded crystalline triene 7 in 97% yield. The Z-triene 7 was purified most conveniently at this stage by recrystalliza-



Scheme 3

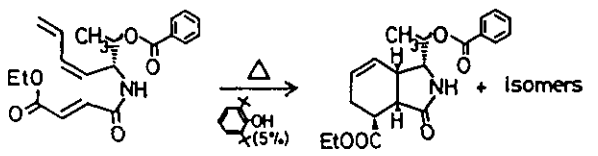
tion from a mixed solvent of ether and n-hexane[15] (1:1) [mp 103-104°C, Rf 0.53 (Et_2O-n-Hexane=3:2), $[\alpha]_D^{25}$+110.2° (c 0.80 $CHCl_3$)]. *The dienophile thus prepared* by N-acylation is the desired compound for the requisite stereochemistry of 1 and 2, but the other dienophile able to be prepared by O-acylation from 6 and ethyl (E)-3-chloroformylacrylate will give the Diels-Alder product **8a** with wrong stereochemistry at the ring junction as shown in Scheme 4.



Scheme 4

Intramolecular Diels-Alder Reaction of the Chiral Z-Triene. Now, the key reaction of the present strategy was investigated as shown in Table 1. Heating a solution of the Z-triene **7** (800mg) in benzene (50ml) at 180°C in a sealed tube for 5h produced bicyclic compound **8** as the only isolable product after purification by column chromatography on SiO_2 (Et_2O:Hexane=1:1) in 95% yield (Rf, 0.50 (Et_2O), $[\alpha]_D^{20}$-52.3° (c 1.07, $CHCl_3$). Careful survey of the product by 400MHz ^1H NMR showed that the desired Diels-Alder adduct is almost exclusively formed and the very minor peaks were assumed to be due to the isomer. The ratio of **8** and the isomer was calculated to be at least 20 to 1, although the isomer was hardly able to be characterized further. This finding demonstrates that cyclization has occurred very stereoselectively through an expected preferred single diastereomeric transition state as shown in Scheme 5. Furthermore, π,π-orbital overlap[12] of the phenyl ring of the ester and the diene moieties probably even more effectively shields the β-face as shown in Figure 1. The structure **8** was strongly supported by 400MHz ^1H NMR as shown in Figure 2.

Intramolecular Diels-Alder reaction of the Z-triene

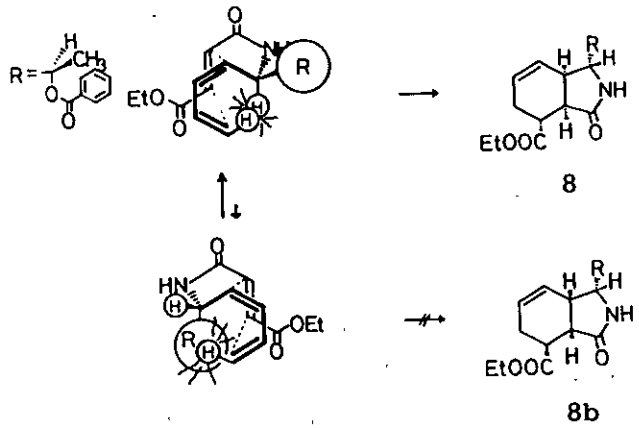


7 8

solv.	temp.(°C)	time(hr.)	ratio	yield(%)
Benzene*	130	50	>20 : 1	91
Benzene*	150	9	>20 : 1	97
Benzene*	180	2	>20 : 1	95
o-Dichlorobenzene	180	2	—	95

* in a sealed tube

Table 1



Scheme 5

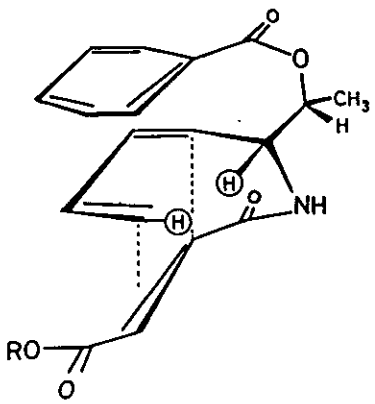


Figure 1

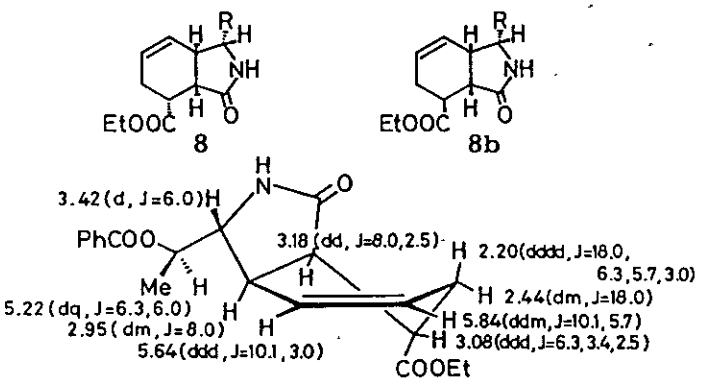
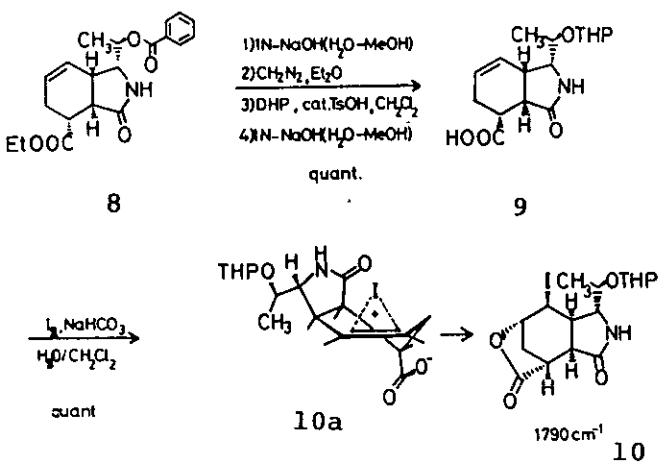


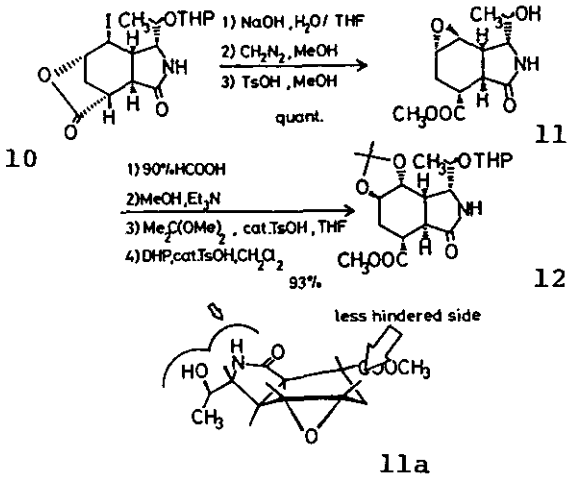
Figure 2

Stereocontrolled Construction of the Common Skeleton (Scheme 6,7, and 8). The required introduction of the vicinal hydroxyl groups was completed in a stereospecific manner. The protective group of the hydroxyl function of **8** was replaced by THP to afford **9** by sucessive treatment with NaOH, CH_2N_2, DHP/TsOH(cat.), and NaOH in almost quantitative yields. Then, the THP derivative **9** was subjected to iodolactonization to afford γ-lactone **10** stereospecifically probably through

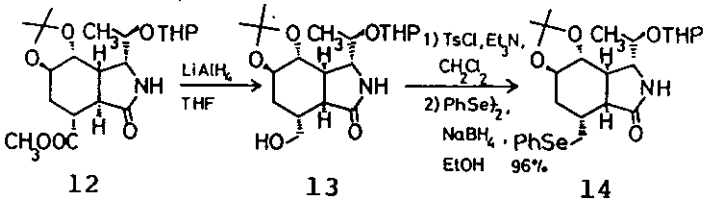


Scheme 6

10a in quantitative yield, [1790 and 1708cm^{-1}, Rf, 0.45 (Et_2O)]. Treatment of **10** with NaOH in aq THF, CH_2N_2 in MeOH and followed by TsOH in MeOH afforded epoxide **11** in almost quantitative yield. The epoxide **11** was considered to undergo selective cleavage from the less hindered side as shown in Formula **11a**. Thus, the epoxide **11** was subjected to acid-catalyzed cleavage (90% HCOOH at 50-60°C for 2h) and then treatment with Et_3N in MeOH to afford the desired glycol. The glycol was protected with isopropylidene group (dimethoxypropane, cat. TsOH) and thence converted to THP derivative to afford **12**, and the structure was fully characterized by spectroscopic analysis[16] (93% overall yields from **11**). The conversion described above clearly showed that the ethoxycarbonyl group is playing key roles in the present strategy. It not only activates the dienophile group but also stereochemically controls the introduction of the glycol of the six-membered ring. Now, the methoxycarbonyl group must be convered to the keto or keto-equivalent group required for **1** and **2**. The ester group of **12** was reduced with $LiAlH_4$ and the resulting alcohol **13** was treated with $TsCl/Et_3N$ followed



Scheme 7

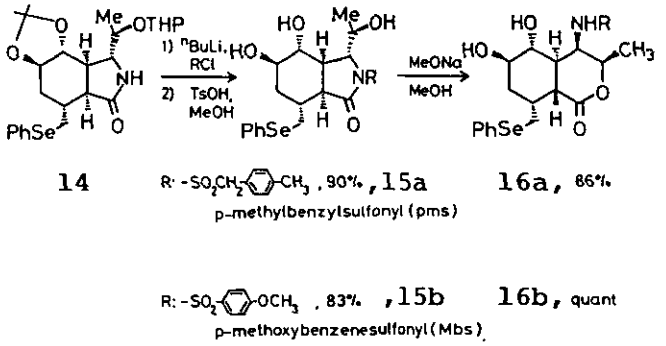


Scheme 8

by sodium selenophenolate generated in situ from diphenyl diselenide and $NaBH_4$ to afford phenylseleno derivative **14**, a common intermediate to **1** and **2**, in 95% yield after purification by column chromatography on SiO_2.

Synthesis of (+)-Actinobolin (1) by Conversion of γ-Lactam to δ-Lactone. The crucial step of the present approach is how to convert the stable γ-lactam to unstable δ-lactone. This problem was solved in the following way. It was considered to be necessary to activate the γ-lactam moiety, since the original Diels-Alder adduct **8** and other lactams were shown to resist strongly acid- and base-catalyzed cleavage. Therefore, Fujino's sulfonyl reagents were selected to cause selective cleavage of the amide bond in the γ-lactam **14**. p-Methylbenzylsulfonyl (pms) derivative[13a] **15a** and p-methoxybenzenesulfonyl (Mbs)[13b] **15b** were

prepared in excellent yields from reactions of **14** and the corresponding sulfonyl chlorides and n-BuLi at -78°C. The sulfonyl derivatives **15a** and **15b** underwent smooth cleavage with MeONa in MeOH under reflux for 1h to afford the desired δ-lactone **16a** and **16b** in 86% and quantitative yield respectively, after separation by column chromatography on SiO_2 (Scheme 9). The δ-lactone **15a** showed



Scheme 9

mp 233-234°C after recrystallization from EtOH, $[\alpha]_D^{20}$ + 35.5° (c 0.234, MeOH). The complete structure of **16**, although firmly supported by spectral analysis, was unambiguously verified by X-ray analysis (Figure 3)[15], showing that the

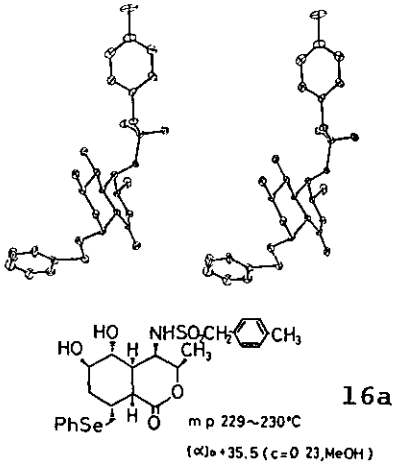
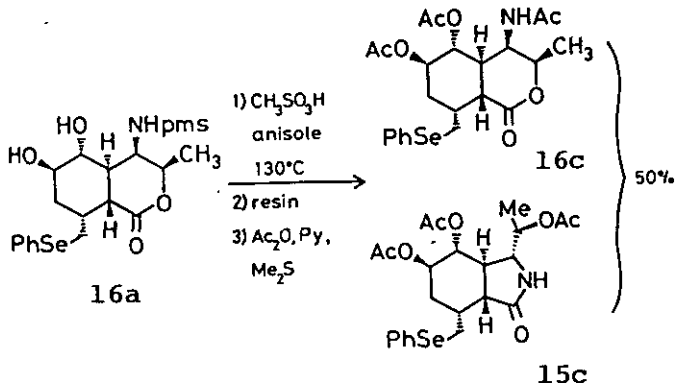
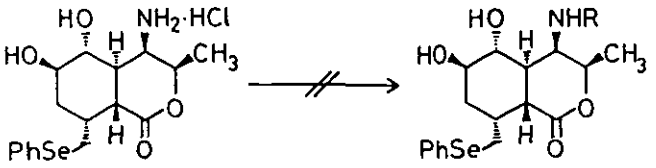


Figure 3

cis junction in **15a** is now isomerized to trans junction in **16a**. The final phase of the present synthesis of **2** is to convert **16a** to the alanyl derivative by removal of the sulfonyl group and to introduce a keto function for the phenylselenomethyl group. All attempts to remove first the sulfonyl group with conventional reagents (HF or CH_3SO_3H) were unsatisfactory not only in the yield (Scheme 10, at best 50%) but in the next amide formation-step with Z-alanine (Scheme 11). A considerable steric hindrance for the axial amino group was considered for the δ-lactone **16a**. Therefore, the introduction of a keto function followed by alanyl formation was considered to be the preferred approach to **2** because there might be far less steric hindrance for the quasi-axial amino group of β-keto-δ-lactone shown in Figure 4. Treatment of **16a** with ozone at -78°C in CH_2Cl_2-MeOH and then pyridine afforded the corresponding exomethylene derivative (93% yield) purified by column chromatography on SiO_2 (Scheme 12). The oily



Scheme 10



16d 16e

- Z-Ala, DCC, Et_3N, DMF
- Z-Ala, $PyS)_2$, Ph_3P, Et_3N, CH_3CN
- Z-Cl, Py, DMF
- Z-Cl, $NaHCO_3$, H_2O
- Boc-S, Et_3N, H_2O, Dioxane

Scheme 11

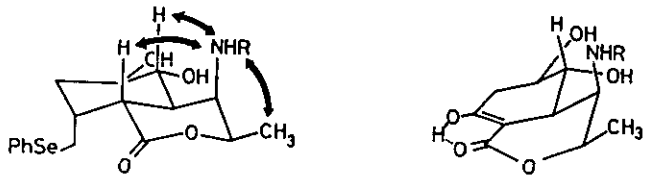
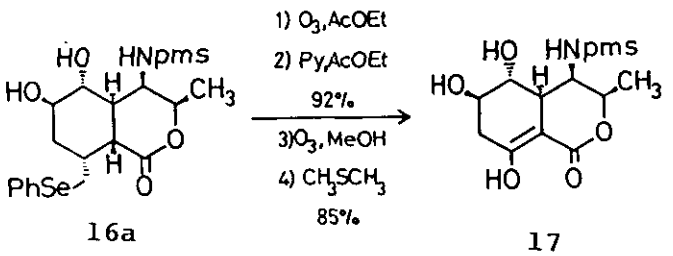


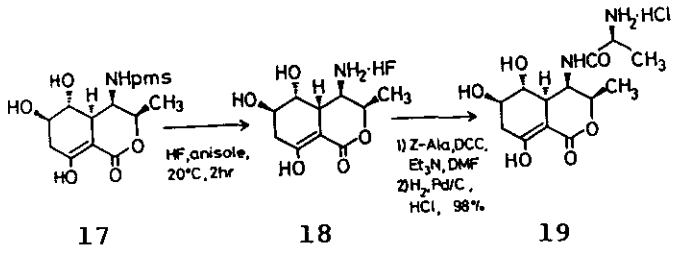
Figure 4



16a 17

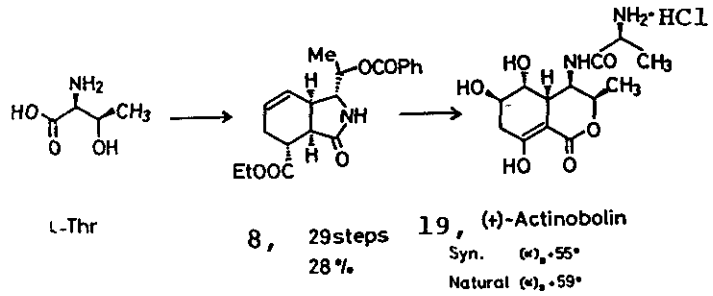
Scheme 12

material was further subjected to ozonolysis at -50°C. After the usual workup with CH_3SCH_3 and chromatography on SiO_2, the β-keto δ-lactone **17** was obtained in 85% yield. Now, removal of the sulfonyl group of **17** proceeded very smoothly with HF(anisole, 20°C, 2h) to afford HF salt **18** in 98% yield. The last step for the total synthesis of **2** was completed by reaction of **18** and Z-alanine in the presence of DCC/Et_3N in DMF followed by hydrogenolysis with H_2/Pd-C in MeOH-AcOH containing 2N HCl, affording the hydrochloride **19** completely identical with natural (+)-actinobolin hydrochloride[16], $[\alpha]_D^{22}$+55° (c 0.47, H_2O) for synthetic **19**; $[\alpha]_D^{22}$+59° (c 0.41, H_2O) for natural **19**](Scheme 13). The total synthesis of (+)-actinobolin consists of 29 steps in 28 overall yields from L-threonine including all steps for protection and removal (Scheme 14).



17 18 19

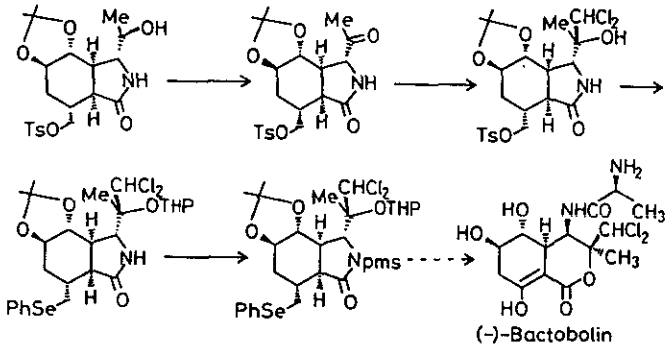
Scheme 13



Scheme 14

Synthetic efforts to (-)-bactobolin using the common intermediate **13** and **14** are now in progress according to the procedures outlined in Scheme 15, and the results will be published in due course.

In conclusion, we have completed the first total synthesis of (+)-actinobolin by asymmetric cyclization and could add a notable example in which the intramolecular Diels-Alder reaction of a chiral Z diene with a substituent at the pentadienylic carbon has been shown to be a really efficient methodology for the construction of a key intermediate to actinobolin and bactobolin.



Scheme 15

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(10) The ^{1}H NMR of the 1,3-diene moiety of 5 showed 3H at 5.04-5.51 (m) for two C_1-H and C_4-H, 1H at 6.16 (t, $J_{2,3}= J_{3,4}$(cis)=11) for C_3-H, and 1H at 6.72 (m, $J_{2,1}$(cis)= $J_{2,3}$=11, $J_{2,1}$(trans)=17).

(11) This was prepared from the half ethyl ester of fumaric acid and $SOCl_2$ and the distilled material was used. See, Anschütz, R. Ann. **1928**, 461, 189.

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(14) p-Methylbenzylsulfonyl (pms) chloride was added at $0^{\circ}C$ in order to avoid the decomposition with n-BuLi.

(15) The detail of the X-ray study will be separately reported in a full paper.

(16) All materials described here gave MS, IR, and NMR spectra well consistent with their structures.