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 pentadienyl 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 chemically2a 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 hydrobromide2b 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

\[
\begin{align*}
\text{(-)-Bactobolin} & \quad \text{(+)-Actinobolin} \\
\begin{array}{cc}
\text{1} & \text{2}
\end{array}
\end{align*}
\]
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 pentadienyl position; (3) the key step is the stereo-
controlled 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-diienes have thus
far been reported. 4, 5, 6 Especially, only Fuchs et al. recently showed remarkable
success in the chiral and stereochcmical control of a potential intermediate
for the synthesis of cytochalasin C by using an intramolecular Diels-Alder reac-
tion of a Z-diene possessing a substituent at the pentadienyl 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 tran-
sition state D will be preferred from the nonbonded interactions between the
substituent (R) at the pentadienyl 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-δ2-oxazoline-4-methanol
by 4 step known procedures 8' (EtOH/HCl - ethyl benzimidate - LiAlH4 - TsCl,
95% overall yields). The phosphonium tosylate 4 obtained by treatment of neat
3 with Ph3P 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 SiO2. 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-H₂O (1:1) at 40°C for 3h (95% yield). Reaction of 6 with ethyl (E)-3-chloroformylacrylate 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 recrystallization from a mixed solvent of ether and n-hexane (1:1) [mp 103-104°C, Rf 0.53 (Et₂O-n-Hexane=3:2), [α]₂⁵°+110.2 (c 0.80 CHCl₃)]. 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.
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 SiO₂ (Et₂O:Hexane=1:1) in 95% yield (Rf, 0.50 (Et₂O), [α]D₂0 = 52.3° (c 1.07, CHCl₃). 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,σ-orbital overlap of the phenyl ring of the ester and the diene moieties probably even more effectively shields the δ-face as shown in Figure 1. The structure 8 was strongly supported by 400MHz 1H NMR as shown in Figure 2.

**Table 1**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Time (hr)</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene*</td>
<td>130</td>
<td>50</td>
<td>&gt;20:1</td>
<td>91</td>
</tr>
<tr>
<td>Benzene*</td>
<td>150</td>
<td>9</td>
<td>&gt;20:1</td>
<td>97</td>
</tr>
<tr>
<td>Benzene*</td>
<td>180</td>
<td>2</td>
<td>&gt;20:1</td>
<td>95</td>
</tr>
<tr>
<td>o-Chlorobenzene</td>
<td>180</td>
<td>2</td>
<td>—</td>
<td>95</td>
</tr>
<tr>
<td>* in a sealed tube</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 stereo-specific manner. The protective group of the hydroxyl function of 8 was replaced by THP to afford 9 by successive treatment with NaOH, CH₂N₂, 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

\[ \text{Scheme 6} \]

10a in quantitative yield, [1790 and 1708 cm⁻¹, Rf, 0.45 (Et₂O)]. Treatment of 10 with NaOH in aq THF, CH₂N₂ 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 Et₃N 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 analysis¹⁶ (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 converted to the keto or keto-equivalent group required for 1 and 2. The ester group of 12 was reduced with LiAlH₄ and the resulting alcohol 13 was treated with TsCl/Et₃N followed
by sodium selenophenolate generated \textit{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$_2$.

\textbf{Synthesis of (+)-Actinobolin (1) by Conversion of \textgreek{\gamma}-Lactam to \textgreek{\delta}-Lactone.} The crucial step of the present approach is how to convert the stable \textgreek{\gamma}-lactam to unstable \textgreek{\delta}-lactone. This problem was solved in the following way. It was considered to be necessary to activate the \textgreek{\gamma}-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 \textgreek{\gamma}-lactam 14. p-Methylbenzylsulfonyl (pms) derivative\textsuperscript{13a} 15a and p-methoxybenzenesulfonyl (Mbs)\textsuperscript{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 1 h to afford the desired 4-lactone 16a and 16b in 86% and quantitative yield respectively, after separation by column chromatography on SiO₂ (Scheme 9). The 4-lactone 15a showed

\[
\text{mp } 233-234°C \text{ after recrystallization from EtOH, } [\alpha]_{D}^{20} + 35.5° (c 0.234, MeOH). \]

The complete structure of 16, although firmly supported by spectral analysis, was unambiguously verified by X-ray analysis (Figure 3)\textsuperscript{15}, showing that the

\[
\begin{align*}
\text{mp } & 229-230°C \\
& ([\alpha]_{D}^{20} + 35.5° (c 0.234, MeOH))
\end{align*}
\]

\textbf{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 phenyl-selenomethyl group. All attempts to remove first the sulfonyl group with conventional reagents (HF or CH₃SO₃H) were unsatisfactory not only in the yield (Scheme 10, at best 50%) but in the next amide formation-step with 2-alanine (Scheme 11). A considerable steric hindrance for the axial amino group was considered for the 6-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 8-keto-6-lactone shown in Figure 4. Treatment of 16a with ozone at -78°C in CH₂Cl₂-MeOH and then pyridine afforded the corresponding exomethylene derivative (93% yield) purified by column chromatography on SiO₂ (Scheme 12). The oily

\[
\begin{align*}
  &\text{Ac}_2\text{O}, \text{Py}, \text{MeS} \\
&16a \\
&\text{130°C} \\
&\text{PhSe} \\
&\text{16c} \\
&\text{15c}
\end{align*}
\]

Scheme 10
\[ \text{HO} \quad \text{NH}_2 \cdot \text{HCl} \quad \text{HO} \quad \text{NH}_2 \cdot \text{HCl} \]

16d

- Z-Ala, DCC, Et$_3$N, DMF
- Z-Ala, PyS$_2$, Ph$_3$P, Et$_3$N, CH$_3$CN
- Z-Cl, Py, DMF
- Z-Cl, NaHCO$_3$, H$_2$O
- Boc-S, Et$_3$N, H$_2$O, Dioxane

Scheme 11

\[ \text{Figure 4} \]

16a

1) O$_3$, AcOEt
2) Py, AcOEt
3) O$_3$, MeOH
4) CH$_3$SCH$_3$

92%, 85%

Scheme 12
material was further subjected to ozonolysis at \(-50^\circ\text{C}\). After the usual workup with \(\text{CH}_3\text{SCH}_3\) and chromatography on \(\text{SiO}_2\), the \(\beta\)-keto \(\delta\)-lactone 17 was obtained in 85% yield. Now, removal of the sulfonyl group of 17 proceeded very smoothly with \(\text{HF}(\text{anisole}, 20^\circ\text{C}, 2\text{h})\) 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/\(\text{Et}_3\text{N}\) in DMF followed by hydrogenolysis with \(\text{H}_2/\text{Pd-C}\) in MeOH-AcOH containing 2N HCl, affording the hydrochloride 19 completely identical with natural \((+)-\text{actinobolin hydrochloride}\)\(^{16}\), \([\alpha]_D^{22} +55^\circ\) (c 0.47, \(\text{H}_2\text{O}\)) for synthetic 19; \([\alpha]_D^{22} +59^\circ\) (c 0.41, \(\text{H}_2\text{O}\)) for natural 19\(\)\(\) (Scheme 13). The total synthesis of \((+)-\text{actinobolin}\) consists of 29 steps in 28 overall yields from \(L\)-threonine including all steps for protection and removal (Scheme 14).

\begin{equation}
\text{Scheme 13}
\end{equation}

\begin{equation}
\text{Scheme 14}
\end{equation}
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 pentadienyllic 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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REFERENCES AND NOTES


(9) The Wittig reaction from the phosphonium iodide and acrolein afforded 5 only in 20% yield, and for such rare Wittig reaction using phosphonium tosylate, see Bestmann, H.J.; Kranz, E. Chem. Ber. 1969, 102, 1802.

(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).
This was prepared from the half ethyl ester of fumaric acid and SOCl₂ and the distilled material was used. See, Anschütz, R. Ann. 1928, 461, 189.


p-Methylbenzylsulfonyl (pms) chloride was added at 0°C in order to avoid the decomposition with n-BuLi.

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

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