The First Total Synthesis of Cochleamycin A and Determination of the Absolute Structure

Sir:

Cochleamycin A (1) was isolated by Kirin Brewery group from a cultured broth of *Streptomyces* sp. to show cytotoxicity against P388 leukemia cells and antimicrobial activities.\(^1\) The structure including the relative stereochemistry was elucidated by exhaustive NMR studies to be endowed with a 5-6-10-6-membered tetracyclic core.\(^2\) After the isolation, its analogs, macquarimicins were independently isolated by Abbott group.\(^3\) Not surprisingly, the combination of architectural complexities and bioactivities has engendered considerable interest, resulting in impressive synthetic studies from the groups of PAQUETTE and TADANO using Diels-Alder reactions.\(^4,5\)

Independently, in 1999 we initiated a synthetic endeavor envisioned to exploit a useful strategy to complete the total synthesis of cochleamycin A (1). For maximum convergency, our synthetic strategy (Fig. 1) called for connection of two segments 5 and 6 through formation of the C12-C13 bond followed by intramolecular Diels-Alder reaction (IDA) of 4 and successive cyclizations of 2 and 3. Stereoselective IDA was rationally expected to provide the target A-B ring from the stereochemistry of the transition state.\(^6\) This plan drew additional advantage from the expectation that 5 and 6 could be derived from compounds 7 and 8, respectively, by our previously developed methodologies.\(^7,8\)

In this paper we describe the first total synthesis of cochleamycin A (1), which determines the absolute structure and features a general method of entry into the families.

The segments 5 and 6 were, in fact, synthesized from readily available γ-lactone 7 and (S)-1,2,4-trihydroxybutane (8).

On one hand, the lactone 7 was stereoselectively converted into the alcohol 10 in five steps in 50% yield through Michael addition of MeMgBr\(^7\) to give 9 (Scheme 1).

On the other hand, the epoxide 12, which was derived from the triol 8 in four steps in 65% yield\(^10\), was led to the alcohol 13 in four steps in 80% yield through opening of the epoxide by lithiated acetylene (Scheme 2). Swern oxidation of the alcohol 13 to give the volatile aldehyde was followed by reaction with lithiated ethyl acetate to

---

\(^*\) The carbon-numbering protocol parallels that of the natural product 1.\(^1,2\)
yield the diastereomeric mixture of the ester 14. This was converted into the properly protected ketone 15 in four steps. The ketone was stereoselectively reduced by NaBH4 in the presence of Et2BOMe11) and O-methoxymethylated to afford 16 as a single diastereomer. The acetylene 16 was brominated to the corresponding 1-bromoalkyne, which was converted into the (E)-1-iodoalkene 6 via hydrostannylation and palladium-catalyzed carbon-bromide cleavage reaction.12)

With both segments 5 and 6 in hand, we turned to the assembly of the carbon backbone of 1 (Scheme 3: R1=TBDPS, R2=MOM). Thus, coupling of 5 and 6 smoothly proceeded to give the alcohol 17 in quantitative yield. This was stereoselectively reduced to the cis, trans-diene structure 18, which was crucial to the construction of the desired A-B ring by IDA. Oxidation of the allyl alcohol gave the α,β-unsaturated aldehyde 4, which was submitted to IDA in the presence of Yb(fod)3 at 140°C.13) The desired adduct 19 was obtained as a single product in high yield and the structure was verified by NMR studies (Table 1). This IDA produced four critical stereocenters as expected.

Horner-Emmons reaction of 19 was followed by selective reduction to give the ester 20. This was de-O-silylated and brominated to the alcohol 21, which was oxidized to the bromo-aldehyde 3. The desired cyclization of 3 was accomplished with SmI2 to give the 10-6-5 membered tricyclic product 22 as a single product,14) comprising the fully elaborated structure ready for conversion to the requisite seco-acid 2 (Scheme 4). The configurations of the newly produced stereocenters were not determined, because they disappeared on the following steps. IBX oxidation of 22 gave the corresponding ketone, which was transformed
Table 1. Significant physico-chemical properties of compounds.

<table>
<thead>
<tr>
<th>Compds.</th>
<th>[α]_D</th>
<th>^1^H-NMR (600 MHz; δ ppm; J Hz)</th>
<th>FAB-MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+97°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 0.92(3H, d, J=6.5, 20-H), 1.68(1H, ddd, J=14.0, 9.5&amp;6.5, 8-H), 1.70(1H, ddd, J=14.0, 10.0&amp;10.0, 8-H), 1.71(1H, ddd, J=17.0, 0&amp;0, 15-H), 1.78(1H, ddd, J=15.0, 3.0&amp;1.5, 17-H), 1.98(1H, ddd, J=17.0, 7.0&amp;6.5, 15-H), 2.08(3H, s, 10-OAc), 2.16(1H, dddq, J=10.0, 9.5, 4.0&amp;6.5, 9-H), 2.50(1H, ddd, J=15.0, 11.5, 4.5&amp;1.0, 17-H), 2.66(1H, dd, J=19.0&amp;1.0, 18-H), 2.74(1H, ddd, J=10.0, 7.0, 6.5&amp;2.5, 7-H), 2.83-2.87(1H, m, 11-H), 2.91-2.96(1H, m, 14-H), 3.12(1H, ddd, J=19.0, 7.5&amp;1.0, 18-H), 3.34(1H, ddd, J=11.5, 5.5&amp;2.5, 6-H), 3.63(1H, ddd, J=11.5, 6.5, 1.5&amp;0, 16-H), 4.90(1H, ddd, J=7.5, 4.5, 3.0&amp;1.0, 1-H), 4.96(1H, dd, J=4.0&amp;0, 10-H), 5.70(1H, ddd, J=10.0, 3.0&amp;3.0, 12-H), 5.91(1H, ddd, J=10.0, 2.0&amp;2.0, 13-H), 6.79(1H, d, J=11.5, 5-H)</td>
<td>FAB-MS: 375(M+H)^+</td>
</tr>
<tr>
<td>2</td>
<td>+66°</td>
<td>1H-NMR(CD\textsubscript{3}OD): δ 1.42(1H, ddd, J=14.0, 9.0&amp;2.5, 17-H), 1.57(1H, ddd, J=14.0, 12.0&amp;0, 17-H), 1.84(1H, ddd, J=14.0, 3.0&amp;0, 18-H), 2.01(1H, ddd, J=14.0, 10.0&amp;3.0, 18-H), 3.54(1H, ddd, J=10.0, 9.0, 0&amp;0, 1-H), 4.79(1H, dd, J=3.0&amp;3.0, 19-H), 6.27(1H, d, J=9.0, 5-H)</td>
<td>FAB-MS: 375(M+Na)^+</td>
</tr>
<tr>
<td>4</td>
<td>-49°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 4.29(1H, dd, J=9.5&amp;7.5, 10-H), 5.14(1H, dd, J=11.5&amp;9.5, 11-H), 5.76(1H, ddd, J=15.0, 7.5&amp;7.5, 14-H), 6.14(1H, ddd, J=15.5, 8.0, 1.5&amp;1.0, 6-H), 6.23(1H, dd, J=11.5&amp;11.5, 12-H), 6.33(1H, dd, J=15.0&amp;11.5, 13-H), 6.85(1H, ddd, J=15.5, 8.0&amp;6.5, 7-H), 9.52(1H, dd, J=8.0, 5-H)</td>
<td>FAB-MS: 705(M+Na)^+</td>
</tr>
<tr>
<td>5</td>
<td>-101°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 2.42(1H, d, J=2.0, 12-H), 4.11(2H, d, J=5.0, 5-H), 4.24(1H, dd, J=5.5&amp;2.0, 10-H), 5.67(1H, ddd, J=15.5, 6.0&amp;5.5, 7-H), 5.71(1H, dt, J=15.5&amp;5.0, 6-H)</td>
<td>FAB-MS: 221(M+Na)^+</td>
</tr>
<tr>
<td>6</td>
<td>-4.8°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 2.24(1H, ddd, J=14.5, 8.0, 6.0&amp;1.0, 15-H), 2.38(1H, dddd, J=14.5, 6.5, 4.5&amp;1.0, 15-H), 6.08(1H, ddd, J=14.0, 1.0&amp;1.0, 13-H), 6.53(1H, ddd, J=14.0, 8.0&amp;6.5, 14-H)</td>
<td>FAB-MS: 615(M+H)^+</td>
</tr>
<tr>
<td>17</td>
<td>-36°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 4.10(2H, dd, J=5.0&amp;4.5, 5-H), 4.34(1H, dd, J=5.0&amp;1.5, 10-H), 5.56(1H, ddd, J=16.0, 1.5, 1.5&amp;1.0, 13-H), 5.67(1H, ddd, J=15.5, 6.0&amp;5.5, 7-H), 5.70(1H, dt, J=15.5&amp;4.5, 6-H), 6.14(1H, ddd, J=16.0, 8.0&amp;6.5, 14-H)</td>
<td>FAB-MS: 705(M+Na)^+</td>
</tr>
<tr>
<td>19</td>
<td>+60°</td>
<td>1H-NMR(CDC\textsubscript{3}): δ 2.40(1H, ddd, J=6.0, 5.0&amp;2.0, 6-H), 2.65-2.69(1H, m, 11-H), 3.69(1H, dd, J=4.5&amp;4.5, 10-H), 5.74(1H, ddd, J=10.0, 3.0&amp;2.0, 12-H), 5.90(1H, ddd, J=10.0, 3.5&amp;2.5, 13-H), 9.71(1H, d, J=2.0, 5-H)</td>
<td>FAB-MS: 705(M+Na)^+</td>
</tr>
</tbody>
</table>

^† The carbon-numbering protocol parallels that of the natural product 1,1,2)
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Compds.</th>
<th>[α]_D</th>
<th>¹H-NMR (600 MHz; δ ppm; J Hz)†</th>
<th>FAB-MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>+58°</td>
<td>δ 1.51-1.63 (3H, m, 5-H, 6-H&amp;15-H), 1.71-1.78 (2H, m, 5-H&amp;8-H), 1.99-2.08 (2H, m, 18-H), 2.67 (1H, d, J=3.5, 19-OH), 2.76-2.82 (1H, m, 4-H), 4.37-4.43 (1H, m, 19-H)</td>
<td>FAB-MS: 515 (M+H)^+</td>
</tr>
<tr>
<td>23</td>
<td>+50°</td>
<td>δ 1.61 (1H, ddd, J=12.0, 12.0, 4.0&amp;3.5, 6-H), 1.82 (1H, dd, J=14.5&amp;12.0, 5-H), 2.58 (1H, dd, J=14.5&amp;4.0, 5-H), 2.82 (1H, dd, J=15.0&amp;8-H), 2.91 (1H, ddd, J=15.0, 5.5&amp;2.0, 18-H), 5.65 (1H, dd, J=9.5&amp;2.5, 12-H), 6.08 (1H, ddd, J=9.5, 6.5&amp;2.5, 13-H), 13.01 (1H, d, J=2.0, 19-OH)</td>
<td>FAB-MS: 513 (M+H)^+</td>
</tr>
<tr>
<td>24</td>
<td>+4.4°</td>
<td>δ 0.76 (1H, dd, J=13.5&amp;7.0, 18-H), 3.03 (1H, ddd, J=10.5, 10.5&amp;4.5, 6-H), 3.10 (1H, dd, J=13.5&amp;2.5, 18-H), 5.78-5.85 (2H, m, 12-H&amp;13-H), 6.36 (1H, d, J=10.5, 5-H)</td>
<td>FAB-MS: 511 (M+H)^+</td>
</tr>
<tr>
<td>25</td>
<td>+77°</td>
<td>δ 1.92-1.99 (2H, m, 18-H), 3.13 (1H, ddd, J=12.5, 9.5&amp;5.0, 6-H), 3.45-3.51 (1H, m, 1-H), 4.90 (1H, dd, J=3.0&amp;3.0, 19-H), 5.77 (1H, dd, J=10.0&amp;3.0, 12-H), 5.90 (1H, ddd, J=10.0, 6.5&amp;2.5, 13-H), 6.32 (1H, d, J=9.5, 5-H)</td>
<td>FAB-MS: 513 (M+H)^+</td>
</tr>
<tr>
<td>26</td>
<td>+58°</td>
<td>δ 1.97 (1H, ddd, J=13.5, 10.0&amp;10.0, 18-H), 2.14 (1H, ddd, J=13.5, 5.0&amp;0, 18-H), 3.05 (1H, ddd, J=12.0, 8.5&amp;5.0, 6-H), 3.11 (1H, ddd, J=10.0, 10.0, 0&amp;0, 1-H), 3.57 (1H, d, J=10.0, 19-OH), 4.18 (1H, ddd, J=10.0, 10.0&amp;5.0, 19-H), 5.77 (1H, dd, J=10.0&amp;4.0, 12-H), 5.87 (1H, ddd, J=10.0, 6.5&amp;2.5, 13-H), 5.88 (1H, d, J=8.5, 5-H)</td>
<td>FAB-MS: 513 (M+H)^+</td>
</tr>
<tr>
<td>27</td>
<td>−9.6°</td>
<td>δ 1.66 (1H, ddd, J=15.0, 1.5&amp;0, 17-H), 1.82 (1H, ddd, J=13.5, 8.0&amp;1.5, 18-H), 2.17 (1H, ddd, J=15.0, 10.5&amp;3.5, 17-H), 2.90 (1H, ddd, J=13.5, 10.0&amp;10.0, 18-H), 4.50 (1H, ddd, J=10.0, 8.0&amp;2.0, 19-H), 4.75-4.79 (1H, m, 1-H), 6.13 (1H, d, J=11.0&amp;2.0, 5-H)</td>
<td>FAB-MS: 335 (M+H)^+</td>
</tr>
<tr>
<td>28</td>
<td>+77°</td>
<td>δ 1.00 (3H, d, J=6.5, 20-H), 1.40 (1H, br s, 10-OH), 1.47 (1H, br d, J=4.5, 16-OH), 1.61 (1H, ddd, J=13.5, 9.5&amp;4.5, 8-H), 1.71 (1H, ddd, J=13.5, 10.5&amp;9.5, 8-H), 1.72 (1H, ddd, J=16.5, 0&amp;0, 15-H), 1.78 (1H, ddd, J=15.0, 2.5&amp;1.5, 17-H), 1.97 (1H, ddd, J=16.5, 7.0&amp;6.5, 15-H), 2.03 (1H, dddd, J=10.5, 9.5, 3.0&amp;6.5, 9-H), 2.49 (1H, ddd, J=15.0, 11.5&amp;4.5, 17-H), 2.66 (1H, dd, J=18.5&amp;0, 18-H), 2.77-2.83 (2H, m, 7-H&amp;11-H), 2.90-2.95 (1H, m, 14-H), 3.12 (1H, dd, J=18.5&amp;7.5, 18-H), 3.33 (1H, ddd, J=11.0, 5.0&amp;0, 6-H), 3.64 (1H, dddd, J=11.5, 6.5, 4.5, 1.5&amp;0, 16-H), 3.88 (1H, dd, J=3.0&amp;0, 10-H), 4.89 (1H, ddd, J=7.5, 4.5, 2.5&amp;0, 1-H), 5.65 (1H, ddd, J=10.5, 2.5&amp;2.0, 12-H), 5.87 (1H, ddd, J=10.5, 1.0&amp;0, 13-H), 6.84 (1H, d, J=11.0, 5-H)</td>
<td>FAB-MS: 333 (M+H)^+</td>
</tr>
</tbody>
</table>
Scheme 3.

Conditions: (a) PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_2$NH/PhMe, rt, 30 minutes; 95% (b) Zn, BrCH$_2$CH$_2$Br, LiCuBr$_2$/EtOH-THF, 70°C, 12 hours (c) IBX/PhMe-DMSO, rt, 3 hours (d) Yb(fod)$_3$, 2,6-di-tert-butyl-p-cresol/xylene, 140°C, 4 hours; 70% in 3 steps (e) triethyl phosphonoacetate, NaH/THF, -30°C, 3 hours; 80% (f) H$_2$, Rh-C/PhMe, rt, 12 hours; 85% (g) n-Bu$_4$NF/THF, 50°C, 3 hours; quant. (h) CBr$_4$, LDA/THF, -78°C, 1 hour; 72% (i) (COCl)$_2$, DMSO, Et$_3$N/CH$_2$Cl$_2$, -78°C to rt, 1 hour (j) SmI$_2$/THF, 0°C, 15 minutes; 61% in 2 steps.

Scheme 4.

Conditions: (a) IBX/PhMe-DMSO, rt, 2 hours; 89% (b) PhSeCl, Li(N(TMS))$_2$/THF, 0°C, 30 minutes then aq. H$_2$O$_2$, 0°C, 1 hour; 62% (c) NaBH$_4$, CeCl$_3$·7H$_2$O/EtOH, 0°C, 10 minutes; 25: 70%, 26: 14% (d) HCl-EtOH, rt, 12 hours (e) LiOH/aq. THF, 60°C, 15 hours; 80% in 2 steps (f) ethyl ethynyl ether, [RuCl$_2$(p-cymene)]$_2$/DMF, 0°C to rt, 2 hours; 68% (g) CSA/THF, rt, 15 minutes; 83% (h) MnO$_2$/AcOEt, rt, 12 hours; 85% (i) AcONa/Ac$_2$O, 60°C, 3 hours; 72%.

1: Cochleamycin A
to the cis enol 23 during silica-gel column chromatography (hexane: acetone 5:1). The cis configuration was deduced by the chemical shift of the enol OH at δ 13.01. The enol 23 was converted into the unsaturated ester 24 by phenylselenenylation and oxidative elimination. However, deprotection of 24 for lactonization resulted in β-elimination of the functional group.

Hydride reduction of 24 provided a mixture of the α-alcohol 25 and β-alcohol 26, which was separated by silica-gel column chromatography (hexane: 2-butanone 3:2): 25: 70% yield; Rf on TLC 0.37; 26: 14%; Rf 0.27 (hexane:2-butanone 3:2). Remarkably, 25 was finally transformed to cochleamycin A (1), while the other 26 could hardly suffer the following lactonization. Although the hydroxy group of 25 was oxidized to the carbonyl group later on, the configuration was clarified by NMR studies, especially the coupling constants J18a,19 and J18b,19 of 25,26 and 27 (Table 1). The stereoselective reduction was effected using CeCl3·7H2O as an additive to give 25 as the major product.

Deprotection of 25 followed by saponification gave the hydroxy acid 2, the NOE studies of which supported the significant configurations. Lactonization of 2 was tested under many conditions to construct the C-D ring and the best result was realized by using Kita’s conditions15) to afford the δ-lactone 27 in fairly good yield. The allyl alcohol was selectively oxidized by MnO2 to the keto-lactone 28.

On the final stage, selective O-acetylation was required for the synthesis and successfully conducted by using Ac2O and AcONa to exclusively give the desired monoacetate 1 [mp 193°C (decomp.), [α]D20 +97° (c 0.12, MeOH)17], [α]D22 +60° (c 0.20, CHCl3); lit.19 mp 200–203°C (decomp.), [α]D25 +107° (c 1.0, MeOH)] in 72% yield with a little (less than 5% yield) of the diacetate. The spectroscopic data of 1 were in complete accord with those of natural cochleamycin A, completing the first total synthesis to establish the absolute structure.

Acknowledgement

The present work was financially supported by Grant-in-Aid for Specially Promoted Research and Scientific Research A from MEXT. We are grateful to 21COE “Practical Nano-Chemistry” from MEXT, Japan and Advanced Research Institute for Science and Engineering, Waseda University for the generous supports of our program.

We also thank Dr. K. SHINDO, Japan Women’s University and Dr. H. KAWAI, Kirin Brewery Co., Ltd. for generously providing IR, UV and NMR spectra of natural cochleamycin A, and Messrs. S. MIYAZAKI and R. IZUMI for their technical assistances.

References

11) CHEN, K.-M.; G. E. HARDTMANN, K. PRASAD, O. REPIC

* Corresponding author: tatsuta@waseda.jp

Compound 1 was found to be less stable in MeOH.


