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.

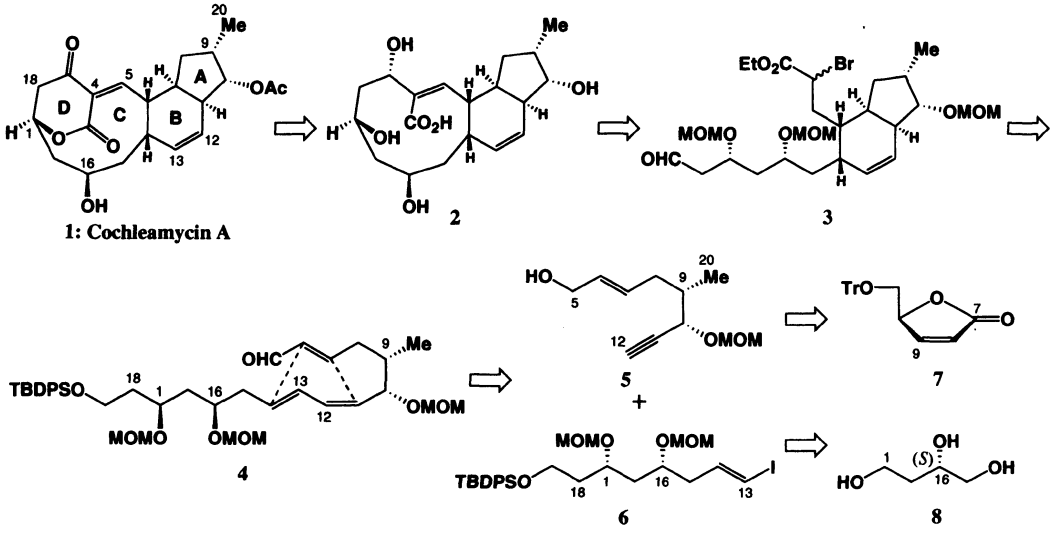
The segments **5** and **6** were, in fact, synthesized from readily available γ-lactone **7** and (*S*)-1,2,4-trihydroxybutane (**8**).

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).

The alcohol **10** was oxidized by *o*-iodobenzoxy acid (IBX) in toluene-DMSO to give the labile aldehyde, which was treated with dimethyl-1-diazo-2-oxopropylphosphonate[9] to afford the alkyne **11** with de-*O*-acylation. Swern oxidation of **11** and Wittig olefination of the resultant aldehyde were carried out in one-pot, followed by DIBAL reduction to the allyl alcohol **5** (Table 1).

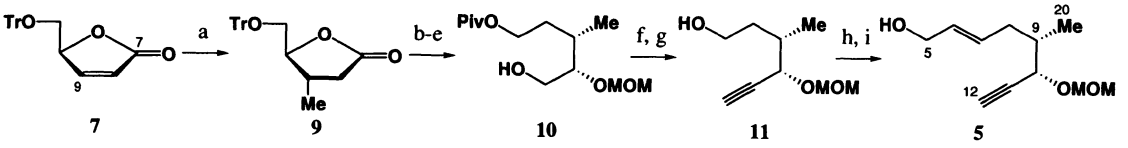
On the other hand, the epoxide **12**, which was derived from the triol **8** in four steps in 65% yield[10], was led to the alcohol **13** in four steps in 80% yield through opening of the epoxide by lithiated acetylene (Scheme 2). Swern oxidation of the alcohol **13** to give the volatile aldehyde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

Fig. 1.



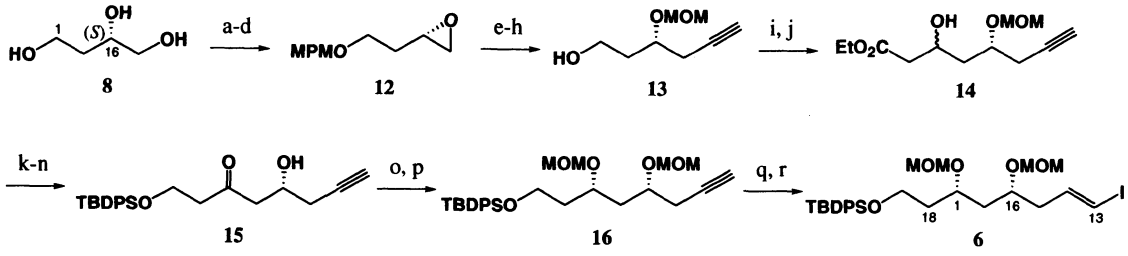
† The carbon-numbering protocol parallels that of the natural product **1**.[1,2]

Scheme 1.



Conditions; (a) MeMgBr, CuBr·SMe_2, HMPA, TMSCl/THF, −78°C to −40°C, 2 hours; 80% (b) $LiAlH_4$/THF, 0°C, 30 minutes (c) PivCl, Py/CH_2Cl_2, 0°C, 5 hours (d) MOMCl, *i*-Pr_2NEt/$ClCH_2CH_2Cl$, 50°C, 5 hours; 80% in 3 steps (e) aq. AcOH, 50°C, 3 hours; 75% (f) IBX/PhMe-DMSO, 50°C, 2 hours (g) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3/MeOH, rt, 3 days; 75% in 2 steps (h) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78°C to rt, 1 hour then $Ph_3P{=}CHCO_2Me$, rt, 5 hours; 75% (i) DIBAL-H/PhMe, rt, 1 hour; 95%.

Scheme 2.



Conditions; (a) Amberlyst 15E/acetone, rt, 12 hours; 90% (b) MPMCl, NaH/DMF, 40°C to rt, 2 hours (c) aq. AcOH, 50°C, 3 hours; 90% in 2 steps (d) 1-(*p*-toluenesulfonyl)imidazole, NaH/THF, 0°C, 1 hour; 80% (e) (trimethylsilyl)acetylene, *n*-BuLi, BF_3·Et_2O/THF, −78°C, 30 minutes (f) NaOH/MeOH, rt, 3 hours (g) MOMCl, *i*-Pr_2NEt/$ClCH_2CH_2Cl$, 50°C, 12 hours (h) DDQ, H_2O/CH_2Cl_2, rt, 30 minutes; 80% in 4 steps (i) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78°C to rt, 1 hour (j) AcOEt, LDA/THF, −78°C, 30 minutes (k) $LiAlH_4$/THF, 0°C, 30 minutes (l) TBDPSCl/Py, rt, 3 hours; 70% in 4 steps (m) IBX/PhMe-DMSO, 60°C, 3 hours (n) $LiBF_4$/aq. MeCN, 70°C, 3 hours; 50% in 2 steps (o) $NaBH_4$, Et_2BOMe/THF-MeOH, −78°C, 1 hour (p) MOMCl, *i*-Pr_2NEt/MeCN, 50°C, 12 hours; 90% in 2 steps (q) NBS, $AgNO_3$/acetone, rt, 30 minutes (r) *n*-Bu_3SnH, $Pd_2(dba)_3$·$CHCl_3$, PPh_3/THF, 0°C, 30 minutes then I_2, 0°C, 30 minutes; 70% in 2 steps.

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 $NaBH_4$ in the presence of Et_2BOMe[11] 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: R^1=TBDPS, R^2=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 SmI_2 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.

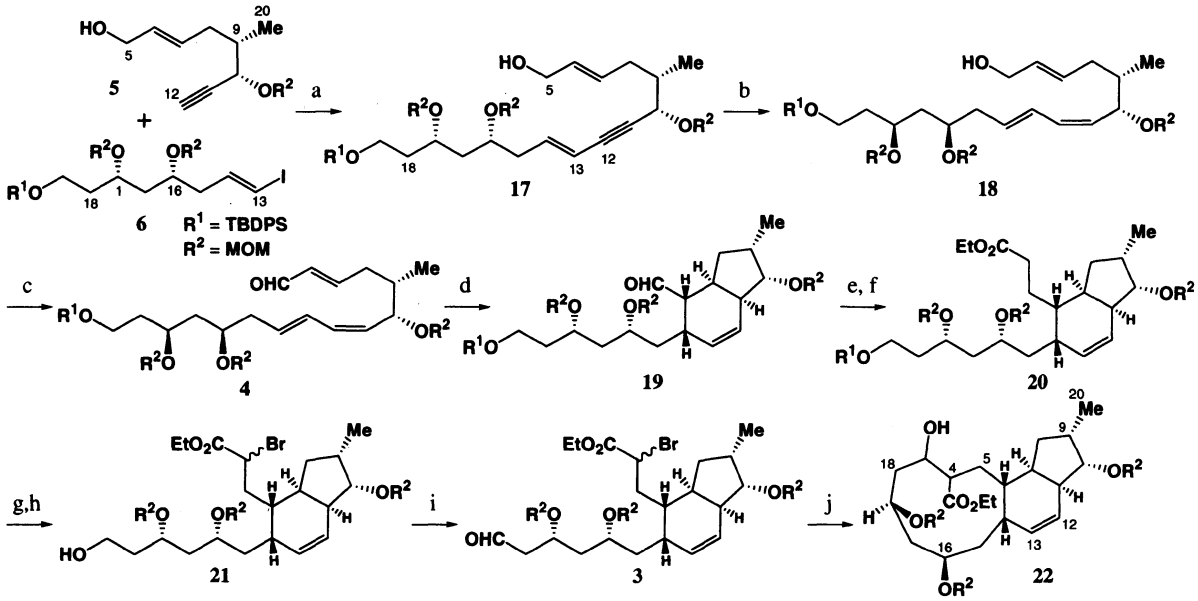
Compds.	$[\alpha]_D$	^{1}H-NMR (600 MHz; δ ppm; *J* Hz)† FAB-MS (*m/z*)
1	+97° (*c* 0.12, MeOH) +60° (*c* 0.20, $CHCl_3$)	^{1}H-NMR($CDCl_3$): δ 0.92(3H, d, *J*=6.5, 20-H), 1.68(1H, ddd, *J*=14.0, 9.5&6.5, 8-H), 1.70(1H, ddd, *J*=14.0, 10.0&10.0, 8-H), 1.71(1H, ddd, *J*=17.0, 0&0, 15-H), 1.78(1H, ddd, *J*=15.0, 3.0&1.5, 17-H), 1.98(1H, ddd, *J*=17.0, 7.0&6.5, 15-H), 2.08(3H, s, 10-OAc), 2.16(1H, dddq, *J*=10.0, 9.5, 4.0&6.5, 9-H), 2.50(1H, dddd, *J*=15.0, 11.5, 4.5&1.0, 17-H), 2.66(1H, dd, *J*=19.0&1.0, 18-H), 2.74(1H, dddd, *J*=10.0, 7.0, 6.5&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&1.0, 18-H), 3.34(1H, ddd, *J*=11.5, 5.5&2.5, 6-H), 3.63(1H, dddd, *J*=11.5, 6.5, 1.5&0, 16-H), 4.90(1H, dddd, *J*=7.5, 4.5, 3.0&1.0, 1-H), 4.96(1H, dd, *J*=4.0&0, 10-H), 5.70(1H, ddd, *J*=10.0, 3.0&3.0, 12-H), 5.91(1H, ddd, *J*=10.0, 2.0&2.0, 13-H), 6.79(1H, d, *J*=11.5, 5-H) FAB-MS: 375$(M+H)^+$
2	+66° (*c* 0.21, MeOH)	^{1}H-NMR(CD_3OD): δ 1.42(1H, ddd, *J*=14.0, 9.0&2.5, 17-H), 1.57(1H, ddd, *J*=14.0, 12.0&0, 17-H), 1.84(1H, ddd, *J*=14.0, 3.0&0, 18-H), 2.01(1H, ddd, *J*=14.0, 10.0&3.0, 18-H), 3.54(1H, dddd, *J*=10.0, 9.0, 0&0, 1-H), 4.79(1H, dd, *J*=3.0&3.0, 19-H), 6.27(1H, d, *J*=9.0, 5-H) FAB-MS: 375$(M+Na)^+$
4	−49° (*c* 1.1, MeOH)	^{1}H-NMR($CDCl_3$): δ 4.29(1H, dd, *J*=9.5&7.5, 10-H), 5.14(1H, dd, *J*=11.5&9.5, 11-H), 5.76(1H, ddd, *J*=15.0, 7.5&7.5, 14-H), 6.14(1H, dddd, *J*=15.5, 8.0, 1.5&1.0, 6-H), 6.23(1H, dd, *J*=11.5&11.5, 12-H), 6.33(1H, dd, *J*=15.0&11.5, 13-H), 6.85(1H, ddd, *J*=15.5, 8.0&6.5, 7-H), 9.52(1H, d, *J*=8.0, 5-H) FAB-MS: 705$(M+Na)^+$
5	−101° (*c* 1.1, MeOH)	^{1}H-NMR($CDCl_3$): 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&2.0, 10-H), 5.67(1H, ddd, *J*=15.5, 6.0&5.5, 7-H), 5.71(1H, dt, *J*=15.5&5.0, 6-H) FAB-MS: 221$(M+Na)^+$
6	−4.8° (*c* 1.0, MeOH)	^{1}H-NMR($CDCl_3$): δ 2.24(1H, dddd, *J*=14.5, 8.0, 6.0&1.0, 15-H), 2.38(1H, dddd, *J*=14.5, 6.5, 4.5&1.0, 15-H), 6.08(1H, ddd, *J*=14.0, 1.0&1.0, 13-H), 6.53(1H, ddd, *J*=14.0, 8.0&6.5, 14-H) FAB-MS: 613$(M+H)^+$
17	−36° (*c* 1.0, MeOH)	^{1}H-NMR($CDCl_3$): δ 4.10(2H, dd, *J*=5.0&4.5, 5-H), 4.34(1H, dd, *J*=5.0&1.5, 10-H), 5.56(1H, dddd, *J*=16.0, 1.5, 1.5&1.0, 13-H), 5.67(1H, ddd, *J*=15.5, 6.0&5.5, 7-H), 5.70(1H, dt, *J*=15.5&4.5, 6-H), 6.14(1H, ddd, *J*=16.0, 8.0&6.5, 14-H) FAB-MS: 705$(M+Na)^+$
19	+60° (*c* 1.1, MeOH)	^{1}H-NMR($CDCl_3$): δ 2.40(1H, ddd, *J*=6.0, 5.0&2.0, 6-H), 2.65-2.69(1H, m, 11-H), 3.69(1H, dd, *J*=4.5&4.5, 10-H), 5.74(1H, ddd, *J*=10.0, 3.0&2.0, 12-H), 5.90(1H, ddd, *J*=10.0, 3.5&2.5, 13-H), 9.71(1H, d, *J*=2.0, 5-H) FAB-MS: 705$(M+Na)^+$

† The carbon-numbering protocol parallels that of the natural product **1**.[1,2]

Table 1. (Continued)

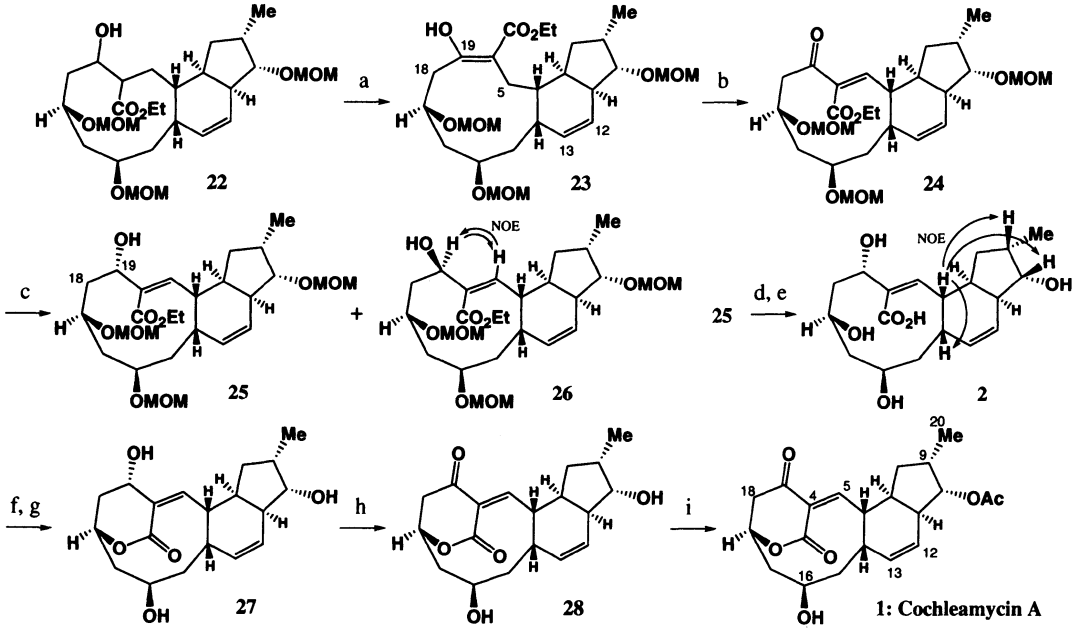
Compds.	$[\alpha]_D$	^{1}H-NMR (600 MHz; δ ppm; *J* Hz)† FAB-MS (*m/z*)
22	+58° (*c* 0.38, MeOH)	^{1}H-NMR($CDCl_3$): δ 1.51-1.63(3H, m, 5-H, 6-H&15-H), 1.71-1.78(2H, m, 5-H&8-H),1.99-2.08(2H, m, 18-H), 2.67(1H, d, *J*=3.5, 19-OH), 2.76-2.82(1H, m, 4-H), 4.37-4.43(1H, m, 19-H) FAB-MS: 515$(M+H)^+$
23	+50° (*c* 0.44, MeOH)	^{1}H-NMR($CDCl_3$): δ 1.61(1H, dddd, *J*=12.0, 12.0, 4.0&3.5, 6-H), 1.82(1H, dd, *J*=14.5&12.0, 5-H), 2.58(1H, dd, *J*=14.5&4.0, 5-H), 2.82(1H, dd, *J*=15.0&0, 18-H), 2.91(1H, ddd, *J*=15.0, 5.5&2.0, 18-H), 5.65(1H, dd, *J*=9.5&2.5, 12-H), 6.08(1H, ddd, *J*=9.5, 6.5&2.5, 13-H), 13.01(1H, d, *J*=2.0, 19-OH) FAB-MS: 513$(M+H)^+$
24	+4.4° (*c* 0.63, MeOH)	^{1}H-NMR($CDCl_3$): δ 2.86(1H, dd, *J*=13.5&7.0, 18-H), 3.03(1H, ddd, *J*=10.5, 10.5&4.5, 6-H), 3.10(1H, dd, *J*=13.5&2.5, 18-H), 5.78-5.85(2H, m, 12-H&13-H), 6.36(1H, d, *J*=10.5, 5-H) FAB-MS: 511$(M+H)^+$
25	+77° (*c* 1.1, MeOH)	^{1}H-NMR($CDCl_3$): δ 1.92-1.99(2H, m, 18-H), 3.13(1H, ddd, *J*=12.5, 9.5&5.0, 6-H), 3.45-3.51(1H, m, 1-H), 4.90(1H, dd, *J*=3.0&3.0, 19-H), 5.77(1H, dd, *J*=10.0&3.0, 12-H), 5.90(1H, ddd, *J*=10.0, 6.5&2.5, 13-H), 6.32(1H, d, *J*=9.5, 5-H) FAB-MS: 513$(M+H)^+$
26	+58° (*c* 0.30, MeOH)	^{1}H-NMR($CDCl_3$): δ 1.97(1H, ddd, *J*=13.5, 10.0&10.0, 18-H), 2.14(1H, ddd, *J*=13.5, 5.0&0, 18-H), 3.05(1H, ddd, *J*=12.0, 8.5&5.0, 6-H), 3.11(1H, dddd, *J*=10.0, 10.0, 0&0, 1-H), 3.57(1H, d, *J*=10.0, 19-OH), 4.18(1H, ddd, *J*=10.0, 10.0&5.0, 19-H), 5.77(1H, dd, *J*=10.0&4.0, 12-H), 5.87(1H, ddd, *J*=10.0, 6.5&2.5, 13-H), 5.88(1H, d, *J*=8.5, 5-H) FAB-MS: 513$(M+H)^+$
27	−9.6° (*c* 0.27, MeOH)	^{1}H-NMR(CD_3OD): δ 1.66(1H, ddd, *J*=15.0, 1.5&0, 17-H), 1.82(1H, ddd, *J*=13.5, 8.0&1.5, 18-H), 2.17(1H, ddd, *J*=15.0, 10.5&3.5, 17-H), 2.90(1H, ddd, *J*=13.5, 10.0&10.0, 18-H), 4.50(1H, ddd, *J*=10.0, 8.0&2.0, 19-H), 4.75-4.79(1H, m, 1-H), 6.13(1H, dd, *J*=11.0&2.0, 5-H) FAB-MS: 335$(M+H)^+$
28	+77° (*c* 0.39, MeOH)	^{1}H-NMR($CDCl_3$): 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&4.5, 8-H), 1.71(1H, ddd, *J*=13.5, 10.5&9.5, 8-H), 1.72(1H, ddd, *J*=16.5, 0&0, 15-H), 1.78(1H, ddd, *J*=15.0, 2.5&1.5, 17-H), 1.97(1H, ddd, *J*=16.5, 7.0&6.5, 15-H), 2.03(1H, dddq, *J*=10.5, 9.5, 3.0&6.5, 9-H), 2.49(1H, ddd, *J*=15.0, 11.5&4.5, 17-H), 2.66(1H, dd, *J*=18.5&0, 18-H), 2.77-2.83(2H, m, 7-H&11-H), 2.90-2.95(1H, m, 14-H), 3.12(1H, dd, *J*=18.5&7.5, 18-H), 3.33(1H, ddd, *J*=11.0, 5.0&0, 6-H), 3.64(1H, ddddd, *J*=11.5, 6.5, 4.5, 1.5&0, 16-H), 3.88(1H, dd, *J*=3.0&0, 10-H), 4.89(1H, dddd, *J*=7.5, 4.5, 2.5&0, 1-H), 5.65(1H, ddd, *J*=10.5, 2.5&2.0, 12-H), 5.87(1H, ddd, *J*=10.5, 1.0&0, 13-H), 6.84(1H, d, *J*=11.0, 5-H) FAB-MS: 333$(M+H)^+$

Scheme 3.



Conditions; (a) $PdCl_2(PPh_3)_2$, CuI, Et_2NH/PhMe, rt, 30 minutes; 95% (b) Zn, $BrCH_2CH_2Br$, $LiCuBr_2$/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_4NF/THF, 50°C, 3 hours; quant. (h) CBr_4, LDA/THF, −78°C, 1 hour; 72% (i) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_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, LiN(TMS)$_2$/THF, 0°C, 30 minutes then aq. H_2O_2, 0°C, 1 hour; 62% (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$/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, $[RuCl_2(p\text{-cymene})]_2$/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_2O, 60°C, 3 hours; 72%.

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 $J_{18a,19}$ and $J_{18b,19}$ of **25**, **26** and **27** (Table 1). The stereoselective reduction was effected using $CeCl_3 \cdot 7H_2O$ 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 conditions[15] to afford the δ-lactone **27** in fairly good yield. The allyl alcohol was selectively oxidized by MnO_2 to the keto-lactone **28**.

On the final stage, selective *O*-acetylation was required for the synthesis and successfully conducted by using Ac_2O and AcONa to exclusively give the desired monoacetate **1** [mp 193°C (decomp.), $[\alpha]_D^{20}$ +97° (*c* 0.12, MeOH)††, $[\alpha]_D^{22}$ +60° (*c* 0.20, $CHCl_3$); lit.[1] mp 200~203°C (decomp.), $[\alpha]_D^{25}$ +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.

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(Received March 28, 2003)

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