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Total Synthesis of Cochleamycin A

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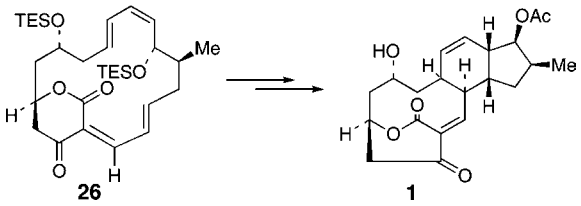
ABSTRACT

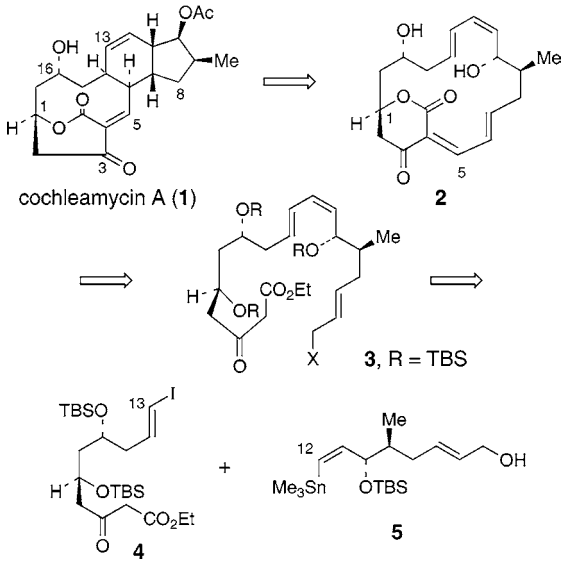


Cochleamycin A (1) was synthesized in 2.4% overall yield via a 23-step linear sequence starting from 3-butene-1-ol. Key features of the synthesis include the synthesis of (*Z*)-1,3-diene 21 via a Stille coupling of 4 and 5 and a transannular Diels–Alder reaction of macrocycle 26 to provide the complete carbon skeleton of 1.

Cochleamycin A (**1**, Scheme 1) was isolated from *Streptomyces* DT136 in 1992 by Shindo and co-workers.[1] In addition to displaying antimicrobial activity against gram-positive bacteria, cochleamycin A is cytotoxic toward a variety of tumor cell lines (IC_{50} = 1.6 μg/mL for P388 leukemia cells).[2,3] Cochleamycin A contains an interesting cis-fused hexahydro-1*H*-indene unit that is fused to a 10-membered lactone. The construction of the bicyclic core via an intramolecular Diels−Alder (IMDA) reaction was the focus of a synthetic study by Paquette[4] and successfully employed in Tatsuta's total synthesis of **1**.[5] Related studies of IMDA reactions directed toward macquarimicin A were reported by Tadano.[6] We also have reported studies of Lewis acid-promoted IMDA reactions targeting the cis-fused hexahydroindene nucleus of **1**.[7]

We report herein our total synthesis of **1**, which utilizes the transannular Diels−Alder (TDA) reaction[8,9] of macrocycle **2** as the key step. An analogous strategy was recently reported by Tadano's group in their total synthesis of the structurally related natural product macquarimicin A.[10] We envisaged that TDA substrate **2** would be prepared via macrocyclic ring closure of β-keto ester **3**, which in turn

Scheme 1. Cochelamycin A: Retrosynthetic Analysis



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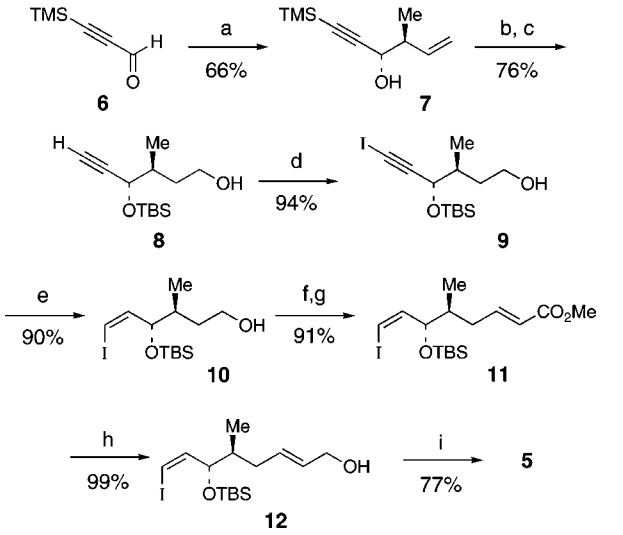
would derive from the Stille coupling[11] of vinyl iodide **4** and (*Z*)-vinylstannane **5**.

Construction of fragment **5** began with the asymmetric (*E*)-crotylboration[12] of aldehyde **6**[13] (Scheme 2), which gave

Scheme 2. Synthesis of Vinyl Stannane **5**[a]

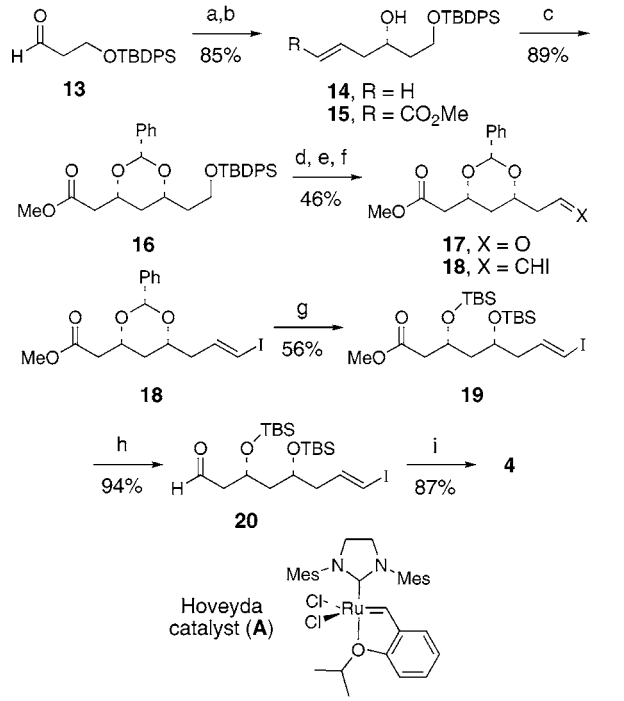


[a] Conditions: (a) (^{d}Ipc)$_2$B-crotyl, THF, −78 °C, then $NaBO_3$·H_2O. (b) TBS−OTf, 2,6-lutidine, CH_2Cl_2, −78 °C. (c) 9-BBN, THF, then aqueous NaOH/H_2O_2. (d) *n*-BuLi, THF, −50 °C, then I_2. (e) *o*-Nitrobenzenesulfonylhydrazide, Et_3N, THF/*i*-PrOH (1:1). (f) SO_3·pyr, DMSO, *i*Pr_2NEt, CH_2Cl_2, 0 °C. (g) Trimethyl phosphonoacetate, LiCl, Et_3N, CH_3CN. (h) DIBAL-H, CH_2Cl_2. (i) MeLi, Et_2O, −40 to 23 °C; *n*-BuLi, −78 °C; then Me_3SnCl, THF, −78 °C.

the anti homoallylic alcohol **7** (90% ee) in 66% yield. Protection of the hydroxyl group of **7** as a TBS ether (90% yield) and then hydroboration of the vinyl group with 9-BBN and cleavage of the alkynylsilane unit during oxidation of the alkylborane provided primary alcohol **8** in 84% yield. This intermediate was iodinated in 94% yield by treatment with *n*-BuLi in THF (−50 °C) and then I_2. (*Z*)-Vinyl iodide **10** was then prepared in 90% yield by reduction of alkynyl iodide **9** with diimide (generated in situ from *o*-nitrobenzenesulfonylhydrazide and Et_3N).[14] Oxidation of primary alcohol **10** by using the Parikh−Doering protocol[15] gave the corresponding aldehyde, which was subjected to standard Horner−Wadsworth−Emmons olefination[16] to give ester **11** in 91% yield for the two steps. Reduction of **11** with DIBAL-H gave allylic alcohol **12** in 99% yield. Finally, sequential treatment of **12** with MeLi (Et_2O, −78 °C) and then *n*-BuLi (−78 °C), followed by addition of Me_3SnCl then provided vinylstannane **5** in 77% yield.

The synthesis of fragment **4** began with the asymmetric allylboration[17] of aldehyde **13**,[18] which provided the known homoallylic alcohol **14**[19] in 99% yield with 88% ee (Scheme 3). Compound **14** was then subjected to olefin cross-

Scheme 3. Synthesis of Vinyl Iodide Fragment **4**[a]



[a] Conditions: (a) (^{d}Ipc)$_2$B-allyl, THF, −78 °C; see ref 17. (b) Methyl acrylate (3 equiv), Hoveyda catalyst **A** (1.5 mol %), CH_2Cl_2, reflux. (c) PhCHO, *t*BuOK, THF, 0 °C. (d) $(HF)_3$·Et_3N, CH_3CN, 40 °C. (e) SO_3·pyr, DMSO, *i*Pr_2NEt, CH_2Cl_2, 0 °C. (f) $CrCl_2$, CHI_3, dioxane/THF (6:1). (g) (i) 80% AcOH, THF, 95 °C; (ii) Amberlite IRA-400(OH), MeOH; (iii) TBS−OTf, 2,6-lutidine, CH_2Cl_2, −78 °C. (h) DIBAL-H, CH_2Cl_2, −78 °C. (i) Ethyl diazoacetate, $SnCl_2$, CH_2Cl_2.

metathesis with methyl acrylate using Hoveyda's catalyst (**A**)[20] to give the α,β-unsaturated ester **15** in 86% yield as the (*E*)-isomer. The benzylidene-protected *syn*-1,3-diol **16** was then prepared in 89% yield by treatment of **15** with benzaldehyde and a catalytic amount of *t*-BuOK in THF.[21] After removal of the TBDPS ether (82% yield), the primary alcohol was oxidized to give aldehyde **17** in 92% yield. This intermediate was then converted into (*E*)-vinyl iodide **18** in 61% yield via the Takai olefination reaction.[22,23] Having served its intended purpose, the benzylidene acetal unit of

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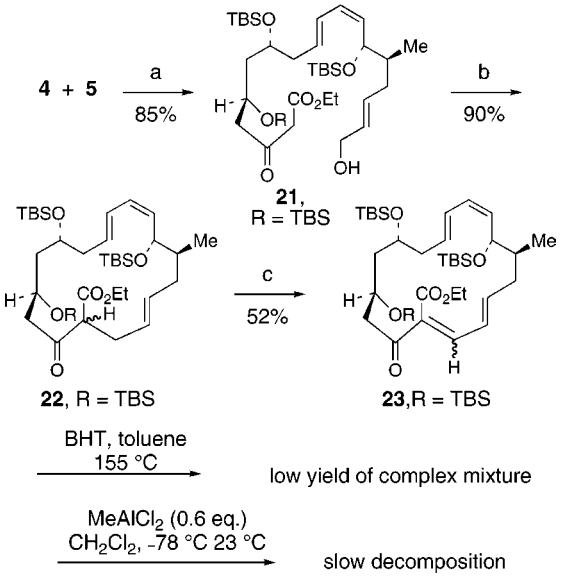
18 was hydrolyzed by treatment with 80% AcOH at 95 °C. This provided a mixture of the 1,3-diol and the corresponding δ-lactone. This mixture was treated with Amberlite IRA-400 basic ion-exchange resin in MeOH to open the lactone. The resulting diol was then immediately treated at −78 °C with TBS−OTf and 2,6-lutidine to give the bis-TBS ether **19** in 56% yield from **18**. Controlled reduction of **19** with DIBAL-H at −78 °C gave aldehyde **20** in 94% yield. This intermediate was then treated with ethyl diazoacetate and $SnCl_2$ to furnish the vinyl iodide fragment **4** in 87% yield.[24]

Fragments **4** and **5** were joined via Stille coupling[25] in 1:1 DMSO−THF in the presence of CuCl,[26] which provided (*Z*)-1,3-diene **21** in 85% yield (Scheme 4). Several methods

Scheme 4. Stille Coupling of **4** and **5**, and Construction of the Macrocycle[a]

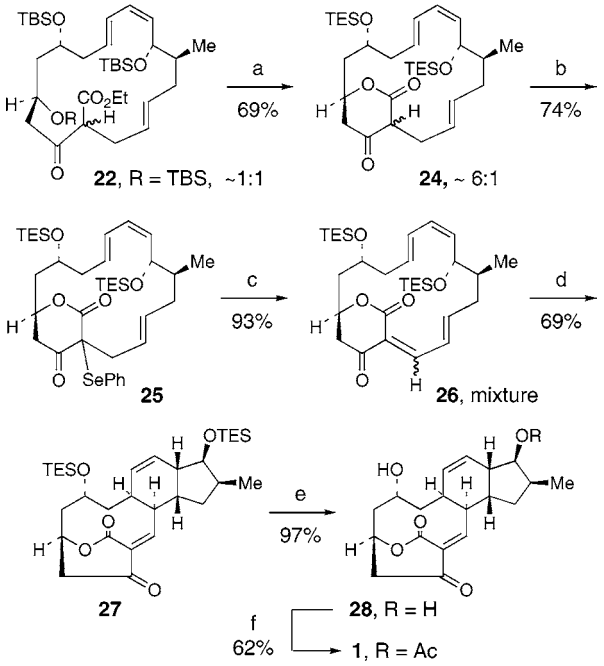


[a] Conditions: (a) $Pd(PPh_3)_4$, CuCl, THF/DMSO (1:1). (b) (i) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C; (ii) Cs_2CO_3, THF, 23 °C. (c) PhSeCl, pyridine, CH_2Cl_2, then aqueous H_2O_2.

were explored for the cyclization of **21** to **22**, including Pd-catalyzed cyclization of the allyl carbonate derived from **21**,[27] but the best results were obtained by using a Cs_2CO_3-mediated intramolecular alkylation of the derived allylic iodide, as pioneered by Deslongchamps.[28] This reaction sequence provided macrocycle **22** as a 1:1 mixture of β-keto ester epimers together with ca. 10−15% of the enol tautomer (^{1}H NMR analysis). Macrocycle **22** was treated with the PhSeCl−pyridine complex followed by H_2O_2 to give **23** as a 2:1 mixture of olefin isomers in 52% yield.[29] Unfortunately, this material failed to undergo transannular cycloaddition at temperatures up to 155 °C, at which point decomposition occurred. This result is consistent with Tadano's observations in his total synthesis of macquarimicin A.[10] Interestingly, under Lewis acidic conditions ($MeAlCl_2$), **23** proved to be stable for several days at 23 °C and only slow decomposition was observed. Because the TDA reaction of **23** was unsuccessful, the intermediate **2** containing the β-keto-δ-lactone unit of cochleamycin A was next targeted as a TDA substrate.

The three silyl ethers of macrocycle **22** were deprotected using $(HF)_2{\cdot}Et_3N$ (generated in situ),[30] and the resulting triol was treated with *i*Pr_2NEt in MeOH to provide the corresponding lactone (Scheme 5). This polar intermediate was

Scheme 5. Completion of the Total Synthesis[a]



[a] Conditions: (a) (i) $(HF)_3{\cdot}Et_3N$, Et_3N, CH_3CN, 45 °C; (ii) *i*Pr_2NEt, MeOH; (iii) TES−Cl, imidazole, DMF. (b) Et_3N, PhSeCl, CH_2Cl_2, −78 °C. (c) *m*CPBA, CH_2Cl_2, −50 °C. (d) cat. BHT, toluene, 125 °C, 21 h. (e) PPTs, MeOH, 23 °C. (f) NaOAc, Ac_2O, 60 °C.

difficult to purify and was insoluble in most organic solvents. Consequently, the diol was protected using TES−Cl and imidazole, which gave lactone **24** in 69% yield over three steps as a ca. 6:1 mixture of epimers. Several methods were explored to introduce the necessary unsaturation in **26**, and a two-step selenenlyation/oxidation protocol was eventually identified as the highest yielding option. Thus, lactone **24** was treated with Et_3N and PhSeCl at −78 °C to furnish the phenyl selenide **25** in 74% yield as a single diastereomer according to ^{1}H NMR analysis. When **25** was treated with purified *m*CPBA at a variety of temperatures, a complex mixture of macrocyclic tetraenes **26** was isolated in 70−

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93% yield. This mixture appears to consist of a 6:2.5:1 mixture of at least three compounds (^{1}H NMR analysis). Unfortunately, this mixture has proven to be difficult to separate, and unambiguous identification of the individual components has not yet been realized. However, when this mixture was heated at 125 °C in toluene in a sealed tube with a catalytic amount of BHT for 21 h, tetracycle **27** was obtained in 69% yield as the sole cycloadduct, together with a small amount of starting material. Interestingly, the composition of the recovered starting material was very similar to the material that was used in the transannular Diels−Alder reaction at the outset. Moreover, heating the recovered "**26**" at 125 °C in toluene resulted in formation of additional quantities of **27**. We have speculated that at least one of the "isomers" in the **26** mixure may be an atropisomer of **26a**, but variable-temperature NMR studies have failed to provide evidence in support of this hypothesis. Nevertheless, the experimental results suggest that the isomer(s) of **26** interconvert with **26a**, since the yield of **27** is greater than the amount of **26a** present in the original mixture.

Assuming that two C(4,5)-olefin isomers are present in **26**, our results indicate that only one of these (**26a)** is able to participate in the TDA reaction. Due to geometric constraints imposed by the δ-lactone unit, each C(4,5)-olefin isomer can access only one TDA transition state.[31] In the case of the isomer **26b** (with the incorrect 4,5-olefin geometry for cochleamycin; Figure 1), the TDA transition state **30** suffers from a 1,3-allylic strain interaction between the OTES group and the (*Z*)-1,3-diene.[32] Fortunately, the TDA transition state **29** for **26a** with the correct olefin geometry for cochelamycin A experiences a much less severe interaction of C(10)−H with the (*Z*)-1,3-diene. As a consequence, only **26a** can undergo the transannular Diels−Alder reaction.

When cycloadduct **27** was treated with catalytic acid in MeOH, the two TES ethers were removed to produce diol **28** (97% yield). Diol **28** is the penultimate intermediate in Tatsuta's total synthesis of cochleamycin A.[5] The spectroscopic data obtained for **28** were in complete agreement with the data reported by Tatsuta.[5] Treatment of **28** with NaOAc in Ac_2O at 60 °C according to Tatsuta's procedure provided **1** in 62% yield, along with 16% of recovered **28**. Synthetic

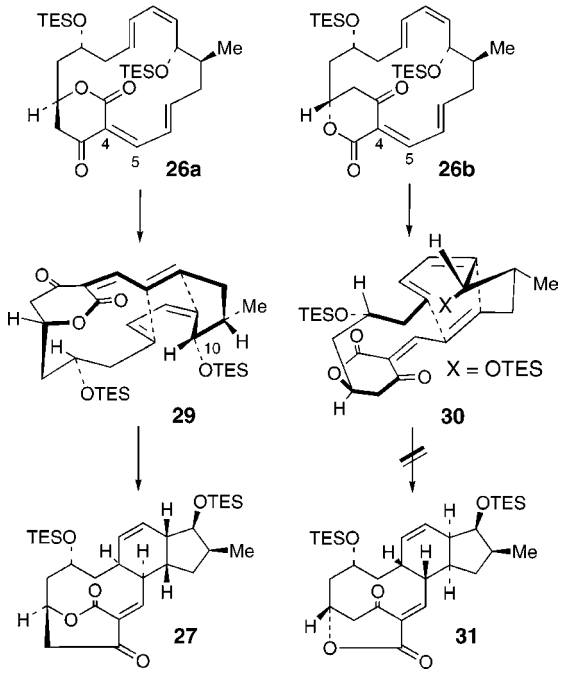

Figure 1. TDA transition states

1 proved to be identical to an authentic sample kindly provided by Prof. Tatsuta.

In summary, cochleamycin A was synthesized in 2.4% overall yield via a 23-step linear sequence from 3-butene-1-ol. Key steps include the Stille coupling of **4** and **5** and the transannular Diels−Alder reaction of **26** that provided the hexahydro-1*H*-indene nucleus of cochleamycin A.

Acknowledgment. The authors thank Professor Tatsuta for providing experimental details, comparative spectroscopic data of **28**, and a sample of cochleamycin A. Financial support by the National Institutes of Health (GM 26782) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full characterization (^{1}H NMR, ^{13}C NMR, IR, HRMS, and optical rotation) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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