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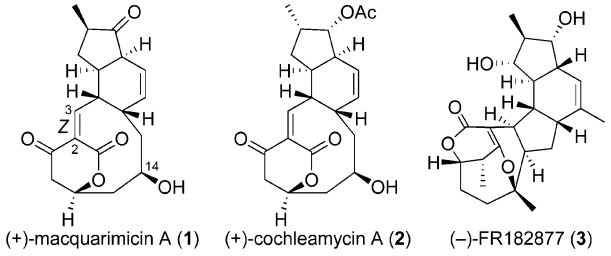
Total Synthesis of (+)-Macquarimicin A

Ryosuke Munakata, Hironori Katakai, Tatsuo Ueki, Jun Kurosaka, Ken-ichi Takao, and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received September 25, 2003; E-mail: tadano@applc.keio.ac.jp

(+)-Macquarimicin A (**1**) was isolated from *Micromonospora chalcea* by researchers at Abott in 1995.[1] Later, researchers at Sankyo found that **1** is a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase) and exhibits antiinflammatory activity in vivo.[2] The structure of **1** is characterized by a unique tetracyclic framework, which comprises a *cis*-tetrahydroindanone ring, a β-keto-δ-lactone ring, and a 10-membered carbocycle.[1b]



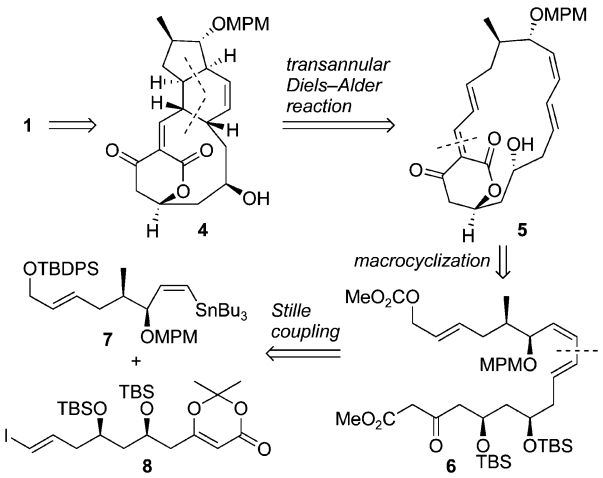
As closely related natural products, an antitumor antibiotic cochleamycin A (**2**)[3] and a microtubule-stabilizing agent FR182877 (**3**)[4] have been isolated. This class of natural products shares a biogenetic hypothesis that involves the intramolecular Diels−Alder (IMDA) reaction of polyketide intermediates.[5] This intriguing feature, combined with biological activities and a formidable molecular architecture, makes them highly attractive synthetic targets.[6] In 2002, Sorensen et al.[7] and Evans and Starr[8] achieved enantioselective total syntheses of (+)- and (−)-**3**, respectively. Very recently, Tatsuta et al.[9] disclosed the total synthesis of (+)-**2**. Herein, we describe the first total synthesis of (+)-**1**, determination of its absolute configuration, and revision of the proposed structure concerning the C(2)−C(3) geometry.[10]

The retrosynthetic analysis is outlined in Scheme 1.[11] The tetracyclic framework of **1** was projected to arise from the transannular Diels−Alder (TADA) reaction[12] of **5**. The macrocycle **5** could be elaborated through the intramolecular Trost−Tsuji reaction of **6**, which in turn would be available via the Stille coupling of (*Z*)-stannylalkene **7** and (*E*)-iodolalkene **8**.

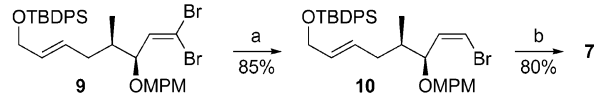
(*Z*)-Stannylalkene **7** was synthesized in two steps from dibromoalkene **9**[11] (Scheme 2). The application of Uenishi's method[13] to **9** generated (*Z*)-bromoalkene **10** exclusively. The halogen−lithium exchange of **10** followed by treatment with Bu_3SnCl produced **7**.

The synthesis of the other coupling substrate **8** started from (*R*)-epichlorohydrin (**11**) via known acetylenic compound **12**[14] (Scheme 3). The conversion of **12** to aldehyde **13** was conducted in a straightforward manner and proceeded in 84% yield from **11**. The vinylogous Mukaiyama aldol reaction between **13** and **14**[15] gave a 1:1 diastereomeric mixture of the adducts, which was converted to β-hydroxyketone **15** in two steps. The diastereoselective reduction[16] of **15** gave the desired *syn*-1,3-diol exclusively. The protection of the resulting diol and conversion to bromoalkyne **16** followed by one-pot hydrostannylation−iodination[17] produced (*E*)-iodoalkene **8**.

Scheme 1. Retrosynthetic Analysis for (+)-Macquarimicin A (**1**)

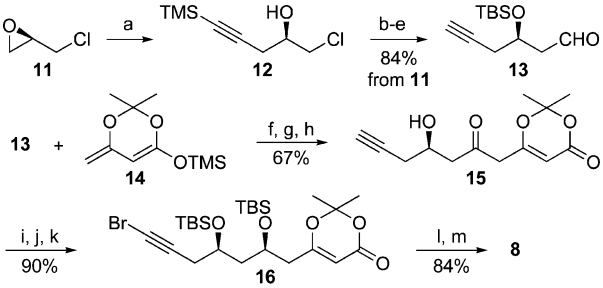


Scheme 2. Preparation of the (*Z*)-Stannylalkene **7**[a]



[a] (a) Bu_3SnH, $Pd(PPh_3)_4$, toluene; (b) *t*-BuLi, Et_2O, −78 °C then Bu_3SnCl.

Scheme 3. Preparation of the (*E*)-Iodoalkene **8**[a]



[a] (a) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 to −30 °C; (b) KCN, NaI, DMSO/H_2O (10:1); (c) K_2CO_3, MeOH; (d) TBSCl, imidazole, DMF; (e) Dibal-H, toluene, −78 °C; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (g) Dess–Martin reagent, CH_2Cl_2; (h) 48% aq. HF/MeCN (5:95); (i) Et_2BOMe, $NaBH_4$, THF/MeOH (4:1), −78 °C; (j) TBSCl, imidazole, DMF; (k) NBS, $AgNO_3$, acetone; (l) Bu_3SnH, $Pd_2(dba)_3$, PPh_3, THF; (m) I_2, CH_2Cl_2, 0 °C.

With stannane **7** and iodide **8** in hand, assembly was undertaken (Scheme 4). The cuprous chloride-promoted Stille coupling[18,19] (97%), followed by selective deprotection[20] of the TBDPS group (94%), afforded **17**. Conversion of **17** to the methyl carbonate followed by thermolysis in toluene/MeOH furnished the β-keto ester **6**. Macroallylation[21] was successfully carried out to form a 17-membered macrocycle **18** (ca. 3:2 diastereomeric mixture) in 84% yield using $Pd(PPh_3)_4$/dppe (1:1) as a catalyst. After removal of

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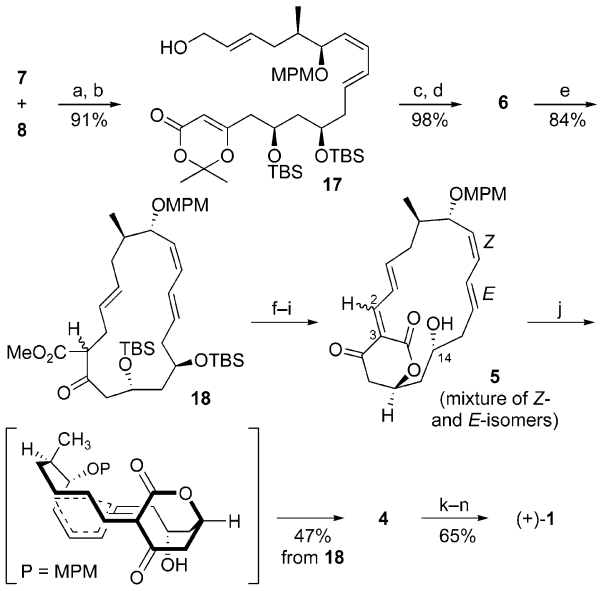
Scheme 4. Total Synthesis of (+)-**1** via TADA of **5**[a]



[a] (a) $Pd(PPh_3)_4$, CuCl, DMSO–THF; (b) NH_4F, MeOH; (c) $ClCO_2Me$, pyr. CH_2Cl_2; (d) MeOH, toluene, 110 °C, in a sealed tube; (e) $Pd(PPh_3)_4$, dppe, THF; (f) HF·pyr., pyr.; (g) MeOH–*i*-Pr_2NEt (10:1); (h) PhSeCl, Et_3N, CH_2Cl_2, –78 °C; (i) mCPBA, CH_2Cl_2, –50 °C; (j) BHT, toluene, 130 °C, in a sealed tube; (k) TESOTf, lutidine, CH_2Cl_2, –78 °C; (l) DDQ, CH_2Cl_2/pH 7 buffer (10:1); (m) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2; (n) PPTS, MeOH.

the TBS groups in **18**, the formation of the β-keto-δ-lactone ring under basic conditions followed by a double-bond introduction was carried out to afford **5** as a mixture of C(2)−C(3) geometrical isomers.[22]

The stage was set for the key TADA reaction. Under thermal conditions (130 °C), the cycloaddition of **5** furnished the desired diastereomer **4** as a sole cycloadduct. In this reaction, the (*Z*,*E*)-geometry of the reacting diene is the origin of *endo* selectivity,[11] while the lactone ring restricts conformation to control the diastereofacical selectivity completely.[23]

The cycloadduct **4** was converted to (+)-**1** as follows. Silylation and removal of the MPM group, followed by Dess−Martin oxidation, gave 14-*O*-TES-**1**. Finally, PPTS-catalyzed cleavage of the TES ether afforded (+)-**1**. Spectral properties (^{1}H and ^{13}C NMR and IR) of synthetic (+)-**1** were completely identical to those of a natural sample, and optical rotation of synthetic (+)-**1** ($[\alpha]^{23}_D$ = +270; *c* 0.20, MeOH) established the absolute configuration of natural (+)-**1** ($[\alpha]^{25}_D$ = +285.6; *c* 0.2, MeOH). Furthermore, extensive NOE experiments on synthetic (+)-**1** revealed that the C(2)−C(3) geometry must be *Z*, not *E* as reported[1b] (see Supporting Information for details).

In conclusion, the first total synthesis of (+)-macquarimicin A (**1**) has been accomplished with 27 linear steps from **11** in 9.9% overall yield (92% average yield per step). The synthesis features the transannular Diels−Alder reaction, which constructed the tetracyclic framework of **1** stereoselectively. Also, the present work established the absolute configuration of (+)-**1** and revised its C(2)−C(3) geometry. Further study for the syntheses of the other members of this class of natural products is currently underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and details on the determination of the C(2)−C(3) geometry (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) A TADA substrate without the lactone ring did not afford the desired cycloadduct.

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