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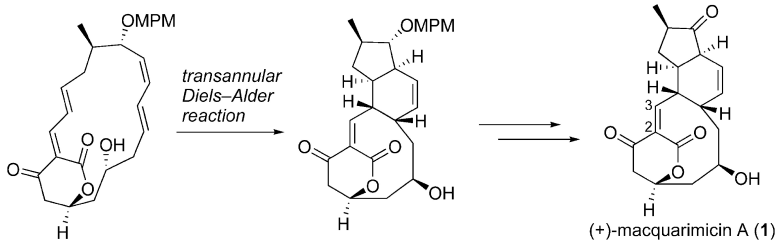
J. Am. Chem. Soc., **2003**, 125 (48), 14722-14723• DOI: 10.1021/ja038732p • Publication Date (Web): 08 November 2003



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Published on Web 11/08/2003

Total Synthesis of (+)-Macquarimicin A

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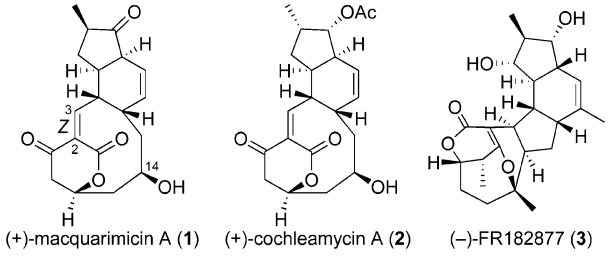
(+)-Macquarimicin A (**1**) was isolated from *Micromonospora chalcea* by researchers at Abott in 1995.[1] Later, researchers at Sankyo found that **1** is a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase) and exhibits antiinflammatory activity in vivo.[2] The structure of **1** 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]



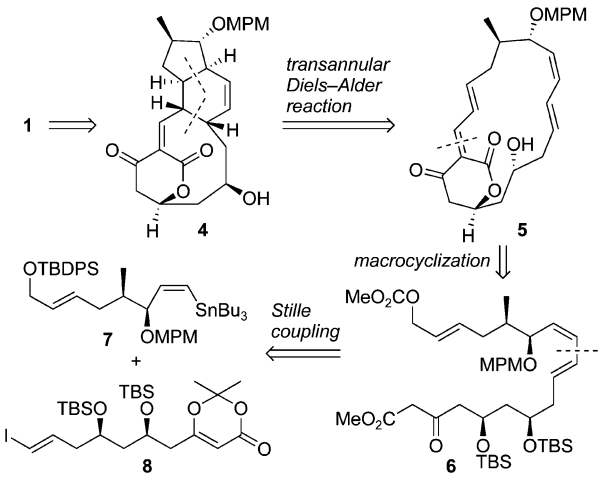
As closely related natural products, an antitumor antibiotic cochleamycin A (**2**)[3] and a microtubule-stabilizing agent FR182877 (**3**)[4] have been isolated. This class of natural products shares a biogenetic hypothesis that involves the intramolecular Diels−Alder (IMDA) reaction of polyketide intermediates.[5] 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**.

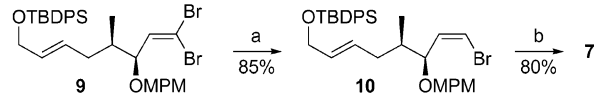
(*Z*)-Stannylalkene **7** was synthesized in two steps from dibromoalkene **9**[11] (Scheme 2). The application of Uenishi's method[13] to **9** generated (*Z*)-bromoalkene **10** exclusively. The halogen−lithium exchange of **10** followed by treatment with Bu_3SnCl produced **7**.

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**)

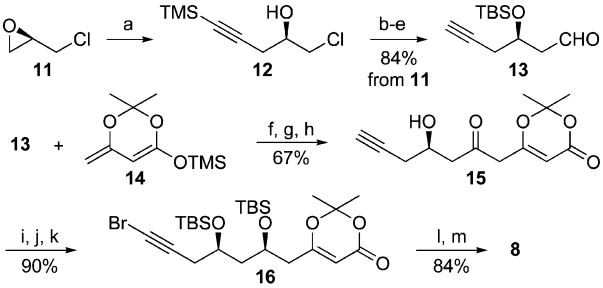


Scheme 2. Preparation of the (*Z*)-Stannylalkene **7**[a]



[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]

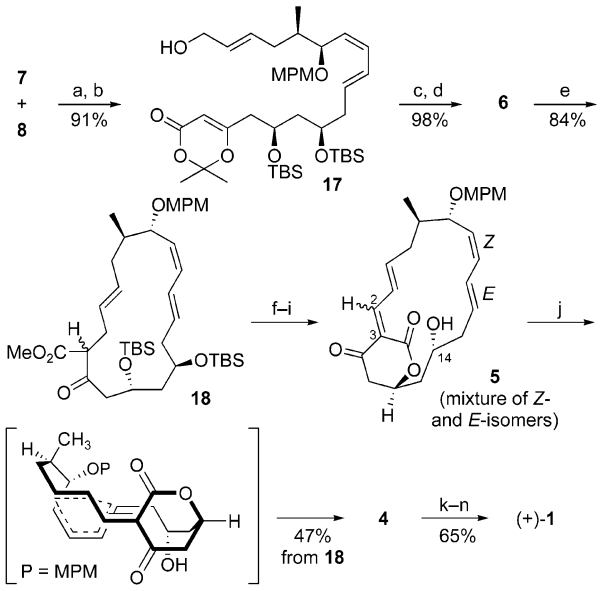


[a] (a) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 to −30 °C; (b) KCN, NaI, DMSO/H_2O (10:1); (c) K_2CO_3, MeOH; (d) TBSCl, imidazole, DMF; (e) Dibal-H, toluene, −78 °C; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (g) Dess–Martin reagent, CH_2Cl_2; (h) 48% aq. HF/MeCN (5:95); (i) Et_2BOMe,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

10.1021/ja038732p CCC: $25.00

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.

Acknowledgment. This research was supported by Grants-in-Aid for Scientific Research on Priority Areas (A) "Targeted Pursuit of Challenging Bioactive Molecules" and for the 21st Century COE program "KEIO LCC" from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank Dr. Takeshi Ogita (Sankyo Co., Ltd.) for providing us with a sample and spectroscopic data of macquarimicin A, and Daiso Co., Ltd. for providing (*R*)-epichlorohydrin.

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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(22) Compound **5** gave a complicated ^{1}H NMR spectrum, making elucidation of the *E*/*Z* ratio difficult. We attribute the complication to the tautomerization of **5** (such as ketalization), in addition to the geometry of the C(2)−C(3) double bond.
(23) A TADA substrate without the lactone ring did not afford the desired cycloadduct.

JA038732P