Total Synthesis

DOI: 10.1002/anie.200906362

Total Synthesis and Absolute Configuration of Macrocidin A, a Cyclophane Tetramic Acid Natural Product**

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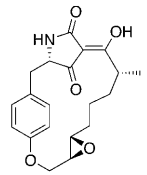
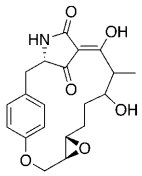
Macrocidin A (**1**) and macrocidin B (**2**) represent a new family of plant pathogens produced by *Phoma macrostoma*, a microorganism parasitic to Canadian thistle.[1] The intriguing structure of **1**, which includes a tetramic acid[2] group installed in a cyclophane skeleton, was determined by extensive 2D NMR studies and single-crystal X-ray analysis, although the absolute configuration remains to be addressed because of a paucity of the natural sample. The macrocidins have significant herbicidal activity on broadleaf weeds but not on grasses, which makes them a potential lead for new herbicide design. Their biological activity and novel chemical structures have made these compounds attractive targets for chemical synthesis. Whilst construction of the macrocyclic skeleton has been addressed,[3] the synthesis of the full structure remains to be achieved. Herein, we describe the first total synthesis of macrocidin A (**1**) using macrolactam formation followed by cyclization.

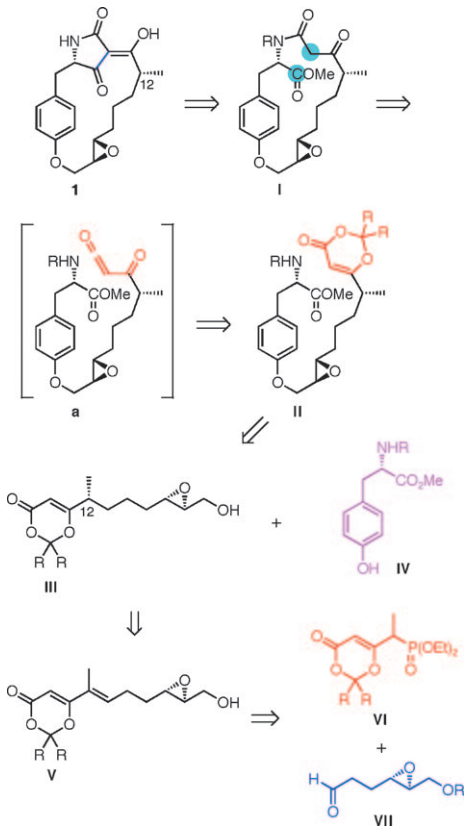


macrocidin A (**1**)



macrocidin B (**2**)

Scheme 1 outlines our retrosynthetic analysis based upon the construction of the acyltetramic acid moiety using the Lacey–Dieckmann cyclization[4] of macrolactam **I**, which in turn would be accessible by the intramolecular trapping of an acylketene species (**a**) that may be thermally generated from dioxinone precursor **II**.[5] This key intermediate (**II**) could be assembled from the stereodefined epoxy alcohol **III** and tyrosine unit **IV**. One of the challenges in the synthesis of **III** was the establishment of the C12 stereogenic center,[6] for which we planned to employ either a substrate- or catalyst-controlled diastereoselective hydrogenation of trisubstituted olefin **V**. Finally, olefin **V** could be obtained from phosphonate **VI** and aldehyde **VII**.



Scheme 1. Retrosynthetic analysis of macrocidin A.

Scheme 2 shows the preparation of trisubstituted olefins **10** and **11**, which began with the two-step conversion of propargyl alcohol into allyl alcohol **5**.[7] Epoxide **6**, which was prepared by a Katsuki–Sharpless asymmetric epoxidation reaction (93% *ee*),[8] was silylated and subjected to rhodium-catalyzed hydroboration,[9] followed by oxidation to give alcohol **8**. Swern oxidation of **8**, followed by a Horner–Emmons reaction with chiral phosphonate **12**[10] afforded olefin **10** (*E*/*Z* = 9:1). Recrystallization (*n*-hexane/ethyl acetate) gave pure (*E*)-**10**, which had a stereodefined trisubstituted olefin and a menthone chiral auxiliary[11] ready for diastereoselective hydrogenation. The substrate for the catalyst-controlled diastereoselective hydrogenation, aceto-

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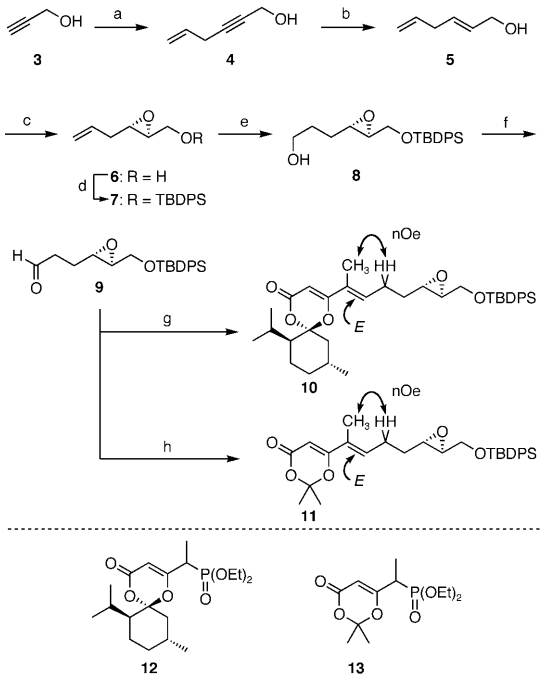
[**] This work was supported by the Global COE program (Chemistry) and a Grant-in-Aid for Scientific Research (JSPS). T.Y. thanks the JSPS for a Research Fellowship for Young Scientists.

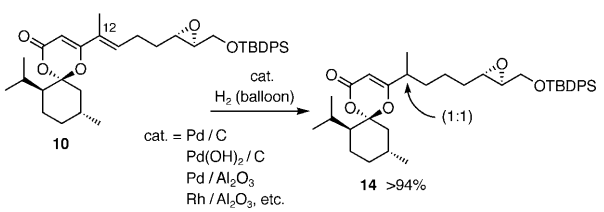
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906362.



Scheme 2. Preparation of substrates **10** and **11**. a) Allyl bromide, CuI, NaI, K_2CO_3, acetone, RT, 5 h (85%). b) $LiAlH_4$, THF, reflux, 2 h (75%). c) $(iPrO)_4Ti$, L-(+)-diethyl tartrate, *t*BuOOH, M.S. 4 Å, CH_2Cl_2, −20 °C, 24 h (80%, 93% *ee*). d) *t*BuPh$_2$SiCl, imidazole, DMF, RT, 1 h (99%). e) Catecholborane, [Rh(PPh$_3$)$_3$Cl], THF, 0 °C, 1.5 h; H_2O_2, pH 7 phosphate buffer (72%). f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→0 °C, 1.5 h, (quant.). g) **12**, LiN(*i*Pr)$_2$, THF, −78→0 °C (99%, *E*/*Z* = 9:1); recrystallization (*n*-hexane/EtOAc), 57%. h) **13**, LiN(*i*Pr)$_2$, HMPA, THF, −78→0 °C (96%, *E*/*Z* = 9:1), SiO_2 gel chromatography. M.S. = molecular sieves, TBDPS = *tert*-butyldiphenylsilyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide.

nide **11**, was also prepared in a similar manner, except for the use of HMPA as a co-solvent in the olefination step to prevent aggregation of the phosphonate anion that is derived from **13**. The *E*/*Z* ratio was again 9:1, but (*E*)-**11** was easily isolated by silica gel column chromatography.

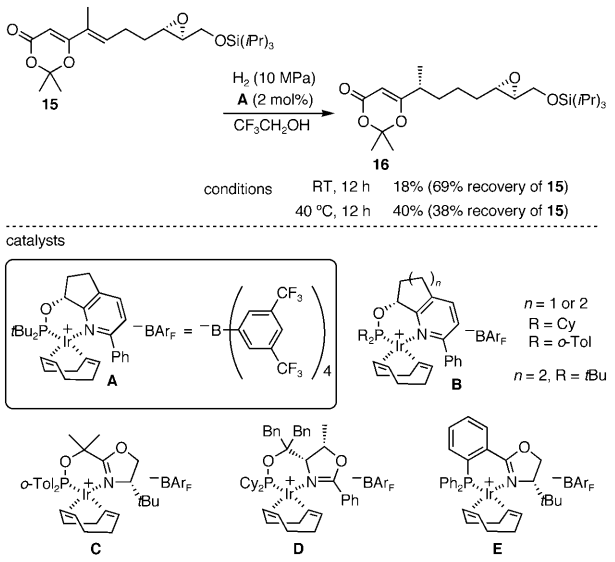
In addressing the controlled construction of the C12 stereogenic center, our initial attempts used the chiral, nonracemic substrate **10**, hoping that the menthone moiety would control the diastereomeric facial selection (Scheme 3). However, no reaction occurred with homogeneous catalysts, such as Wilkinson[12a] or Crabtree[12b] complexes, presumably owing to the high steric hindrance around the olefin. Conversely, several heterogeneous catalysts were active enough to give



Scheme 3. Diastereoselective hydrogenation of **10**.

the product (**14**) in excellent yield, although the stereoselectivity was uniformly 1:1. Therefore, unfortunately, the stereoselective influence of the chiral auxiliary on the hydrogenation reaction was negligible.

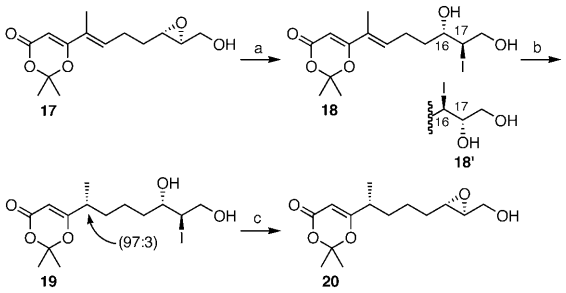
At this stage, we decided to investigate the catalyst-controlled asymmetric hydrogenation reaction, primarily considering iridium catalysts with chiral N,P ligands that are known to be uniquely effective for unfunctionalized olefins and do not require neighboring group participation.[13] Attempts at the enantioselective hydrogenation of prochiral substrate **15** with catalysts **A**–**E** (Scheme 4) were mostly



Scheme 4. The attempted asymmetric hydrogenation of **15**.

disappointing, with poor catalytic activities observed except in the case of catalyst **A**.[13a] In the presence of 2 mol% of **A** (CF_3CH_2OH; room temperature; 12 h), the highly enantioselective hydrogenation of **15** did proceed to give the desired product **16** with excellent stereoselectivity (97:3), albeit in low yield (18%). The problem was the low reactivity, and even at pressures as high as 10 MPa the reaction was sluggish. When carried out at 40 °C, a slightly higher yield of **16** was obtained (40%) with recovery of **15** in 38% yield. However, no further improvement was possible, either by extending the reaction time or by increasing the catalyst loading, because the epoxide moiety seemed to be damaged by the fairly high Lewis acidity of the iridium catalyst or the Brønsted acidity of iridium hydride intermediates.

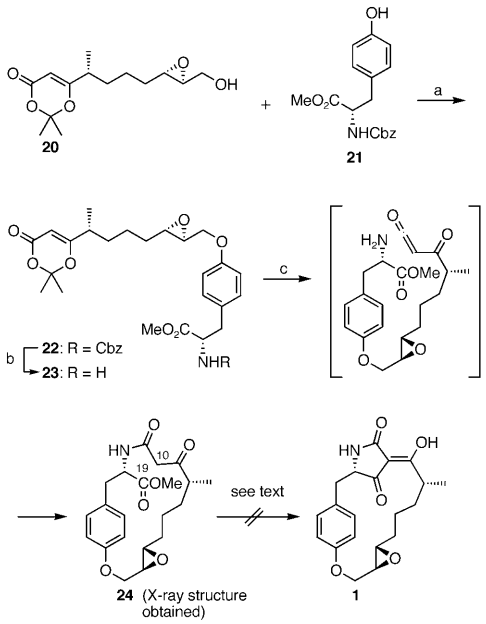
After considerable experimentation, a solution was found by converting the epoxide into the corresponding iodohydrin prior to the hydrogenation (Scheme 5). Therefore, alcohol **17** was prepared by the desilylation of **11** (nBu_4NF, THF, 0 °C, 1 h, 99%), which allowed the highly regioselective (92:8) epoxide ring opening (NaI, $B(OAc)_3$, AcOH, acetone),[14] to give 1,3-diol **18** as the major product along with a small amount of 1,2-diol **18′** in 94% combined yield (**18**/**18′** = 92:8); these products were easily separated by silica gel column



Scheme 5. Hydrogenation of **18**. a) NaI, $B(OAc)_3$, AcOH, acetone, −20→0 °C, 2 h (94%). b) H_2 (10 MPa), **A** (2 mol%), CF_3CH_2OH, 40 °C, 12 h (96%). c) K_2CO_3, methanol, RT, 1 h (quant.).

chromatography.[15] Pleasingly, the attempted hydrogenation of **18** in the presence of iridium catalyst **A** proceeded smoothly, without any reductive fission of the C–I bond,[16] affording the desired compound **19** in excellent yield (96%) and excellent stereoselectivity (97:3).[17] Treatment of **19** with potassium carbonate in methanol regenerated the oxirane ring to regioselectively afford epoxy alcohol **20** in quantitative yield.[18]

For preparation of the macrolactam precursor, tyrosine unit **21**[19] was coupled with epoxy alcohol **20** using the Mitsunobu reaction (TMAD and nBu_3P);[20] detachment of the benzyloxycarbonyl protecting group then gave amine **23**. The pivotal construction of the macrocidin skeleton involved two stages: 1) macrolactam formation via intramolecular ketene trapping, and 2) Lacey–Dieckmann cyclization for constructing the tetramic acid (Scheme 6).



Scheme 6. Attempts for the macrolactam formation and the Lacey–Dieckmann condensation. a) TMAD, nBu_3P, toluene, RT, 3 h (89%). b) H_2, $Pd(OH)_2/C$, MeOH, RT, 4 h (98%). c) Toluene, reflux, 2 h (90%). Cbz = benzyloxycarbonyl, TMAD = *N*,*N*,*N*′,*N*′-tetramethyl azodicarboxamide.

Indeed, we were pleased to find that the first step was realized quite smoothly by the heating of **23** in toluene (reflux, 2 h), giving macrolactam **24** in 90% yield, ready for the final step of the total synthesis. However, we were disappointed by the complete failure of the attempted Lacey–Dieckmann condensation to convert macrolactam **24** into macrocidin A (**1**) using *t*BuOK or various other basic reagents (e.g. nBu_4NF, NaOMe).

Single-crystal X-ray diffraction analysis of **24**[21] suggested an inherent problem in the cyclization substrate: the distance between C10 and C19[6] was too large (4.61 Å) to allow bond formation (Figure 1). To bring the two centers closer together,

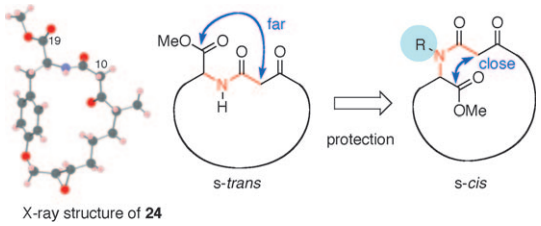
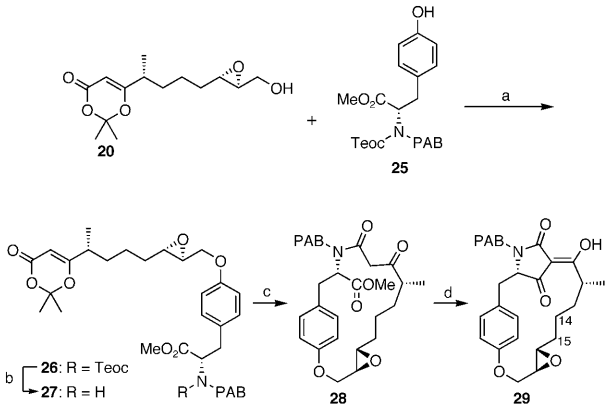


Figure 1. Conformational analysis of macrolactam **24** and a strategy for the construction of the tetramic acid ring.

the geometry of the amide group would have to be changed from the s-*trans* to the s-*cis* conformation. It occurred to us that such a conformational change would be achieved if a protecting group was introduced at the amide nitrogen atom, thus providing a more favorable situation for the cyclization.

Along these lines, we prepared *para*-azidobenzyl (PAB)[22] derivative **28**, which was later employed in the eventual route, starting from the Mitsunobu reaction (DEAD, PPh_3) of epoxy alcohol **20** and phenol **25**[23] (Scheme 7). In this instance, the

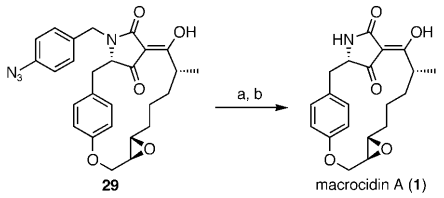


Scheme 7. Synthesis of *para*-azidobenzyl-protected macrocidin A (**29**). a) DEAD, PPh_3, toluene, RT, 3 h (89%). b) nBu_4NF, THF, RT, 4 h (91%). c) Toluene, reflux, 2 h (86%). d) *t*BuOK, *t*BuOH, THF, RT, 30 min (87%). DEAD = diethyl azodicarboxylate, Teoc = 2-(trimethylsilyl)ethoxycarbonyl. PAB = *p*-azidobenzyl.

use of TMAD and nBu_3P was not suitable, because the azide moiety in phenol **25** was reduced by the latter reagent. The 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group in **26** was

removed to give compound **27**, which smoothly underwent macrolactam formation to **28** in 86% yield by heating to reflux in toluene. To our delight, the protected substrate **28** indeed underwent Lacey–Dieckmann cyclization upon treatment with *t*BuOK (room temperature, 0.5 h) to give the corresponding tetramic acid **29** in 87% yield. Notably, the C14 and C15 proton signals of **29** appeared at higher field (C14, $\delta = 0.49$; C15, $\delta = 0.80$); this is ascribable to the anisotropic effect of the benzene ring within a rigid cyclophane skeleton.

The final step was the particularly problematic removal of the amide protecting group. After a number of unsuccessful attempts using other protecting groups,[24] the *para*-azidobenzyl protecting group,[22] employed in **29**, was found to be the only group that could be successfully removed in the final step of the synthesis. Reduction of the azide moiety in **29** gave the corresponding amine, which, upon exposure to DDQ in the presence of water, afforded macrocidin A (**1**) as a pale beige solid that exhibited physical properties consistent with the reported data (^{1}H and ^{13}C NMR, IR, mass spectra).[1] Although the melting point was not reported in the original paper,[1] reprecipitation (dichloromethane/methanol) gave **1** as a fine, pale beige powder with a melting point of 205–207 °C. The sign and magnitude of the optical rotation concurred well with the reported values of natural macrocidin A: $[\alpha]_D^{27} = +42$ ($c = 0.18$, methanol), lit. $[\alpha]_D^{25} = +45$ ($c = 0.35$, methanol), thus establishing the absolute configuration of the natural product as shown (Scheme 8).



Scheme 8. Total synthesis of macrocidin A. a) H_2, 10% Pd/C, MeOH, THF, RT, 2 h. b) DDQ, H_2O, THF, room temperature, 0.5 h (78%, 2 steps). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In summary, we have achieved the first total synthesis of macrocidin A. and have established the absolute configuration. Further work is ongoing to synthesize macrocidin B and other analogues of biological relevance.

Received: November 11, 2009
Published online: December 28, 2009

Keywords: asymmetric catalysis · hydrogenation · iridium · natural products · total synthesis

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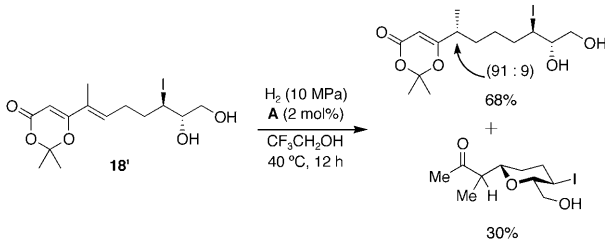
[15] It is noted that regioisomer **18'** underwent the hydrogenation with slightly lower stereoselectivity and in lower yield. A side product was obtained that was derived from tetrahydropyran formation as well as the deacetonization/decarboxylation as shown below.



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