

Total Synthesis of (+)-Cylindramide A

Amy C. Hart and Andrew J. Phillips*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received December 1, 2005; E-mail: Andrew.Phillips@colorado.edu

In 1993, Fusetani and co-workers described the structure of cylindramide A, a macrocyclic tetramic acid isolated from the sponge *Halichondria cylindrata* that was cytotoxic to B16 melanoma cells with an IC_{50} of $0.8 \mu\text{g mL}^{-1}$.^{1a} Cylindramide A is structurally related to a number of other tetramic acid-containing macrolactams that have been isolated from a variety of sources, including aburatubolactam A,^{1b} geodin A,^{1c} xanthobaccin A,^{1d} ikarugamycin,^{1e} discoderamide,^{1f} and the alteramides.^{1g} Because of their complex structures and diverse biological activities including cytotoxicity, antimicrobial activity, and inhibition of superoxide generation, these compounds have generated a significant degree of interest in the synthesis community,² and in this Communication we report a synthesis of cylindramide A.

Our strategy for the synthesis of cylindramide A is outlined in Figure 1. We planned to couple two large domains: a subunit containing the bicyclo[3.3.0]octene (**4**), and a 3-hydroxyornithine-derived subunit (**5**). The bicyclo[3.3.0]octene ring system was envisioned to arise from a tandem ring-opening–ring-closing–cross metathesis (ROM–RCM–CM) of readily available norbornene **2** to give **3**.³

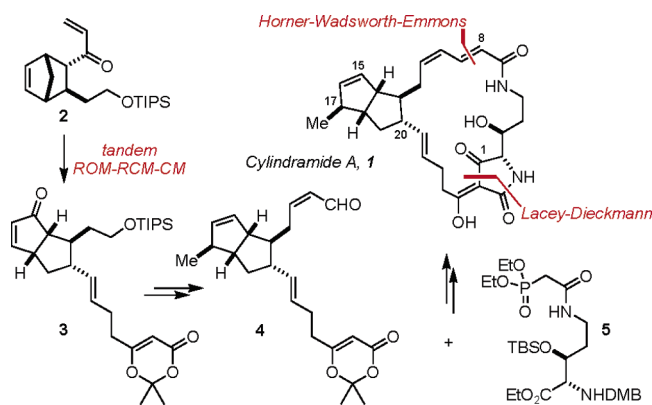
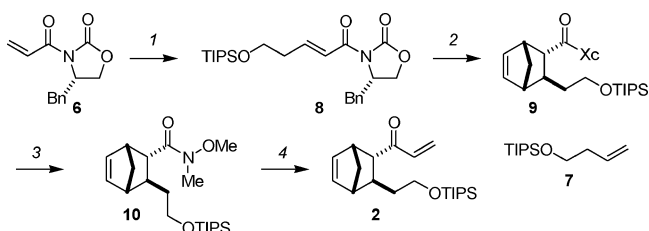


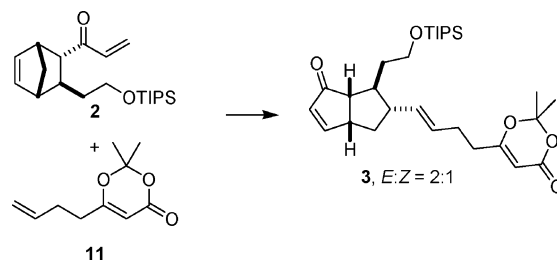
Figure 1. Structure of cylindramide A (**1**) and synthetic strategy.

Norbornene **2** was obtained by a five-step sequence that was initiated by the cross metathesis of acryloyl oxazolidinone **6** with alkene **7** to give **8** in 59% yield (Scheme 1). Diels–Alder reaction with cyclopentadiene under the conditions described by Evans led to **9** (96%, dr = 45:1).⁴ Although direct conversion of the oxazolidinone to Weinreb amide **10** was not possible, simple hydrolysis to the acid and a 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI)-mediated coupling provided a suitable alternative (52% over two steps). Addition of vinylmagnesium bromide to a solution of **10** at reflux provided **2** in 98% yield and set the stage for the key tandem ROM–RCM–CM sequence.

When **2** was treated with 4 mol % Grubbs's catalyst in the presence of 3.0 equiv of **11**, tandem ROM–RCM–CM occurred to give **3** in 59% yield and as a 2:1 mixture of separable diastereoisomers (Scheme 2).

Scheme 1^a

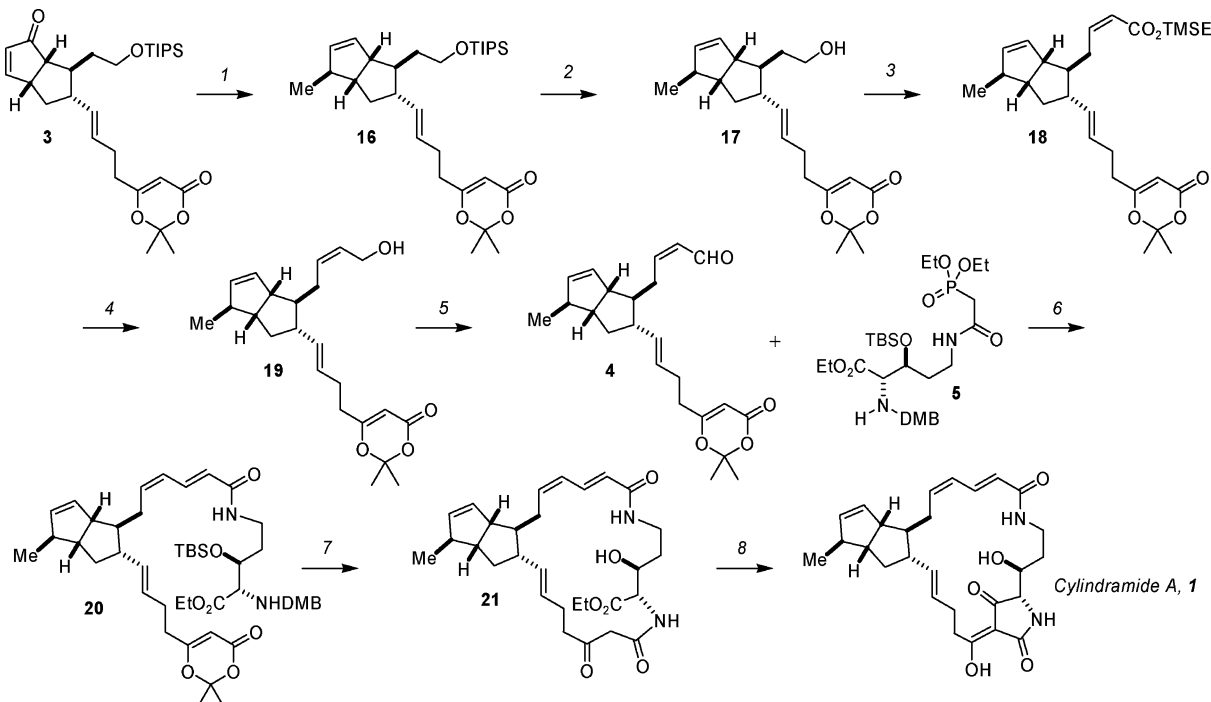
^a Reagents and conditions: (1) 10% Grubbs's II catalyst, **7**, CH_2Cl_2 , 40 °C, 59%; (2) cyclopentadiene, Et_2AlCl , CH_2Cl_2 , –78 °C, 96%, dr = 45:1; (3) (a) LiOH , H_2O_2 , THF, H_2O , –10 °C; (b) $\text{HCl} \cdot \text{HN}(\text{OMe})\text{Me}$, DMAP, EDCI, CH_2Cl_2 , 52% (two steps); (4) $\text{H}_2\text{C}=\text{CHMgBr}$, THF, 67 °C, 98%.

Scheme 2^a

^a Reagents and conditions: 4% Grubbs's catalyst, **11** (3.0 equiv), CH_2Cl_2 , 40 °C, 59%.

Conversion of **3** to **4** commenced with installation of the C17 methyl group and $\Delta^{15,16}$ olefin by a sequence consisting of conjugate addition (Me_2CuLi , 90%, Scheme 3) followed by ketone reduction and elimination of the resultant secondary alcohol (NaBH_4 and then Martin sulfurane,⁵ 53%) to give **16**. Removal of the triisopropylsilyl (TIPS) ether with HF /pyridine provided alcohol **17** in 86% yield. Oxidation with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO), followed by immediate reaction with [bis(2,2,2-trifluoroethoxy)phosphoryl]acetic acid (2-trimethylsilyl)ethyl ester⁶ under Still–Gennari conditions,⁷ yielded **18** in 51% yield for the two steps. Cleavage of the 2-(trimethylsilyl)ethyl (TMSE) group with tetrabutylammonium fluoride (TBAF) and reduction of the isobutyl chloroformate-derived mixed anhydride with NaBH_4 (**18**→**19**, 51% over two steps), followed by Dess–Martin oxidation, gave **4** and completed the synthesis of the bicyclo[3.3.0]octene domain.

Coupling of key fragments **4** and **5**⁸ was achieved by Horner–Wadsworth–Emmons reaction, which led to **20** in 90% overall yield from allylic alcohol **19**. Heating **20** in toluene at reflux under dilute conditions resulted in macrocyclization to give the expected β -ketoamide in 65% yield as a complex mixture of tautomers. Removal of the *tert*-butyldimethylsilyl (TBS) ether with HF provided **21** in 95% yield. The synthesis was completed by Lacey–Dieckmann cyclization⁹ to form the tetramic acid (NaOMe , 90%), and finally removal of the 2,4-dimethoxybenzyl protecting group (trifluoroacetic acid (TFA), 67 °C, 65%) provided cylindramide

Scheme 3^a

^a Reagents and conditions: (1) (a) Me_2CuLi , Et_2O , -78°C , 90%; (b) NaBH_4 , MeOH , 0°C ; (c) Martin sulfuran, CH_2Cl_2 , 0°C , 53% (two steps); (2) HF/pyr , THF , 86%; (3) (a) TPAP, NMO, CH_2Cl_2 , 4 Å MS; (b) [bis(2,2,2-trifluoroethoxy)phosphoryl]acetic acid (2-trimethylsilyl)ethyl ester, KHMDS, 18-C-6, THF , -78°C , 51% (two steps); (4) (a) TBAF, THF ; (b) IBCF, NMM, THF , 0°C , then NaBH_4 , MeOH , H_2O , 50% (two steps); (5) Dess–Martin periodinane, CH_2Cl_2 ; (6) **5**, NaHMDS, then add **4**, THF , $-78^\circ\text{C} \rightarrow \text{rt}$, 90% (from **19**); (7) (a) PhMe , 105°C , 65%; (b) HF , MeCN , 95%; (8) (a) NaOMe , MeOH , 90%; (b) TFA , 67°C , 65%.

A. Synthetic cylindramide A had physical and spectroscopic properties in accord with those reported.¹⁰

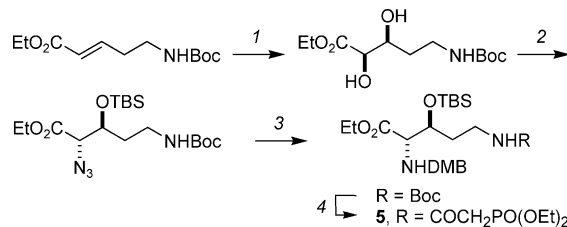
In conclusion, we have delineated a synthesis of cylindramide A that proceeds in 19 steps (longest linear sequence) and highlights the utility of the tandem ROM–RCM–CM of simple norbornenes in the context of complex natural products synthesis.

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Supporting Information Available: Experimental procedures, data, and spectra for compounds **1–3**, **8–10**, and **16–21**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) Amine **5** was synthesized by the sequence shown below:



Reagents and conditions: (1) AD mix α , MeSO_2NH_2 , $\text{H}_2\text{O}/t\text{-BuOH}$, 90%, >98% ee; (2) (a) SOCl_2 , NEt_3 , CH_2Cl_2 ; (b) NaN_3 , DMF, 55°C ; (c) TBSOTf, CH_2Cl_2 , 80% (three steps); (3) (a) $\text{H}_2(\text{g})$, Pd/C, EtOAc , (b) 2,4-dimethoxybenzaldehyde, 4 Å MS, MeOH , then NaBH_3CN , 70% (two steps); (4) TFA , CH_2Cl_2 , then diethylphosphonoacetic acid, thiazolidine-2-thione, EDCI, DMAP, Et_3N , 61% (two steps).

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- (10) See the Supporting Information for details.

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