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Total Synthesis of (+)-Cylindramide A

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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 μg 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] discodermide,[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]

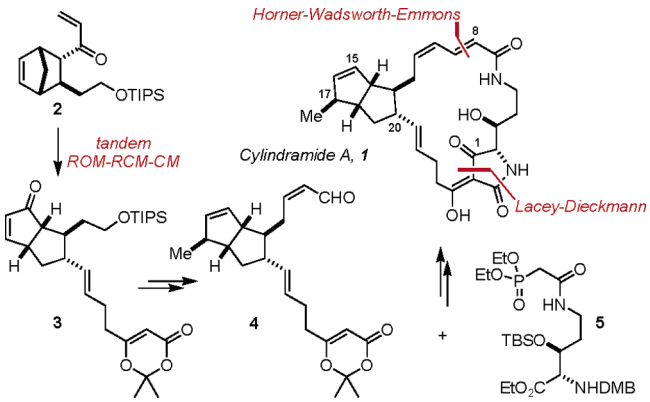
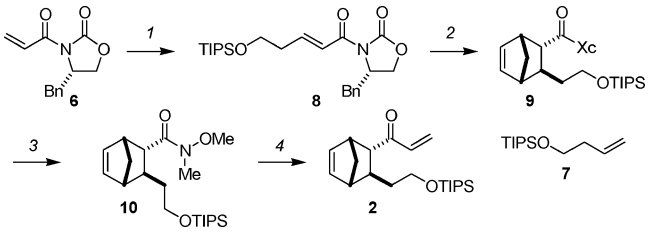


Figure 1. Structure of cylindramide A (**1**) and synthetic strategy.

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.

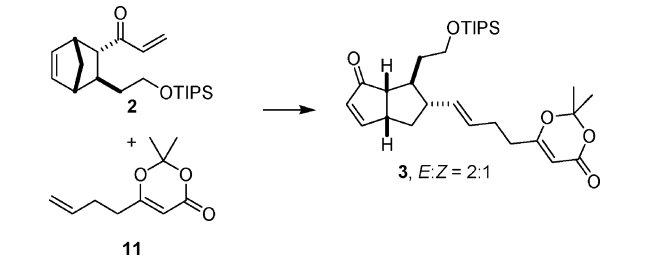
When **2** was treated with 4 mol % Grubbs's catalyst in the presence of 3.0 equiv of **11**, tandem ROM−RCM−CM occurred to give **3** in 59% yield and as a 2:1 mixture of separable diastereoisomers (Scheme 2).

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) HCl·HN(OMe)Me, DMAP, EDCI, CH_2Cl_2, 52% (two steps); (4) H_2C=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 ester[6] 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 cyclization[9] to form the tetramic acid (NaOMe, 90%), and finally removal of the 2,4-dimethoxylbenzyl protecting group (trifluoroacetic acid (TFA), 67 °C, 65%) provided cylindramide

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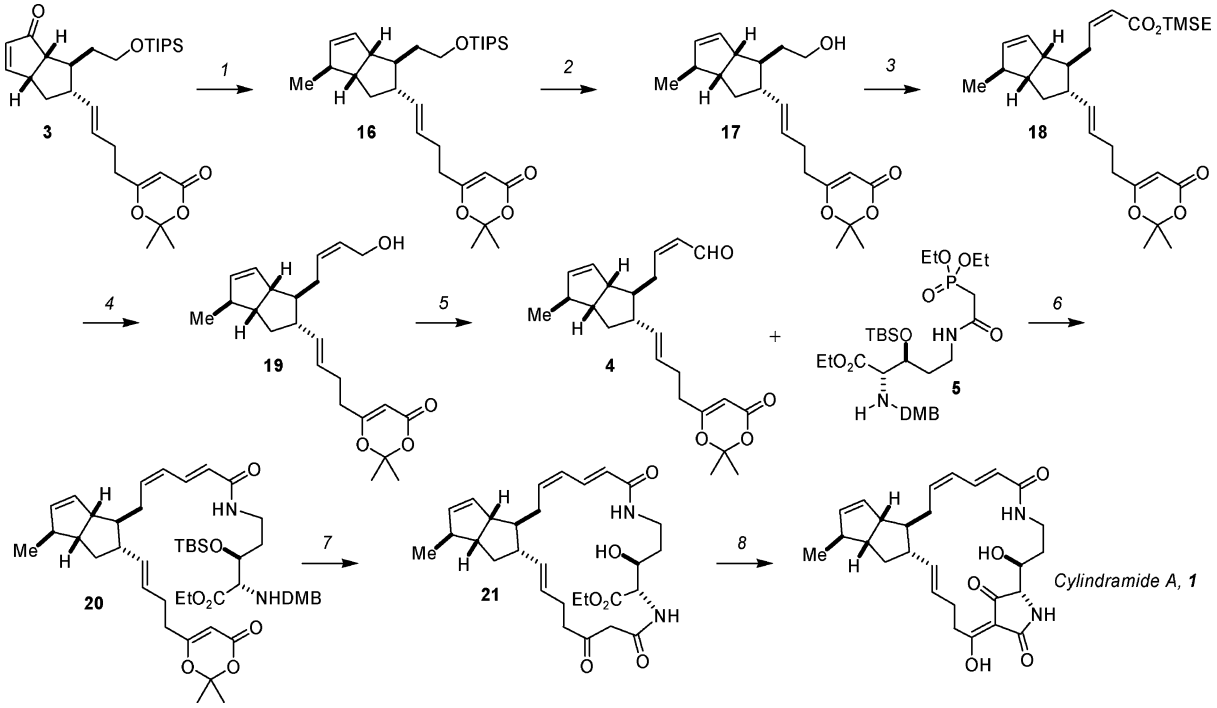
Scheme 3 [a]



[a] Reagents and conditions: (1) (a) Me_2CuLi, Et_2O, −78 °C, 90%; (b) $NaBH_4$, MeOH, 0 °C; (c) Martin sulfurane, 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 °C → 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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(1) (a) Kanazawa, S.; Fusetani, N.; Matsunaga, S. *Tetrahedron Lett.* **1993**, *34*, 1065. (b) Bae, M. A.; Yamada, K.; Ijuin, Y.; Tsuji, T.; Yazawea, K.; Tomono, Y.; Uemura, D. *Heterocycl. Commun.* **1996**, *2*, 315. (c) Capon, R. J.; Skene, C.; Lacey, E.; Gill, J. H.; Wadsworth, D.; Friedel, T. *J. Nat. Prod*. **1999**, *62*, 1256. (d) Hashidoko, Y.; Nakayama, T.; Homma, Y.; Tahara, S. *Tetrahedron Lett.* **1999**, *40*, 2957. (e) Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271. (f) Gunasekera, S. P.; Gunasekera, M.; McCarthy, P. *J. Org. Chem.* **1991**, *56*, 4830. (g) Shigemori, H.; Bae, M. A.; Yazawa, K.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 4317.

(2) For a previous synthesis of cylindramide A, see: (a) Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 820. For syntheses of ikarugamycin, see: (b) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (c) Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037. (d) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151.

(3) For other examples of tandem metathesis sequences of this general type, see: (a) Stragies, R.; Blechert, S. *Synlett*. **1998**, 169. (b) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974. (c) Arjona, O.; Csakye, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380. (d) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (e) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357 and references therein.

(4) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

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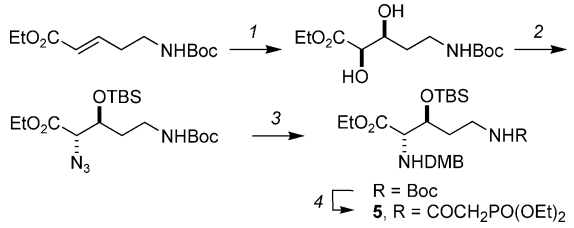
(8) Amine **5** was synthesized by the sequence shown below:



Reagents and conditions: (1) AD mix α, $MeSO_2NH_2$, H_2O/*t*-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) H_2(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).

(9) Lacey, R. N. *J. Chem. Soc.* **1954**, 850.

(10) See the Supporting Information for details.

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