JOC The Journal of Organic Chemistry

Article

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Stereoselective Total Synthesis of Marine Cyclodepsipeptide Calcaripeptides A−C

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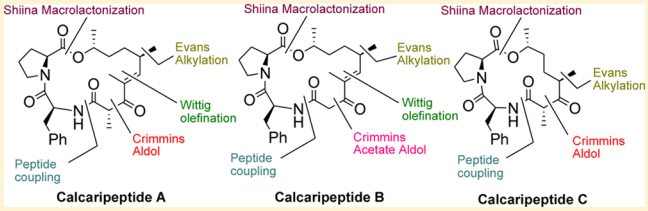
Supporting Information

ABSTRACT: The first stereoselective total syntheses of marine cyclodepsipeptides, calcaripeptides A−C, have been accomplished. Emphasis was given particularly in identification of an efficient strategy for the macrocyclization. The notable features of our synthesis include Evans alkylation, Crimmins *syn*-aldol, Crimmins acetate aldol, Wittig olefination, and Shiina macrolactonization reactions. An anomaly in the ^{1}H NMR of the proposed calcaripeptide B has been amended during this synthetic study.



INTRODUCTION

Marine cyclodepsipeptides exhibit a wide range of bioactivities, and many of them are used as potential leads in the pharmaceutical industry.[1] The synthesis of this class of natural products has always remained a subject of great interest. In 2013, Imhoff and co-workers isolated three new cyclic depsipeptides, namely, calcaripeptides A−C (**1**−**3**)[2] (Figure 1) during the analysis of the metabolic profile of a fungal strain

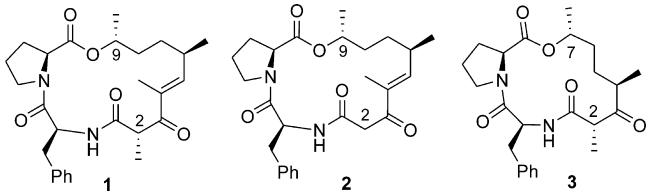


Figure 1. Chemical structures of calcaripeptides A−C (**1**−**3**).

(KF525) of genus *Calcarisporium* sp. collected from the German Wadden Sea. The structures of calcaripeptides A−C were deduced by extensive NMR study, HPLC analysis of hydrolyzed products, and finally by functional group characterization through derivatizations. The relative configuration of calcaripeptide A (**1**) was confirmed by X-ray crystallographic analysis.[2] Architecturally, calcaripeptides A−B and calcaripeptide C are the 16- and 14-membered hybrid macrocycles, respectively, which feature a dipeptide scaffold and polypropionate chains connected by amide and ester linkages. The dipeptide unit is composed of L-proline and L-phenylalanine. The polypropionate moiety varies in structure among the three compounds. As a continuation of our[3] interest toward asymmetric synthesis of bioactive natural products, we embarked on the total synthesis of structurally intriguing marine cyclodepsipeptides, calcaripeptides A−C. We have also planned to execute the systematic SAR monitoring around the molecular framework[4] to come up possibly with novel cyclodepsipeptide(s). Before investigating the structure−activity studies, we initially concentrated on developing a flexible and convergent synthetic strategy for the target molecules. This is important as the ring disconnection in cyclodepsipeptides is strategically crucial, which, eventually, will determine the success of their efficient syntheses. The cyclization strategies, such as macrolactamization,[5] macrolactonization,[6] RCM (ring-closing metathesis),[7] and intramolecular cross-coupling,[8] have been employed for the synthesis of various classes of cyclodepsipeptides in the literature. Herein, we report our investigation with particular emphasis on the development of a facile and general synthetic strategy leading to efficient ring-closing and finally to accomplish the first stereoselective total synthesis of proposed calcaripeptides A−C in solution phase.

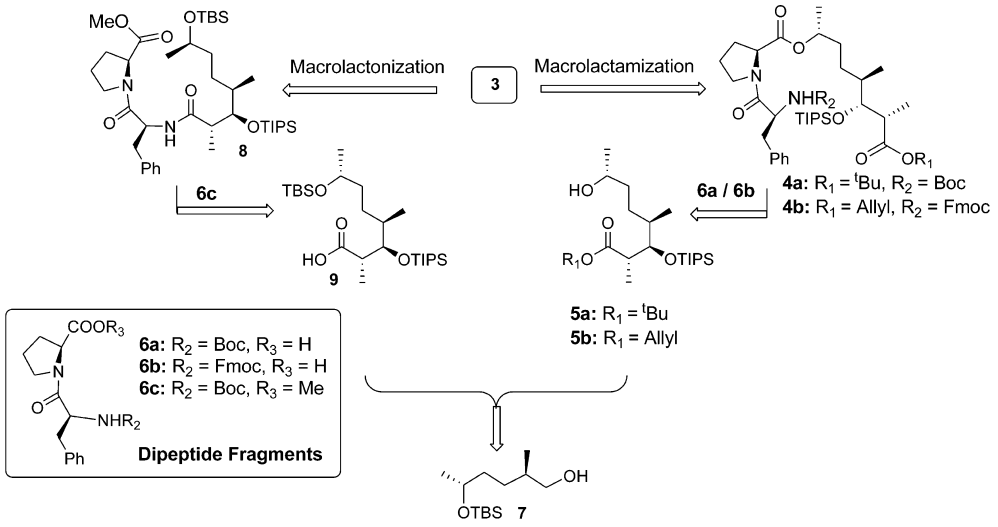
RESULTS AND DISCUSSION

To search for a common macrocyclization strategy for the calcaripeptide family, we initially ruled out RCM or intramolecular cross-coupling type cyclization due to the structural variance of polyketide chains observed between the different members of this family. The members of the calcaripeptide family possess one ester and two amide linkages. Each of them could possibly be considered as the sites of macrocyclization. We first planned to examine both the macrolactamization and the macrolactonization strategies separately for the smallest cyclic member, calcaripeptide C (**3**), to understand the effective way of cyclization for this family of cyclodepsipeptides. The key disconnections of calcaripeptide C (**3**) are outlined in Scheme 1. We initially attempted macrolactamization as it is generally more favorable over macrolactonization.[9] In order to adopt the shorter synthetic route, we selected the amide bond originated from L-Phe-NH_2 and the carboxylic acid functionality of the

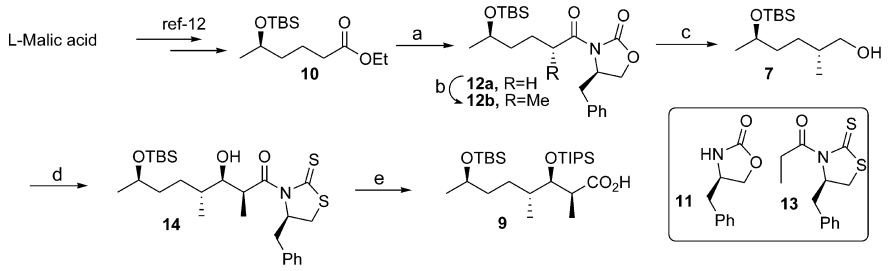
Received: August 27, 2014

   dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Retrosynthetic Analysis of Calcaripeptide C (3)

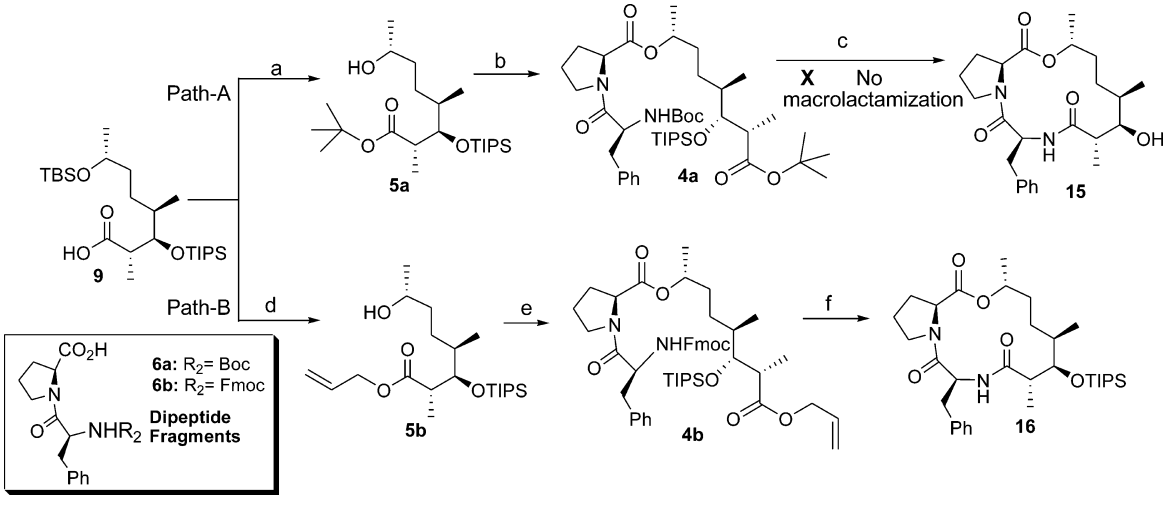


Scheme 2. Synthesis of Polyketide Acid Fragment (9)[a]



[a]Reagents and conditions: (a) (i) $LiOH{\cdot}H_2O$, $THF{:}H_2O$ (3:1), 0 °C to rt, 12 h, quantitative; (ii) **11**, Et_3N, PivCl, LiCl, −20 to 0 °C, THF, 4 h, 89%; (b) NaHMDS, MeI, THF, −78 °C, 4 h, 76%, (*dr* > 10:1); (c) $LiBH_4$, THF, 0 °C, 30 min, 91%; (d) (i) IBX, EtOAc, reflux, 3 h, 93%; (ii) **13**, $TiCl_4$, DIPEA, CH_2Cl_2, 0 to −78 °C, 1 h, 74% (single detectable isomer); (e) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 3 h, 96%; (ii) $LiOH{\cdot}H_2O$, 30% aqueous H_2O_2, $THF{:}H_2O$ (3:1), 0 °C, 10 min, 81%.

Scheme 3. Effort toward Synthesis of Calcaripeptide C (3) Using Macrolactamization Approach[a]



[a]Reagents and conditions: Path A: (a) (i) Boc_2O, DMAP, ^tBuOH, rt, 2 h, 81%; (ii) CSA, CH_2Cl_2:MeOH (5:1), 0 °C, 4 h, 52%; (b) **6a**, EDCI, DMAP, CH_2Cl_2, rt, 12 h, 78%; (c) (i) 40% TFA/CH_2Cl_2, 0 °C to rt, 4 h, quantitative; (ii) attempted macrolactamization with EDCI/HOBt or HATU/DIPEA or PyBOP/DIPEA conditions; Path B: (d) (i) allyl bromide, K_2CO_3, DMF, 0 °C to rt, 14 h, 95%; (ii) CSA, CH_2Cl_2:MeOH (5:1), 0 °C, 3 h, 93%; (e) **6b**, EDCI, DMAP, CH_2Cl_2, rt, 12 h, 73%; (f) (i) $Pd(PPh_3)_4$, morpholine, THF, rt, 30 min, 88%; (ii) Et_2NH, CH_3CN, rt, 30 min; (iii) Table 1.

polyketide fragment for the possible site of macrolactamization rather than the amide bond accessed from the amino acids L-Phe-COOH and L-Pro-NH_2. The C-2 methyl group is presumably sensitive to epimerization as it is flanked between

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

the C-1 amide carbonyl and C-3 keto functionalities. We planned to keep the C-3 keto functionality suitably protected as the hydroxy group that could be deprotected and oxidized at an advanced stage of synthesis to avoid epimerization of the C-2 center. Calcaripeptide C (**3**) could be constructed from the intermediates **4a** or **4b** using macrolactamization as one of the key steps. Compounds **4a** or **4b** could be synthesized from known dipeptide fragments[10a,b] **6a** or **6b** and alcohols **5a** or **5b**, respectively, by intermolecular esterification.

Alternatively, the macrolactonization strategy would disconnect the target molecule **3** into the protected ester **8** (Scheme 1) that could be synthesized from the, suitably protected, dipeptide fragment[10c] **6c** and the polyketide counterpart **9** by the intermolecular peptide coupling reaction. It is worthy to mention that the fragment **9** is the precursor of intermediates **5a** or **5b** and could be accessed from alcohol **7** using the Crimmins *syn*-aldol reaction[11] as one of the pivotal steps.

Our synthetic endeavor (Scheme 2) began from the known compound **10**, prepared from L-malic acid following the reported procedure.[12] Ester **10** was saponified with $LiOH·H_2O$ to get the corresponding acid and subsequently coupled with the Evans oxazolidinone **11**[13] to get compound **12a**, which was further reacted with MeI in the presence of NaHMDS[14] to produce methylated compound **12b** as the major isomer with good diastereoselectivity (*dr* > 10:1) and good yield (76%). Careful reduction of compound **12b** with $LiBH_4$ yielded alcohol **7**, which was oxidized to the corresponding aldehyde with IBX and concomitantly subjected to the Crimmins *syn*-aldol reaction[11] with thiazolidinethione **13**[11a] in the presence of $TiCl_4$ and DIPEA to achieve compound **14** as single detectable isomer. The hydroxy group of compound **14** was then protected as the TIPS ether and subsequently hydrolyzed with $LiOH·H_2O$ in the presence of 30% aqueous H_2O_2 to afford the required acid **9** (Scheme 2) in 78% yield after two steps.

Macrolactamization. Our efforts toward the synthesis of calcaripeptide C (**3**) using macrolactamization as the key ring-closing step are summarized in Scheme 3. The free carboxylic acid of compound **9** was first protected as *tert*-butyl ester by Boc_2O/DMAP[15] for future synthetic convenience and subsequently subjected to selective TBS ether deprotection (Path A, Scheme 3). We avoided using any acidic conditions because of the coexistence of other acid sensitive groups in the reacting moiety. When the reaction was performed at 0 °C in the presence of TBAF for the same, surprisingly only the TIPS deprotected compound was formed and not the desired TBS-deprotected compound. It is likely that the rate of deprotection was faster for the bulkier TIPS group to rid the system of the severe steric repulsion caused by the presence of a methyl and *tert*-butyl ester groups in the α- and β-positions, respectively. CSA then has been used carefully (with constant monitoring of reaction by TLC) to produce the required product **5a** with moderate yield (52%). However, a substantial amount of both TBS and *tert*-butyl deprotected compound was also formed during this deprotection process. The known dipeptide acid **6a**[10a] was esterified with alcohol **5a** in the presence of EDCI/DMAP[16] to access compound **4a**, which was treated further with 40% TFA/CH_2Cl_2 to result in the formation of the corresponding globally deprotected precursor for macrolactamization in quantitative yield. A number of reagents (EDCI/HOBt, HATU/DIPEA, and PyBOP/DIPEA), known[17] for cyclic depsipeptide synthesis, were tested at this stage to achieve the cycloamidation product **15**, but it was very unfortunate that none of these cyclizing agents succeeded. In most of the cases, the starting material either decomposed or converted to a mixture of several unidentified products. To get insight whether the free hydroxy group β to the carboxylic acid in the surrogate molecule exerted any unfavorable situation impeding a successful macrolactamization, we adopted Path B (Scheme 3). The intermediate **9** was treated with allyl bromide in the presence of K_2CO_3[18] to get the corresponding allyl ester that next was reacted with CSA to result in the TBS deprotected ester **5b** in good overall yield (88% over two steps). Both compounds **5b** and **6b**[10b] were coupled under standard esterification conditions (EDCI/DMAP)[16] to provide compound **4b**, which subsequently was subjected to stepwise removal of the allyl ester using $Pd(PPh_3)_4$ in the presence of morpholine[19] and the Fmoc group with diethylamine[20] to get the suitably protected precursor for macrolactamization. Under high dilute conditions (10^{-3} M), a number of reagents[17] were screened (Table 1) to achieve the cyclic intermediate **16**. It was found that HATU/DIPEA (entry 2) and PyBOP/DIPEA (entry 3) conditions afforded the required cyclic product **16**, but the overall yield of macrolactamization was poor (14−22%) to proceed further. The carboxylic acid that participated in the macrolactamization reaction was sterically encumbered due to the presence of the adjacent bulky TIPS group, which, possibly, was the key factor responsible for this inefficient macrocyclization.

Table 1. Efforts toward Optimization of Macrolactamization for Calcaripeptide C

entry	reagents	conditions	time (h)	yield
1	EDCI/HOBt, CH_2Cl_2	0 °C to rt	16	NR[a]
2	HATU/DIPEA, CH_2Cl_2	rt	18	22
3	PyBOP/DIPEA, CH_2Cl_2	0 °C to rt	20	14

[a]NR = No reaction.

Macrolactonization. The macrolactonization approach was also investigated in parallel to macrolactamization, which is depicted in Scheme 4. The acid **9** was coupled with the Boc deprotected counterpart of dipeptide **6c**[10c] following the standard EDCI/HOBt condition[21] to result in compound **8** in excellent yield (88%). The compound **8** was next treated with CSA to provide compound **17**, which was saponified with $LiOH·H_2O$ to get the corresponding seco acid in 83% yield after two steps. To prepare the cyclic compound **16** efficiently, we did a comparative study for optimization of the macrolactonization reaction. The Yamaguchi,[6,22] Shiina,[23] and Kita[24] cyclization protocols were evaluated individually at this stage. Highly dilute conditions ($\sim 10^{-3}$ M) were maintained in every case to minimize the possibility of the formation of homomeric and/or oligomeric products. It was observed that the Shiina macrolactonization protocol functioned best (57%) compared to the others in this case (Table 2). Compound **16** was reacted next with TBAF to deprotect the TIPS ether and subsequently oxidized by Dess−Martin periodinane[25] to afford compound **3** successfully. The spectral data and specific rotation {observed $[\alpha]_D^{26} = -74.6$ (*c* 0.13, MeOH); reported $[\alpha]_D^{20} = -79.0$ (*c* 0.2, MeOH)} of the present synthesized compound **3** were in good accordance with those reported for the isolated compound,[2] which unambiguously concludes the first total synthesis of calcaripeptide C.

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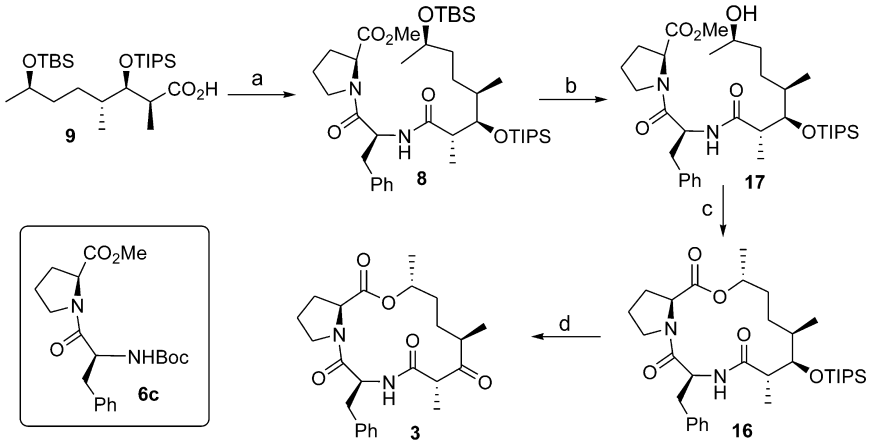
Scheme 4. Synthesis of Calcaripeptide C (3) by Macrolactonization Approach[a]



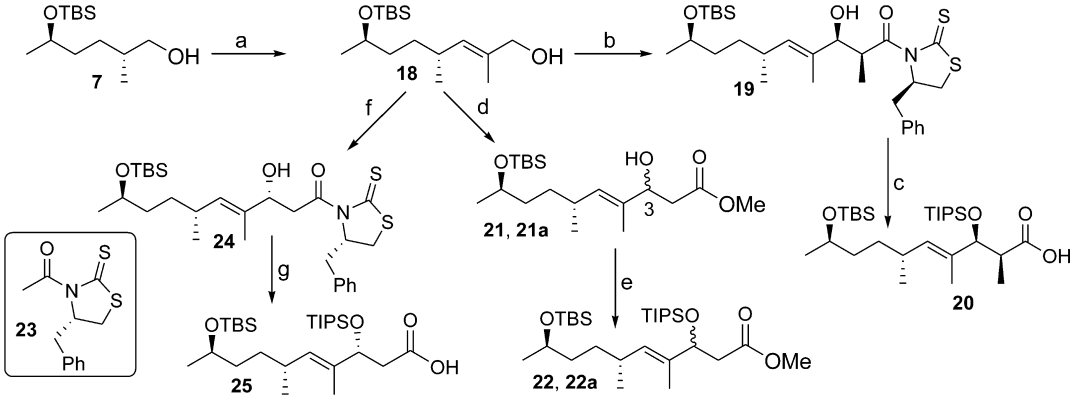
[a]Reagents and conditions: (a) Boc deprotected counterpart prepared from **6c** using 30% TFA/CH_2Cl_2 at 0 °C to rt in 2 h time, EDCI, HOBt, DIPEA, DMF, 0 °C to rt, 13 h, 88% from compound **9**; (b) CSA, CH_2Cl_2: MeOH (4:1), 0 °C, 3 h, 83%; (c) (i) LiOH·H_2O, THF:H_2O (3:1), 0 °C to rt, 1 h, quantitative; (ii) Table 2; (d) (i) TBAF, THF, 0 °C, 2 h, 88%; (ii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 2.5 h, 93%.

Table 2. Optimization of Macrolactonization for Calcaripeptide C (3)

entry	macrolactonization protocols[a]	conditions	time (h)	yield (%)
1	**Yamaguchi** (TCBC, Et_3N, DMAP, toluene)	80 °C	13	41
2	**Shiina** (MNBA, DMAP, CH_2Cl_2)	rt	12	57
3	**Kita** (ethoxyacetylene, $[RuCl_2(p\text{-cymene})]_2$, CSA, toluene)	50 °C	2.5	37

[a]TCBC = 2,4,6-trichlorobenzoyl chloride; MNBA = 2-methyl-6-nitrobenzoic anhydride.

Scheme 5. Synthesis of Polyketide Fragments 20 for Calcaripeptide A and 25 for Calcaripeptide B[a]



[a]Reagents and conditions: (a) (i) IBX, EtOAc, reflux, 3 h, 93%; (ii) $Ph_3P{=}CH(Me)CO_2Et$, toluene, 80 °C, 6 h, 86%; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 91%; (b) (i) IBX, EtOAc, reflux, 2.5 h, quantitative; (ii) **13**, $TiCl_4$, DIPEA, CH_2Cl_2, 0 to −78 °C, 1 h, 81%, (*dr* > 18:1); (c) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 2 h, 94%; (ii) LiOH·H_2O, 30% aqueous H_2O_2, THF:H_2O (3:1), 0 °C, 10 min, 83%; (d) (i) IBX, EtOAc, reflux, 2.5 h, quantitative; (ii) LiHMDS, MeOAc, −78 °C to rt, 4.5 h, 61%; (e) TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 2 h, 82%; (f) (i) IBX, EtOAc, reflux, 2.5 h, quantitative; (ii) **23**, $TiCl_4$, DIPEA, CH_2Cl_2, −40 to −78 °C, 1 h, 73%, (*dr* > 8:1); (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 2 h, 93%; (ii) LiOH·H_2O, 30% aqueous H_2O_2, THF:H_2O (3:1), 0 °C, 10 min, 85%.

With an optimized protocol of macrocyclization for calcaripeptide C (**3**) at hand, we next proceeded to complete the syntheses of calcaripeptides A (**1**) and B (**2**). The polyketide fragments of both calcaripeptides A and B are the three carbons higher homologues compared to the polyketide unit of calcaripeptide C with defined functionalities and stereochemistry (Figure 1).[2] We planned to construct the suitably protected C_1−C_{10} polyketide fragments **20** and **25** (Scheme 5) for calcaripeptides A (**1**) and B (**2**), respectively, from common precursor **7**. Alcohol **7** was oxidized with IBX and subsequently subjected to Wittig olefination[26] with the ylide $Ph_3P{=}CH(Me)CO_2Et$ to afford the corresponding *α,β*-unsaturated ester (*E*:*Z* > 8:1). The major *trans*-isomer was separated easily by column chromatography and finally reduced with DIBAL-H to afford alcohol **18** with good overall yield (73% in three steps). Alcohol **18** was oxidized to the corresponding aldehyde with IBX and subsequently subjected to the Crimmins *syn*-aldol reaction[11] with thiazolidinethione **13**[11a] in the presence of $TiCl_4$ and DIPEA to provide compound **19** as major isomer with 81% overall yield (*dr* > 18:1). The compound **19** was next transmuted to the corresponding TIPS ether with TIPSOTf using 2,6-lutidine as base and finally hydrolyzed with LiOH·H_2O in the presence of 30% aqueous H_2O_2 to achieve the suitably protected polyketide

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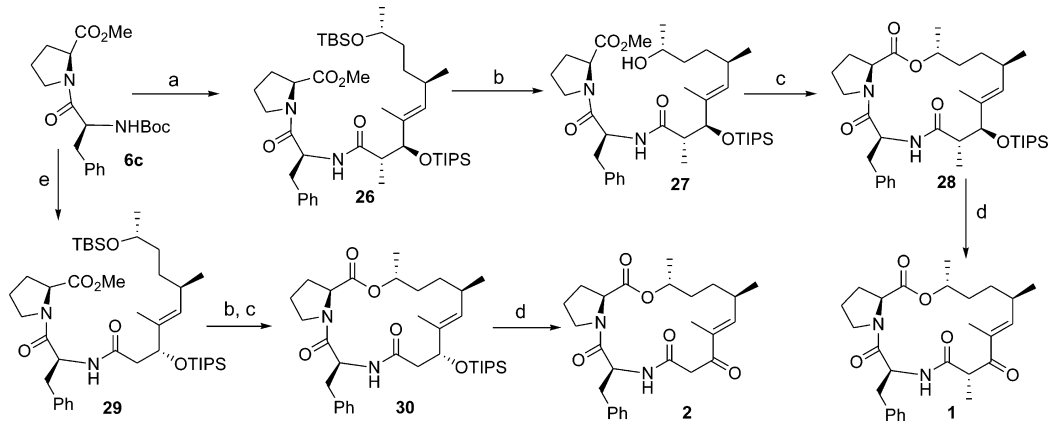
Scheme 6. Completion of Calcaripeptides A (1) and B (2)[a]



[a]Reagents and conditions: (a) (i) 30% TFA, CH_2Cl_2, 0 °C to rt, 2 h, quantitative; (ii) **20**, EDCI, HOBt, DIPEA, DMF, 0 °C to rt, 12 h, 86% from compound **20**; (b) CSA, CH_2Cl_2:MeOH (4:1), 0 °C, 2 h, 84−86%; (c) (i) LiOH·H_2O, THF:H_2O (3:1), 0 °C to rt, 1 h, quantitative; (ii) MNBA, DMAP, CH_2Cl_2, rt, 12 h, 61−64%; (d) (i) TBAF, THF, 0 °C, 2 h, 90−92%; (ii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 89−94%; (e) (i) same as conditions (a)−(i); (ii) **25**, EDCI, HOBt, DIPEA, DMF, 0 °C to rt, 12 h, 83% from compound **25**.

fragment **20** for calcaripeptide A (**1**) in 78% overall yield after two steps.

To construct fragment **25**, we started our synthesis from the corresponding aldehyde prepared from alcohol **18** by IBX oxidation. This was subsequently reacted with an enolate[27] generated from MeOAc in the presence of LiHMDS to get the mixture of adducts **21** and **21a** in 61% yield. We did not attempt to separate these diastereomers (having very close R_f values) at this stage or even at a later stage because the newly developed C-3 hydroxy center would be transmuted to the keto functionality at the final step of calcaripeptide B (**2**) synthesis. The mixture of compounds **21** and **21a** was next converted to TIPS ethers **22** and **22a** using TIPSOTf/2,6-lutidine and subsequently attempted for saponification using bases like LiOH·H_2O, NaOH, and KOH in variable conditions. Embarrassingly, none of these conditions were found to be efficient enough to produce the corresponding acids. It is noteworthy that both compounds **21** and **21a** with a free C-3 hydroxy group were susceptible to saponification, whereas their TIPS protected counterparts **22** and **22a** were inert toward base hydrolysis, most likely due to steric reasons. The three-step reaction protocol, reduction of ester with DIBAL-H, followed by IBX oxidation, and finally by Pinnick oxidation,[28] however, produced the required acid, but the poor overall yield and lengthy protocol urged us to explore the Crimmins acetate aldol strategy[29] (Scheme 5) as an alternative route. The aforementioned aldehyde obtained from alcohol **18** was then treated with titanium enolate generated in situ from (*S*)-phenylalanine derived *N*-acetylthiazolidinethione **23**[30] in the presence of $TiCl_4$ and DIPEA to provide **24** as a major isomer in 73% yield (*dr* > 8:1). Although the separation of the diastereomers was not necessary, we discarded the negligible amounts of the unwanted isomer during purification to preclude any possible complication during NMR characterization. Next, the compound **24** was converted to the required acid **25** in two steps: protection of the free secondary hydroxy group as the TIPS ether, followed by hydrolysis of the resultant compound with LiOH·H_2O in the presence of 30% aqueous H_2O_2.

The final strategy for the syntheses of calcaripeptides A (**1**) and B (**2**) is outlined in Scheme 6. Following a similar chemistry adopted for the synthesis of calcaripeptide C (**3**) as outlined in Scheme 4, we synthesized the intermediate **26** from dipeptide unit **6c**[10c] and polyketide fragment **20** in good overall yield. Compound **26** was reacted with CSA to get TBS deprotected compound **27** in 84% yield. It was next saponified with LiOH·H_2O to provide the corresponding seco acid, which was subsequently subjected to the Shiina macrolactonization protocol[23] to achieve the cyclic compound **28** in 64% overall yield after two steps. The two-step reaction protocol involving TBAF mediated TIPS deprotection, followed by oxidation of the resultant alcohol with Dess−Martin periodinane,[25] afforded compound **1** in 86% overall yield. The spectral data, specific rotation {observed $[\alpha]_D^{27}$ = −138.1 (*c* 0.23, MeOH); reported $[\alpha]_D^{20}$ = −133.0 (*c* 1.4, MeOH)}, and X-ray crystallographic data (Figure 2; please see the Supporting Information) of synthesized compound **1** were in good agreement with the reported values,[2] which unanimously confirm its first stereoselective synthesis.

The intermediate **29** (Scheme 6), prepared from the dipeptide unit **6c**[10c] and the polyketide acid fragment **25** following a similar chemistry as described in Scheme 4, was subjected sequentially to TBS deprotection, followed by ester hydrolysis and finally to the Shiina macrolactonization reaction,[23] to afford the cyclic product **30** in 52% overall yield after three steps. It was next reacted with TBAF to cleave the TIPS ether and subsequently oxidized with Dess−Martin periodinane[25] to furnish the proposed calcaripeptide B (**2**) in 80% overall yield after two steps (Scheme 6).

The ^{13}C NMR, COSY, HMBC, HRMS, and specific rotation {observed $[\alpha]_D^{20}$ = −117.6 (*c* 0.35, MeOH); reported $[\alpha]_D^{20}$ = −113.0 (*c* 0.31, MeOH)} of synthesized compound **2** were in accordance with the reported values.[2] However, an anomaly was noticed in the ^1H NMR spectrum of synthesized calcaripeptide B when compared to the one reported for the isolated product. The signal intensities of C-2 methylene protons having the chemical shifts of δ 4.32 and δ 3.15 ppm were surprisingly too low in the isolated compound when compared to the other aliphatic protons present in the spectrum. Those unusually low intensity signals were confirmed by HSQC NMR experiment. However, the same C-2 methylene protons in synthesized compound **2** behaved normally and those could be recognized easily from the ^1H NMR spectrum without any ambiguity. Moreover, the splitting

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. Observed Inconsistency in ^{1}H NMR of Proposed Calcaripeptide B and Its Rectification

	isolated calcaripeptide B			synthesized calcaripeptide B		
position	δ (ppm)	mult	integral value	δ (ppm)	mult	integral value
2-H_a	4.32	**bs**	**< 1H**	4.35	**d, J = 15.0 Hz**	**= 1H**
2-H_b	3.15	**bs**	**≪ 1H**	3.18	**d, J = 15.0 Hz**	**= 1H**

patterns of C-2 methylene protons in the isolated natural product were reported as broad singlets, whereas a strong germinal coupling[31] (J = 15.0 Hz) was observed between these diastereotopic protons in synthesized compound **2**. This resulted in the formation of two discrete doublets in the ^{1}H NMR spectrum (please see the Supporting Information). The unusual reduction of signal intensity of C-2 methylene protons in isolated calcaripeptide B was thought[2] to be due to their acidic or exchangeable nature. We were keen to ensure in this context whether the presence of impurities in the NMR solvents could affect its ^{1}H NMR spectrum. Apart from acetone-d_6, we also have recorded the ^{1}H NMR of synthesized compound **2** in acetone-d_6 mixed with one drop of D_2O. It was observed that only the amide proton present in the molecule exchanged slowly with deuterium, but the protons of our interest (C-2 methylene) remained unaltered for a long time. No reduction of signal intensity or change of splitting patterns for those C-2 protons were seen when acetone-d_6 was mixed with basic pyridine-d_5. Even using pyridine-d_5 for NMR did not lead to any change in the spectrum (please see the spectrum in the Supporting Information). Next, we have recorded the ^{1}H NMR of the synthesized compound **2** under acidic conditions using acetone-d_6 mixed with one drop of TFA-d to catalyze the H/D exchange. Indeed, both the amide proton and the diastereotopic C-2 methylene protons exchanged with deuterium with time. We did not observe the formation of any detectable amount of the enol tautomer during this process. The detection of the enol tautomer in the NMR time scale was difficult probably due to its transient nature. The changes of signal intensities of these protons in the synthesized compound **2** under acidic conditions were very similar to the reported ^{1}H NMR data of the isolated compound. It is possible that the observed anomaly in ^{1}H NMR spectrum of isolated calcaripeptide B was most likely due to the presence of some acidic contaminant in the medium. Thus, the observed inconsistency in the reported ^{1}H NMR spectrum of proposed calcaripeptide B needs to be corrected, as depicted in Table 3.

CONCLUSION

In short, we have demonstrated a general and flexible synthetic route for calcaripeptides A (**1**), B (**2**), and C (**3**) for the first time from known compound **10** with 11, 9, and 11% overall yields, respectively. The salient features of our synthesis include Evans alkylation, Crimmins *syn*-aldol, Crimmins acetate aldol, Wittig olefination, and Shiina macrolactonization reactions. Various macrocyclization conditions have been screened during the synthetic studies of this class of cyclodepsipeptides, and the total syntheses of proposed calcaripeptides A, B, and C have been achieved using the best macrocyclization conditions obtained. Finally, the inconsistency in ^{1}H NMR data for proposed calcaripeptide B has been rectified through chemical synthesis. Having established a synthetically viable route, the synthesis of structural variants of calcaripeptides A–C and the biological studies are in progress, which will be reported in due course.

EXPERIMENTAL SECTION

(*R*)-4-Benzyl-3-((*R*)-5-(*tert*-butyldimethylsilyloxy)hexanoyl)-oxazolidin-2-one (12a). A solution of saturated ester **10** (5.68 g, 20.70 mmol) in THF:H_2O (3:1, 50 mL) was cooled to 0 °C, and LiOH·H_2O (2.61 g, 62.1 mmol) was added at once. Stirring was continued at room temperature for another 12 h. The reaction mixture was cooled to 0 °C and cold 1 N aqueous HCl was added dropwise until the resulting mixture became just acidic (monitored by pH paper). The reaction mixture was quickly taken into a separating funnel and extracted with EtOAc (4 × 50 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatographic purification (SiO_2, 60–120 mesh, EtOAc as eluant) provided pure acid (5.10 g, quantitative) as a colorless oil: R_f = 0.32 (30% EtOAc in hexane); $[\alpha]_D^{28}$ = −14.3 (*c* 1.05 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.83–3.79 (m, 1H), 2.36 (t, J = 7.5 Hz, 2H), 1.74–1.70 (m, 1H), 1.66–1.61 (m, 1H), 1.48–1.43 (m, 2H), 1.13 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.3, 68.3, 38.9, 34.2, 26.0, 23.9, 21.1, 18.3, −4.3, −4.6 ppm; IR(neat): ν_{max} 2930, 1713 cm^{-1}; HRMS (ESI) m/z calculated for $C_{12}H_{26}O_3SiNa$ $[M + Na]^+$ 269.1549, found 269.1547.

To a stirred solution of the above acid (5.02 g, 20.37 mmol) in anhydrous THF (50 mL) at −20 °C under argon, Et_3N (7.10 mL, 50.93 mmol) and PivCl (2.76 mL, 22.41 mmol) were added sequentially. After 1 h stirring at −20 °C, LiCl (1.30 g, 30.56 mmol), followed by oxazolidinone 11 (3.97 g, 22.41 mmol), were added. The reaction was continued further for 1 h at −20 °C and another 2 h at 0 °C prior to quenching with saturated NH_4Cl solution (15 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100–200 mesh, 15% EtOAc in hexane as eluant) afforded compound **12a** (7.35 g, 89%) as a colorless oil: R_f = 0.53 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = −42.9 (c 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.20 (m, 5H), 4.67 (m, 1H), 4.21–4.15 (m, 2H), 3.86–3.83 (m, 1H), 3.30 (dd, J = 13.3, 3.5 Hz, 1H), 2.98–2.89 (m, 2H), 2.76 (dd, J = 10.0, 9.5 Hz, 1H), 1.78–1.68 (m, 2H), 1.55–1.47 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 153.6, 135.5, 129.6, 129.1, 127.5, 68.4, 66.3, 55.3, 39.1, 38.1, 35.7, 26.1, 23.9, 20.6, 18.3, −4.2, −4.6 ppm; IR(neat): ν_{max} 2928, 1786, 1703 cm^{-1}; HRMS (ESI) m/z calculated for $C_{22}H_{35}NO_4SiNa$ [M + Na]+ 428.2233, found 428.2236.

(*R*)-4-Benzyl-3-((2*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-methylhexanoyl)oxazolidin-2-one (12b). To a stirred solution of compound **12a** (7.30 g, 18.0 mmol) in dry THF (25 mL) at −78 °C under argon, NaHMDS (1.0 M solution in THF, 27.0 mL, 27.0 mmol) was added dropwise. After 30 min, MeI (3.36 mL, 54.0 mmol) was added, and the mixture was stirred further for 3.5 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and warmed up to room temperature before extracting with EtOAc (2 × 60 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Column chromatography (SiO_2, 230–400 mesh, 8% EtOAc in hexane as eluant) gave pure **12b** (5.74 g, 76%, dr > 10:1) as a colorless oil: R_f = 0.68 (20% EtOAc in hexane); $[\alpha]_D^{27}$ = −57.2 (*c* 4.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.19 (m, 5H), 4.66 (m, 1H), 4.20–4.14 (m, 2H), 3.78 (q, J = 6.0 Hz, 1H), 3.68 (q, J = 6.4 Hz, 1H), 3.26 (dd, J = 13.6, 3.2 Hz, 1H), 2.76 (dd, J = 13.6, 9.6, 1H), 1.82–1.78 (m, 1H), 1.44–1.38 (m, 3H), 1.22 (d, J = 6.4 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3, 153.2, 135.5, 129.6, 129.1, 127.5, 68.4, 66.1, 55.4, 38.0, 37.7, 37.1, 29.3, 26.0, 23.7, 18.2, 17.5, −4.3, −4.6 ppm;

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX–XXX

IR(neat): ν_{max} 2930, 1782, 1699 cm^{-1}; HRMS (ESI) m/z calculated for $C_{23}H_{37}NO_4SiNa$ $[M + Na]^+$ 442.2390, found 442.2393.

(2*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylhexan-1-ol (7). To an ice cold solution of compound **12** (5.70 g, 13.58 mmol) in anhydrous THF (25 mL) moist with a catalytic amount of water, $LiBH_4$ (592 mg, 27.17 mmol) was added portionwise under argon. After 30 min of stirring at the same temperature, the reaction was quenched cautiously with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2 × 60 mL). The organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) provided pure compound **7** (3.05 g, 91%) as a colorless oil: R_f = 0.50 (20% EtOAc in hexane); $[\alpha]_D^{27}$ = −2.73 (*c* 8.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.75 (q, *J* = 6.0 Hz, 1H), 3.49−3.45 (m, 1H), 3.41−3.36 (m, 1H), 1.88 (s, 1H), 1.59−1.54 (m, 1H), 1.47−1.38 (m, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 1.10−1.00 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.0, 68.3, 37.0, 35.9, 29.2, 26.1, 26.0, 23.8, 18.3, 16.8, −4.3, −4.6 ppm; IR(neat): ν_{max} 3350, 2930, 1255 cm^{-1}; HRMS (ESI) m/z calculated for $C_{13}H_{30}O_2SiNa$ $[M + Na]^+$ 269.1913, found 269.1914.

(2*S*,3*R*,4*R*,7*R*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-7-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4-dimethyloctan-1-one (14). To a stirred solution of compound **7** (971 mg, 3.95 mmol) in EtOAc (12 mL), IBX (1.77 g, 6.3 mmol) was added, and the mixture was refluxed for 3 h. The reaction mixture was then cooled to room temperature, filtered through Celite, washed with EtOAc (3 × 25 mL), and concentrated in vacuo. The crude aldehyde (R_f = 0.56, 10% EtOAc in hexane) was subjected to flash chromatography and used (896 mg, 93%) for the next reaction without further characterizations.

To a stirred solution of thiazolidinethione **13** (1.07 g, 4.04 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C under argon, freshly distilled $TiCl_4$ (0.47 mL, 4.22 mmol) was added dropwise. The resultant yellow slurry was stirred for 5 min prior to addition of DIPEA (0.77 mL, 4.40 mmol) in a dropwise fashion and stirred for another 15 min at 0 °C. The reaction mixture was then cooled to −78 °C, and the aldehyde from the previous step (896 mg, 3.66 mmol, dissolved in 8 mL of CH_2Cl_2) was cannulated into it. The reaction was continued further at −78 °C for 40 min prior to quenching with saturated NH_4Cl aqueous solution (3 mL). The mixture was warmed to ambient temperature and extracted with EtOAc (3 × 20 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 8% EtOAc in hexane as eluant) afforded aldol adduct **14** (1.38 g, 74%) as a yellow oil: R_f = 0.29 (15% EtOAc in hexane); $[\alpha]_D^{27}$ = −77.9 (*c* 3.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.25 (m, 5H), 5.36−5.32 (m, 1H), 4.94−4.86 (m, 1H), 3.81−3.70 (m, 2H), 3.36 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.25 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.03 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 1.87−1.76 (m, 1H), 1.56−1.40 (m, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 201.4, 179.3, 136.4, 129.4, 128.9, 127.3, 74.2, 69.1, 68.9, 40.3, 36.9, 36.4, 35.5, 31.7, 28.9, 25.9, 25.8, 23.6, 18.1, 15.3, 10.1, −4.5, −4.7 ppm; IR(neat): ν_{max} 3535, 2929, 1678, 1464, 1256 cm^{-1}; HRMS (ESI) m/z calculated for $C_{26}H_{43}NO_3S_2SiNa$ $[M + Na]^+$ 532.2351, found 532.2352.

(2*S*,3*R*,4*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(triisopropylsilyloxy)octanoic Acid (9). To an ice cold solution of compound **14** (1.37 g, 2.69 mmol) in anhydrous CH_2Cl_2 (12 mL) under argon, 2,6-lutidine (0.95 mL, 8.06 mmol) and TIPSOTf (1.1 mL, 4.04 mmol) were added sequentially. The reaction mixture was then warmed to ambient temperature and stirred for 3 h prior to quenching with saturated $NaHCO_3$ solution (3 mL). The resulting mixture was extracted with EtOAc (2 × 20 mL), washed with aqueous $CuSO_4$ solution, water, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 3% EtOAc in hexane as eluant) furnished the corresponding TIPS protected compound (1.73 g, 96%) as a yellow liquid: R_f = 0.57 (10% EtOAc in hexane); The product formation was confirmed by mass spectroscopy [HRMS (ESI) m/z calculated for $C_{35}H_{63}NO_3S_2Si_2Na$ $[M + Na]^+$ 688.3686, found 688.3684] and taken directly into the next reaction without any more characterizations.

To a stirred solution of the above TIPS ether (1.73 g, 2.60 mmol) in THF:H_2O (3:1) (10 mL) at room temperature, $LiOH·H_2O$ (327 mg, 7.77 mmol) and a 30% aqueous solution of H_2O_2 (0.75 mL) were added sequentially. The yellow color of the reaction mixture disappeared gradually. A TLC after 10 min indicated the completion of the reaction. The reaction mixture was then concentrated and directly loaded into a flash column chromatograph (SiO_2, 230−400 mesh, 10% EtOAc in hexane as eluant) to afford pure acid **9** (996 mg, 81%) as a colorless oil: R_f = 0.39 (15% EtOAc in hexane); $[\alpha]_D^{27}$ = +1.4 (*c* 1.86, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.18 (t, *J* = 4.2 Hz, 1H), 3.78−3.73 (m, 1H), 2.65−2.60 (m, 1H), 1.69−1.65 (m, 1H), 1.50−1.33 (m, 4H), 1.21 (d, *J* = 6.9 Hz, 1H), 1.11−1.01 (m, 24H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 181.4, 68.8, 42.0, 40.2, 38.1, 29.3, 26.0, 23.7, 18.4, 18.3, 18.2, 14.9, 13.2, 12.9, −4.4, −4.6 ppm; IR(neat): ν_{max} 2929, 1707, 1215 cm^{-1}; HRMS (ESI) m/z calculated for $C_{25}H_{54}O_4Si_2Na$ $[M + Na]^+$ 497.3458, found 497.3456.

(2*S*,3*R*,4*R*,7*R*)-*tert*-Butyl 7-Hydroxy-2,4-dimethyl-3-(triisopropylsilyloxy)octanoate (5a). To a solution of acid **9** (252 mg, 0.53 mmol) in ^tBuOH (5 mL) at room temperature, DMAP (20 mg, 0.16 mmol) and Boc_2O (0.24 mL, 1.06 mmol) were added. The reaction mixture was stirred for 2 h, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 100−200 mesh, 2% EtOAc in hexane as eluant) to give the corresponding *tert*-butyl ester (228 mg, 81%) as a colorless oil: R_f = 0.61 (5% EtOAc in hexane); $[\alpha]_D^{28}$ = −2.5 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.21−4.19 (m, 1H), 3.78−3.73 (m, 1H), 2.66−2.63 (m, 1H), 1.71−1.67 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.49−1.37 (m, 4H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.11−1.07 (m, 30H), 0.94 (d, *J* = 6.8 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 75.8, 68.7, 42.9, 40.3, 38.1, 29.1, 28.2, 26.1, 23.6, 18.5, 18.4, 14.9, 13.3, 13.2, −4.3, −4.6 ppm; IR(neat): ν_{max} 2928, 1732 cm^{-1}; HRMS (ESI) m/z calculated for $C_{29}H_{62}O_4Si_2Na$ $[M + Na]^+$ 553.4084, found 553.4081.

To an ice cold solution of the above *tert*-butyl ester (222 mg, 0.42 mmol) in anhydrous CH_2Cl_2:MeOH (5:1, 4 mL) under argon, CSA (10 mg, 0.04 mmol) was added, and the mixture was stirred further for 4 h at the same temperature before quenching with Et_3N (0.2 mL). The mixture was concentrated and purified by column chromatography (SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) to provide the required hydroxy ester **5a** (91 mg, 52%) as a colorless oil: R_f = 0.63 (25% EtOAc in hexane); $[\alpha]_D^{28}$ = −5.1 (*c* 1.66, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.13−4.10 (m, 1H), 3.78−3.72 (m, 1H), 2.52−2.43 (m, 1H), 1.71−1.66 (m, 2H), 1.52−1.46 (m, 3H), 1.44 (s, 9H), 1.19−1.16 (m, 6H), 1.08 (s, 21H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 80.3, 76.4, 68.6, 43.0, 40.3, 37.9, 29.8, 29.1, 28.2, 23.6, 18.5, 18.4, 14.9, 14.6, 13.3 ppm; IR(neat): ν_{max} 3437, 2926, 1728 cm^{-1}; HRMS (ESI) m/z calculated for $C_{23}H_{48}O_4SiNa$ $[M + Na]^+$ 439.3220, found 439.3222.

(*S*)-((2*R*,5*R*,6*R*,7*S*)-8-*tert*-Butoxy-5,7-dimethyl-8-oxo-6-(triisopropylsilyloxy)octan-2-yl) 1-((*S*)-2-(*tert*-Butoxycarbonyl)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (4a). To a stirred solution of acid **6a** (175 mg, 0.48 mmol), DMAP (128 mg, 1.05 mmol), and EDCI (82 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon, alcohol **5a** (89 mg, 0.21 mmol, dissolved in 2 mL of CH_2Cl_2) was cannulated. The reaction was continued at room temperature for 12 h prior to quenching with a saturated solution of NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 230−400 mesh, 20% EtOAc in hexane as eluant) gave the required ester **4a** (127 mg, 78% with respect to **5a**) as a colorless oil: R_f = 0.53 (25% EtOAc in hexane); $[\alpha]_D^{28}$ = −12.7 (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.22 (m, 5H), 5.27 (d, *J* = 9.0 Hz, 1H), 4.95−4.86 (m, 1H), 4.67−4.60 (m, 1H), 4.49−4.51 (m, 1H), 4.13−4.06 (m, 1H), 3.67−3.62 (m, 1H), 3.34−3.28 (m, 1H), 3.12−3.05 (m, 1H), 2.89−2.80 (m, 1H), 2.51−2.40 (m,

dx.doi.org/10.1021/jo5019798 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

1H), 2.19−2.12 (m, 1H), 1.94−1.93 (m, 3H), 1.62−1.59 (m, 5H, merged with water peak), 1.43 (s, 9H, minor rotamer at 1.41), 1.36 (s, 9H), 1.20 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.08 (s, 21H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, with observed rotamer peaks are given in parentheses) δ 175.4, 171.4, 170.7, 155.3, 136.7, 129.8(129.6), 128.5(128.7), 126.9, 80.2, 79.7, 76.4, 72.1(73.0), 59.4, 53.3, 46.9, 43.3, 40.1(39.9), 39.3, 34.1, 29.2, 28.4, 28.2, 28.2, 24.9, 19.6, 18.5, 18.4, 14.8, 14.4, 13.3, 13.2 ppm; IR(neat): ν_{max} 2930, 1726, 1647 cm^{-1}; HRMS (ESI) m/z calculated for $C_{42}H_{72}N_2O_8SiNa$ [M + Na]$^+$ 783.4956, found 783.4958.

Attempted Synthesis for Compound 15. To a cooled solution of ester **4a** (120 mg, 0.16 mmol) in CH_2Cl_2 (3 mL), TFA (1.2 mL) was added. The reaction was warmed to room temperature in 30 min and continued further for 3.5 h. The solvent was evaporated under reduced pressure, and the residue was azeotroped with toluene (3 × 5 mL) to get the respective globally deprotected precursor for macrolactamization {confirmed by mass spectroscopy, HRMS (ESI) m/z calculated for $C_{24}H_{37}N_2O_6$ [M + H]$^+$ 449.2652, found 449.2654}. Attempted cyclization using EDCI/HOBt, HATU/DIPEA, PyBOP/DIPEA conditions did not produce the required compound **15** at all.

(2*S*,3*R*,4*R*,7*R*)-Allyl 7-Hydroxy-2,4-dimethyl-3-(triisopropylsilyloxy)octanoate (5b). To a stirred solution of acid **9** (375 mg, 0.79 mmol) in DMF (5 mL) at 0 °C under argon, allyl bromide (0.14 mL, 1.58 mmol) and K_2CO_3 (208 mg, 1.50 mmol) were added. The reaction mixture was warmed slowly to ambient temperature and stirred further for 14 h. The reaction was quenched with water (5 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water and brine and dried ($NaSO_4$). The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO_2, 100−200 mesh, 2% EtOAc in hexane as eluant) to provide the corresponding allyl ester (386 mg, 95%) as a colorless oil: R_f = 0.68 (5% EtOAc in hexane); $[\alpha]_D^{28}$ = −2.8 (c 4.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97−5.84 (m,1H), 5.34−5.19 (m, 2H), 4.56−4.52 (m, 2H), 4.19−4.16 (m, 1H), 3.78−3.71 (m, 1H), 2.65−2.57 (m, 1H), 1.66 (m, 1H), 1.49−1.33 (m, 2H), 1.21 (d, J = 7.0 Hz, 3H), 1.11−1.01 (m, 24H), 0.93 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 175.7, 132.4, 118.3, 68.9, 65.2, 41.9, 40.4, 38.1, 29.2, 26.1, 23.7, 18.4, 18.4, 18.3, 14.9, 13.4, 13.3, 13.2, −4.3, −4.6 ppm; IR(neat): ν_{max} 2945, 1738 cm^{-1}; HRMS (ESI) m/z calculated for $C_{28}H_{58}O_4Si_2Na$ [M + Na]$^+$ 537.3771, found 537.3772.

To an ice cold solution of the above ester (380 mg, 0.74 mmol) in anhydrous CH_2Cl_2:MeOH (5:1, 4 mL) under argon, CSA (17 mg, 0.074 mmol) was added at once. The reaction mixture was stirred for 3 h at the same temperature before quenching with Et_3N (0.2 mL). The resultant mixture was concentrated and purified by column chromatography (SiO_2, 100−200 mesh, 20% EtOAc in hexane as eluant) to provide hydroxy ester **5b** (274 mg, 93%) as a colorless oil: R_f = 0.66 (25% EtOAc in hexane); $[\alpha]_D^{27}$ = −5.8 (c 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98−5.85 (m, 1H), 5.32 (dd, J = 17.2, 1.5 Hz, 1H), 5.23 (dd, J = 10.4, 1.5 Hz, 1H), 4.56−4.54 (m, 2H), 4.19−4.16 (m, 1H), 3.77−3.70 (m, 1H), 2.67−2.58 (m, 1H), 1.75−1.67 (m, 1H, partially merged with water peak), 1.53−1.37 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H), 1.07 (s, 21H), 0.95 (d, J = 6.9 Hz, 3H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 132.2, 118.4, 76.3, 68.5, 65.2, 41.9, 40.1, 37.7, 29.3, 23.5, 18.3, 18.3, 14.8, 13.5, 13.2 ppm; IR(neat): ν_{max} 3425, 2926, 1736, 1462 cm^{-1}; HRMS (ESI) m/z calculated for $C_{22}H_{44}O_4SiNa$ [M + Na]$^+$ 423.2906, found 423.2908.

(*S*)-((2*R*,5*R*,6*R*,7*S*)-8-(Allyloxy)-5,7-dimethyl-8-oxo-6-(triisopropylsilyloxy)octan-2-yl) 1-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (4b). Following the same procedure as described in the preparation of ester **4a**, the acid **6b** (751 mg, 1.55 mmol) and alcohol **5b** (270 mg, 0.67 mmol) were coupled in anhydrous CH_2Cl_2 (8 mL) using DMAP (409 mg, 3.35 mmol) and EDCI (257 mg, 1.34 mmol) in 12 h to provide ester **4b** (427 mg, 73% with respect to compound **5b**, purification SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) as a colorless oil: R_f = 0.42 (25% EtOAC in hexane); $[\alpha]_D^{29}$ = −23.4 (c 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76−7.73 (m, 2H), 7.61−7.51 (m, 2H), 7.40−7.36 (m, 2H), 7.31−7.23 (m, 7H), 5.89−5.87 (m, 1H), 5.62 (d, J = 8.7 Hz, 1H), 5.30 (dd, J = 17.3, 1.5 Hz, 1H), 5.21 (dd, J = 10.4, 1.5 Hz, 1H), 4.94−4.92 (m, 1H), 4.73−4.71 (m, 1H), 4.54 (dd, J = 5.7, 0.8 Hz, 1H), 4.48−4.46 (m, 2H), 4.33−4.29 (m, 1H), 4.25−4.15 (m, 3H), 3.62 (m, 1H), 3.31−3.28 (m, 1H), 3.17−3.10 (m, 1H), 2.97−2.92 (m, 1H), 2.63−2.61 (m, 1H), 2.18 (m, 1H), 1.94 (m, 3H), 1.71−1.61 (m, 3H, merged with water peak), 1.49−1.41 (m, 2H), 1.23−1.21 (m, 6H), 1.07 (s, 18H), 1.04 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, with observed rotamer peaks in parentheses) δ 175.6, 171.4, 170.3, 155.9, 143.9, 141.4, 136.3, 132.3(132.3), 129.8(129.6), 128.6(128.7), 127.8, 127.2, 127.0, 125.4, 125.3, 120.1, 118.4, 76.5, 72.1(73.1), 67.2, 65.3, 59.4, 53.8, 47.2, 47.1, 42.1, 39.9, 39.1, 34.1, 29.2, 28.5, 24.9, 19.6(19.4), 18.4, 18.4, 14.8, 13.4, 13.3 ppm; IR(neat): ν_{max} 2943, 1732, 1645, 1450 cm^{-1}; HRMS (ESI) m/z calculated for $C_{51}H_{70}N_2O_8SiNa$ [M + Na]$^+$ 889.4799, found 889.4777.

Macrocycle 16 through Lactamization. To a stirred solution of ester **4b** (419 mg, 0.48 mmol) and morpholine (0.08 mL, 0.96 mmol) in dry THF (3 mL) under argon, $Pd(PPh_3)_4$ (55 mg, 0.05 mmol) was added at ambient temperature. After being stirred at the same temperature for 30 min, the reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 230−400 mesh, 40% EtOAc in hexane as eluant) to give the corresponding *N*-Fmoc protected acid (352 mg, 88%) as a thick colorless liquid. The product formation was confirmed by mass spectroscopy {HRMS (ESI) m/z calculated for $C_{48}H_{66}N_2O_8SiNa$ [M + Na]$^+$ 849.4486, found 849.4484}.

HATU/DIPEA Mediated Cyclization. To a solution of the above *N*-Fmoc protected acid (100 mg, 0.12 mmol) in dry CH_3CN (2 mL) under argon, Et_2NH (1.0 mL) was added. After being stirred at room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was azeotroped with dry toluene (2 × 2 mL) and dissolved in anhydrous CH_2Cl_2 (120 mL). DIPEA (0.2 mL, 1.08 mmol) and HATU (136 mg, 0.36 mmol) were added sequentially to the reaction mixture under an argon atmosphere. After being stirred for 18 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) to give TIPS protected cyclic amide **16** (16 mg, 22%) as a colorless oil: R_f = 0.58 (25% EtOAc in hexane); $[\alpha]_D^{28}$ = −40.7 (c 0.44 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.20 (m, 5H), 6.55 (d, J = 6.3 Hz, 1H), 5.16 (m, 1H), 4.72 (m, 1H), 3.91 (d, J = 4.9 Hz, 1H), 3.52 (d, J = 7.2 Hz, 1H), 3.41−3.35 (m, 2H), 3.25 (dd, J = 12.3, 4.5 Hz, 1H), 2.83 (dd, J = 12.3, 11.3 Hz, 1H), 2.46−2.42 (m, 1H), 2.04−2.00 (m, 1H), 1.80−1.63 (m, 4H, merged with water peak), 1.43−1.37 (m, 1H), 1.35−1.29 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.10 (s, 18H), 1.02 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.92−0.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 170.8, 170.3, 137.0, 129.6, 128.7, 127.1, 74.1, 58.8, 53.4, 45.6, 41.3, 35.4, 28.6, 22.2, 21.0, 18.5, 13.1 ppm; IR(neat): ν_{max} 2930, 1736, 1639, 1624 cm^{-1}; HRMS (ESI) m/z calculated for $C_{33}H_{55}N_2O_5Si$ [M + H]$^+$ 587.3880, found 587.3878.

PyBOP/DIPEA Mediated Cyclization. The above *N*-Fmoc protected acid (93 mg, 0.11 mmol) was first treated with Et_2NH according to the aforementioned procedure to yield the corresponding cycloamidation precursor, which was dissolved in dry CH_2Cl_2 (110 mL) in an argon atmosphere and cooled to 0 °C prior to sequential addition of DIPEA (0.11 mL, 0.66 mmol) and PyBOP (114 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 20 h and finally concentrated in vacuo. Purification by chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) afforded **16** (10 mg, 14%) as a colorless liquid. The spectroscopic data were found to be identical as before.

(*S*)-Methyl 1-((*S*)-2-((2*S*,3*R*,4*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(triisopropylsilyloxy)octanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (8). Following the same procedure as described in the attempted synthesis of compound **15**, a solution (6 mL, CH_2Cl_2) of dipeptide **6c** (335 mg, 0.89 mmol) was treated with TFA (1.8 mL) to get the corresponding Boc deprotected compound. The crude compound was subsequently dissolved in anhydrous DMF (6 mL) under argon and cooled to 0 °C.

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

DIPEA (0.26 mL, 1.48 mmol) was added, and the mixture was stirred for 15 min at 0 °C. Acid **9** (352 mg, 0.74 mmol, dissolved in anhydrous 5 mL DMF) was cannulated, and HOBt (120 mg, 0.89 mmol) was then added. Stirring was continued further at the same temperature for 15 min before addition of EDCI (171 mg, 0.89 mmol). The reaction was warmed slowly to room temperature and stirred further for 12.5 h. DMF was removed under reduced pressure, and the resultant residue was extracted with EtOAc (2 × 20 mL). The organic layers were washed with saturated NH_4Cl solution, water, and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 230−400 mesh, 30% EtOAC in hexane as eluant) gave the required amide **8** (478 mg, 88% with respect to compound **9**) as a thick colorless liquid: R_f = 0.28 (15% EtOAc in hexane); $[\alpha]_D^{25}$ = −19.1 (*c* 1.41 $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.25 (m, 3H), 7.22−7.21 (m, 2H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.93−4.92 (m, 1H), 4.45−4.42 (m, 1H), 4.05−4.03 (m, 1H), 3.73 (s, 3H), 3.70−3.69 (m, 1H), 3.59−357 (m, 1H), 3.12−3.07 (m, 2H), 2.94 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.37−2.34 (m, 1H), 2.14−2.10 (m, 1H), 1.93−1.84 (m, 3H), 1.64−1.58 (m, 1H), 1.43−1.32 (m, 4H), 1.11−1.10 (m, 3H, additional rotamer peak at 1.08), 1.06−1.04 (m, 21H), 1.00−0.96 (m, 3H), 0.88−0.86 (m, 12H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz, with observed rotamer peaks in parentheses) δ 174.8, 172.4, 170.3, 136.4, 129.9(129.6), 128.5(128.7), 126.9, 68.8, 59.0, 52.3, 51.7, 46.9, 43.9, 40.0, 38.9, 38.2, 29.2, 28.9, 26.1, 25.0, 23.4, 18.5(18.5),18.4(18.3), 14.9(14.9), 13.3(13.4), −4.4, −4.5 ppm; IR(neat): ν_{max} 2955, 1749, 1645, 1636 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{40}H_{72}N_2O_6Si_2Na$ $[M + Na]^+$ 755.4827, found 755.4824.

(*S*)-Methyl 1-((*S*)-2-((2*S*,3*R*,4*R*,7*R*)-7-Hydroxy-2,4-dimethyl-3-(triisopropylsilyloxy)octanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (17). To an ice cold solution of amide **8** (453 mg, 0.62 mmol) in CH_2Cl_2:MeOH (4:1, 5 mL) under argon, CSA (14 mg, 0.06 mmol) was added at once. The reaction mixture was stirred for 3 h at the same temperature before quenching it with Et_3N (0.3 mL). The mixture was concentrated in vacuo and purified by column chromatography (SiO_2, 100−200 mesh, 40% EtOAc in hexane as eluant) to provide the required hydroxy amide **17** (317 mg, 83%) as a thick colorless liquid: R_f = 0.21 (40% EtOAc in hexane); $[\alpha]_D^{27}$ = −23.7 (*c* 3.21 $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.20 (m, 5H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.96−4.91 (m, 1H), 4.47−4.44 (m, 1H), 3.98−3.97 (m, 1H), 3.77−3.74 (m, 1H), 3.73 (s, 3H), 3.71 (m, 1H), 3.21−3.18 (m, 1H), 3.11 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.92−2.88 (m, 1H), 2.41 (t, *J* = 7.0 Hz, 1H), 2.18−2.15 (m, 1H), 1.93−1.90 (m, 3H), 1.61−1.48 (m, 4H), 1.26−1.24 (m, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.10 (m, 3H, additional rotamer peak at 1.13), 1.07 (s, 18H), 1.00 (bs, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, with observed rotamer peaks in parentheses) δ 175.3, 172.3, 170.8, 136.3, 129.6(129.5), 128.5(128.7), 127.0, 68.6, 59.2, 52.3(53.1), 51.6(51.8), 47.1, 44.2, 39.6, 38.4(38.5), 38.1, 30.8, 29.2, 28.5, 25.0, 24.1, 18.5, 18.4, 18.1, 16.2, 15.4, 13.4 ppm; IR(neat): ν_{max} 3312, 2961, 1747, 1634, 1454 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{34}H_{59}N_2O_6Si$ $[M + H]^+$ 619.4142, found 619.4135.

Macrocycle 16 through Macrolactonization. Following the same procedure as that adopted in the hydrolysis of ester **10**, we hydolyzed compound **17** (312 mg, 0.50 mmol) in THF:H_2O (3:1, 5 mL) using LiOH·H_2O (63 mg, 1.5 mmol) in 1 h at room temperature to get the corresponding seco acid {305 mg, purification SiO_2, 60−120 mesh, EtOAc as eluant, viscous colorless oil, R_f = 0.29 (EtOAc)} in quantitative yield, which was confirmed by mass spectroscopy {HRMS (ESI) *m*/*z* calculated for $C_{33}H_{56}N_2O_6SiNa$ $[M + Na]^+$ 627.3805, found 627.3804} and taken into the next reaction without any more characterizations.

Yamaguchi Protocol. 2,4,6-Trichlorobenzoyl chloride (0.11 mL, 0.7 mmol) was added to a stirred solution of the above seco acid (85 mg, 0.14 mmol) and Et_3N (0.2 mL, 1.4 mmol) in dry THF (2 mL) at room temperature under argon. After being stirred for 3 h, the resultant Et_3N·HCl salt was filtered off quickly and the filtrate was concentrated under reduced pressure. The mixed anhydride thus obtained was dissolved in dry toluene (15 mL) and added slowly via syringe pump over 8 h to a stirred solution of DMAP (171 mg, 1.4 mmol) in dry toluene (100 mL) at 80 °C. After being stirred for 2 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) solution. The toluene layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) afforded pure macrocycle **16** (34 mg, 41%) as a colorless liquid. The R_f value and other spectroscopic properties were found to be identical with those of the macrocycle **16** obtained earlier via macrolactamization.

Shiina Protocol. To a stirred solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 54 mg, 0.16 mmol) and DMAP (31 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (50 mL) under argon, a solution of the above seco acid (63 mg, 0.10 mmol) dissolved in anhydrous CH_2Cl_2 (30 mL) was added dropwise at room temperature. The reaction was continued for 12 h at the same temperature prior to quenching with saturated $NaHCO_3$ (10 mL) solution. The mixture was taken in a separating funnel and washed thoroughly with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) afforded pure macrocycle **16** (35 mg, 57%) as a colorless liquid. Spectroscopic data were found to be the same as before.

Kita Protocol. Ethoxyacetylene (40% in hexane, 0.02 mL, 0.15 mmol) was added to a solution of the above seco acid (62 mg, 0.10 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (1.2 mg, 2 μmol) in dry toluene (5 mL) at 0 °C under argon. The reaction mixture was allowed to come to room temperature and stirred further for 30 min. The reaction mixture was then quickly filtered through a pad of silica gel. The pad was washed with Et_2O (3 × 15 mL), and the filtrate was concentrated under reduced pressure to get the corresponding crude ethoxyvinyl ester, which was next dissolved in dry toluene (30 mL) and added slowly to a solution of CSA (0.2 mg, 1 μmol) in dry toluene (50 mL) under argon. After heating at 50 °C for 2 h, the reaction mixture was filtered through Celite and concentrated. Purification by column chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluant) afforded pure macrocycle **16** (22 mg, 37%) as a colorless liquid. Spectroscopic data were found to be identical as before.

Calcaripeptide C (3). To an ice cold solution of macrocycle **16** (31 mg, 0.05 mmol) in dry THF (2 mL) under argon, TBAF (1 M solution in THF, 0.07 mL, 0.07 mmol) was added. The reaction mixture was stirred for 2 h at the same temperature prior to quenching with saturated NH_4Cl solution (1 mL). The mixture was extracted with EtOAC (2 × 10 mL), washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 40% EtOAc in hexane as eluant) afforded the corresponding TIPS deprotected compound (20 mg, 88%) as a colorless oil. R_f = 0.17 (40% EtOAc in hexane); $[\alpha]_D^{29}$ = −56.3 (*c* 0.69 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.20 (m, 5H), 6.71 (d, *J* = 7.2 Hz, 1H), 5.23−5.16 (m, 1H), 4.78−4.71 (m, 1H), 3.73 (d, *J* = 5.4 Hz, 1H), 3.66 (d, *J* = 7.2 Hz, 1H), 3.46−3.36 (m, 2H), 3.19 (dd, *J* = 12.3, 4.5 Hz, 1H), 2.88 (dd, *J* = 12.3, 10.8 Hz, 1H), 2.49−2.45 (m, 1H), 1.99−1.92 (m, 1H), 1.85−1.66 (m, 5H, merged with water peak), 1.52−1.43 (m, 1H), 1.35−1.26 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.94−0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ173.3, 170.9, 170.3, 136.9, 129.6, 128.7, 127.1, 74.4, 59.0, 53.2, 45.7, 44.1, 41.1, 35.6, 34.9, 28.7, 28.6, 22.1, 20.9, 18.5, 15.3 ppm; IR(neat): ν_{max} 3418, 3296, 2932, 1732, 1622, 1454 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{24}H_{35}N_2O_5$ $[M + H]^+$ 431.2546, found 431.2544.

To an ice cold solution of the above TIPS deprotected compound (18 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) under argon, DMP (28 mg, 0.07 mmol) and $NaHCO_3$ (1.5 mg, 0.04 mmol) were added sequentially. The reaction mixture was warmed slowly to room temperature and stirred further for 2.5 h prior to quenching with a mixture of a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 1 mL). The mixture was stirred vigorously for 2 h and extracted with Et_2O (3 × 10 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 30% EtOAc in hexane eluant) afforded pure

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

calcaripeptide C (**3**) (17 mg, 93%) as a colorless liquid: R_f = 0.34 (40% EtOAc in hexane); $[\alpha]_D^{26}$ = −74.6 (*c* 0.13 MeOH); ^{1}H NMR (Acetone-d_6, 400 MHz) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.32−7.28 (m, 2H), 7.25−7.22 (m, 3H), 4.97 (m, 1H), 4.83 (m, 1H), 3.90 (d, *J* = 8.0 Hz, 1H), 3.65 (q, *J* = 6.8 Hz, 1H), 3.39−3.35 (m, 2H), 3.06 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.92 (dd, *J* = 12.4, 10.0 Hz, 1H), 2.85 (m, 1H), 1.89−1.85 (m, 2H), 1.71 (m, 1H), 1.67 (m, 1H), 1.52 (m, 2H), 1.48 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.07 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 209.3, 172.3, 170.9, 169.6, 138.3, 130.2, 129.2, 127.5, 74.0, 59.8, 54.3, 52.4, 46.4, 44.1, 40.7, 35.4, 31.9, 30.3, 22.4, 21.0, 15.6, 14.5 ppm; IR(neat): ν_{max} 3292, 2930, 1738, 1639, 1626 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{24}H_{32}N_2O_5Na$ [M + Na]$^+$ 451.2209, found 451.2206.

(4*R*,7*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyloct-2-en-1-ol (18). Alcohol **7** (1.02g, 4.14 mmol) was oxidized by IBX (1.85g, 6.62 mmol) in distilled EtOAc (15 mL) in 3 h according to the procedure described in preparation of aldol adduct **14** to provide the corresponding aldehyde (941 mg, 93%) as a pale yellow liquid. The crude aldehyde was taken for the next reaction without further characterizations.

To a solution of the above aldehyde (941 mg, 3.85 mmol) in anhydrous toluene (15 mL) at 80 °C under argon, $Ph_3P{=}CH(Me)CO_2Et$ (2.79 g, 7.70 mmol) was added at once. The reaction was continued for 6 h at the same temperature and cooled to room temperature prior to evaporating the toluene under reduced pressure. The residue obtained was purified by flash chromatography (SiO_2, 230−400 mesh, 2% EtOAc in hexane as eluant) to afford the corresponding α,β-unsaturated ester (1.09 g, 86% over 2 steps) as a colorless oil: R_f = 0.55 (5% EtOAc in hexane); $[\alpha]_D^{28}$ = −21.6 (*c* 6.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.50 (dd, *J* = 9.9 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.73−3.72 (m, 1H), 2.43 (m, 1H), 1.80 (*d*, *J* = 1.5 Hz, 3H), 1.37−1.34 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 5.7 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H, 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 147.9, 126.5, 68.5, 60.5, 37.4, 33.3, 32.8, 25.9, 23.9, 20.1, 18.2, 14.4, 12.6, −4.3, −4.7 ppm; IR(neat): ν_{max} 2932, 1711, 1254 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{18}H_{36}O_3SiNa$ [M + Na]$^+$ 351.2331, found 351.2335.

To a cold solution (−78 °C) of the above ester in dry CH_2Cl_2 (15 mL) under argon, DIBAL-H (1.0 M in toluene, 9.90 mL, 9.90 mmol) was added slowly, and the reaction was continued for 30 min at the same temperature before quenching with MeOH (5 mL). A saturated solution of sodium potassium tartrate (8 mL) was then added, and the mixture was warmed to room temperature. After 2 h of vigorous stirring, the resultant mixture was extracted with EtOAc (2 × 30 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 20% EtOAc in hexane as eluant) afforded pure alcohol **18** (860 mg, 91%) as a colorless liquid: R_f = 0.17 (10% EtOAc in hexane); $[\alpha]_D^{28}$ = −5.4 (*c* 3.82 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (dd, *J* = 9.4, 1.2 Hz, 1H), 3.98 (s, 2H), 3.76−3.71 (m, 1H), 2.35−2.31 (m, 1H), 1.65 (d, *J* = 1.2 Hz, 3H), 1.42−1.24 (m, 4H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ133.5, 132.9, 69.2, 68.8, 37.6, 33.6, 32.2, 26.1, 23.9, 21.2, 18.3, 14.0, −4.2, −4.6 ppm; IR(neat): ν_{max} 3340, 2930, 1462, 1256 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{16}H_{34}O_2SiNa$ [M + Na]$^+$ 309.2226, found 309.2224.

(2*S*,3*S*,6*R*,9*R*,*E*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4,6-trimethyldec-4-en-1-one (19). Following the same procedure as described in the preparation of aldol adduct **14**, alcohol **18** (320 mg, 1.12 mmol) was first oxidized by IBX (501 mg, 1.79 mmol) in distilled EtOAc (8 mL) in 2.5 h to provide the corresponding aldehyde [R_f = 0.49 (10% EtOAc in hexane)] in quantitative yield, which was subjected to aldol reaction using thiazolidinethione **13** (327 mg, 1.23 mmol), $TiCl_4$ (0.14 mL, 1.29 mmol), and DIPEA (0.23 mL, 1.34 mmol) in dry CH_2Cl_2 (10 mL) to achieve compound **19** (497 mg, 81%, *dr* > 18:1, purification SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) in 1 h as a yellow liquid: R_f = 0.41 (15% EtOAc in hexane); $[\alpha]_D^{26}$ = −108.9 (*c* 1.59 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.33 (m, 2H), 7.29−7.26 (m, 3H), 5.39−5.36 (m, 2H), 4.95−4.91 (m, 1H), 4.48 (s, 1H), 3.75−3.71 (m, 1H), 3.39−3.35 (m, 1H), 3.26 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.04 (dd, *J* = 13.0, 10.3 Hz, 1H), 2.89 (d, *J* = 12.0 Hz, 1H), 2.39−2.35 (m, 1H), 1.60 (s, 3H), 1.42−1.39 (m, 1H), 1.38−1.28 (m, 4H), 1.11−1.08 (m, 6H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6, 178.9, 136.6, 132.8, 131.7, 129.6, 129.1, 127.4, 74.1, 69.1, 68.8, 41.0, 37.9, 37.2, 33.8, 32.3, 31.9, 26.1, 24.0, 21.2, 18.3, 14.1, 10.7, −4.2, −4.6 ppm; IR(neat): ν_{max} 3495, 2928, 1691, 1676, 1256 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{29}H_{47}NO_3S_2SiNa$ [M + Na]$^+$ 572.2664, found 572.2667.

(2*S*,3*S*,6*R*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyl-3-(triisopropylsilyloxy)dec-4-enoic Acid (20). Following the same procedure as described in the preparation of acid **9**, aldol adduct **19** (491 mg, 0.89 mmol) was first converted to its TIPS ether {593 mg, 94%, as a yellow liquid, purification SiO_2, 100−200 mesh, 2% EtOAc in hexane as eluant}: R_f = 0.61 (10% EtOAc in hexane), HRMS (ESI) *m*/*z* calculated for $C_{38}H_{67}NO_3S_2Si_2Na$ [M + Na]$^+$ 728.3999, found 728.3997} using TIPSOTf (0.36 mL, 1.34 mmol) and 2, 6-lutidine (0.31 mL, 2.67 mmol) in dry CH_2Cl_2 (6 mL), which next was treated with $LiOH{\cdot}H_2O$ (106 mg, 2.52 mmol) and 30% aqueous H_2O_2 (0.3 mL) in a THF:H_2O (3:1, 5 mL) solvent system to provide acid **20** as a colorless oil (359 mg, 83%, purification SiO_2, 100−200 mesh, 8% EtOAc in hexane as eluant): R_f = 0.44 (10% EtOAc in hexane); $[\alpha]_D^{29}$ = −2.9 (*c* 3.88 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.17 (d, *J* = 9.3 Hz, 1H), 4.34 (d, *J* = 6.6 Hz, 1H), 3.76−3.70 (m, 1H), 2.70−2.61 (m, 1H), 2.36−2.26 (m, 1H), 1.60 (s, 3H), 1.36−1.26 (m, 4H), 1.14−1.06 (m, 27H), 0.86 (m, 12H), 0.04 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.9, 135.8, 132.9, 80.5, 68.6, 44.9, 37.7, 33.4, 32.2, 26.0, 24.1, 20.7, 18.3, 18.2, 12.9, 12.7, 11.8, −4.2, −4.6 ppm; IR(neat): ν_{max} 2960, 1709, 1466 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{28}H_{58}O_4Si_2Na$ [M + Na]$^+$ 537.3771, found 537.3774.

(*S*)-Methyl 1-((*S*)-2-((2*S*,3*S*,6*R*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyl-3-(triisopropylsilyloxy)dec-4-enamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (26). The same experimental procedure as described in the preparation of compound **8**. Dipeptide **6c** (186 mg, 0.49 mmol) in dry CH_2Cl_2 (3 mL) was first treated with 30% TFA (0.9 mL) to generate the corresponding Boc deprotected TFA salt, which was subsequently reacted with acid **20** (212 mg, 0.41 mmol) in the presence of DIPEA (0.14 mL, 0.82 mmol), EDCI (95 mg, 0.49 mmol), and HOBt (67 mg, 0.49 mmol) in dry DMF (5 mL) to yield amide **26** (274 mg, 86% from **20**, purification SiO_2, 100−200 mesh, 20% EtOAc in hexane as eluant) as a thick colorless liquid: R_f = 0.62 (25% EtOAc in hexane); $[\alpha]_D^{29}$ = −23.5 (*c* 2.81 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.19 (m, 5H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.04 (d, *J* = 9.6 Hz, 1H), 4.92−4.84 (m, 1H), 4.41 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.21 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 3H), 3.72−3.67 (m, 1H), 3.58−3.51 (m, 1H), 3.12−3.03 (m, 2H), 2.93 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.40−2.35 (m, 1H), 2.22−2.20 (m, 1H), 2.10−2.04 (m, 1H), 1.94−1.81 (m, 4H), 1.52 (d, *J* = 0.9 Hz, 3H), 1.37−1.23 (m, 3H), 1.11−1.08 (m, 6H), 1.06 (s, 21H), 0.87 (s, 9H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.02 (d, *J* = 2.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 172.3, 170.2, 136.4, 134.8, 133.7, 129.9, 128.4, 126.9, 80.9, 68.6, 58.9, 52.3, 51.7, 46.9, 46.7, 39.2, 37.6, 33.3, 31.9, 29.2, 26.0, 24.9, 24.1, 20.5, 18.4, 18.3, 18.2, 14.1, 12.7, 11.3, −4.2, −4.6 ppm; IR(neat): ν_{max} 3329, 2949, 1755, 1641, 1630, 1443 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{43}H_{77}N_2O_6Si_2$ [M + H]$^+$ 773.5320, found 773.5314.

(*S*)-Methyl 1-((*S*)-2-((2*S*,3*S*,6*R*,9*R*,*E*)-9-Hydroxy-2,4,6-trimethyl-3-(triisopropylsilyloxy)dec-4-enamido)-3-phenylpropanoyl)-pyrrolidine-2-carboxylate (27). The same experimental procedure as described in the preparation of compound **17**. Compound **26** (269 mg, 0.35 mmol) was treated with CSA (8 mg, 0.04 mmol) in CH_2Cl_2:MeOH (4:1, 4 mL) under argon to yield compound **27** (193 mg, 84%, purification SiO_2, 100−200 mesh, 40% EtOAc in hexane as eluant) as a thick colorless liquid: R_f = 0.36 (50% EtOAc in hexane); $[\alpha]_D^{29}$ = −25.1 (*c* 2.59 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28−7.20 (m, 5H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.08 (d, *J* = 9.5 Hz, 1H), 4.90−4.88 (m, 1H), 4.42−4.40 (m, 1H), 4.18 (d, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 3.70−3.68 (m, 1H), 3.60−3.58 (m, 1H), 3.10−3.05 (m, 2H), 2.92 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.38−2.37 (m, 1H), 2.27−2.24 (m, 1H), 2.11−2.07 (m, 1H), 1.92−1.82 (m, 4H), 1.52 (s, 3H), 1.41−1.31

dx.doi.org/10.1021/jo5019798 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

(m, 1H), 1.29−1.23 (m, 2H), 1.14 (d, J = 6.0 Hz, 3H), 1.11−1.07 (m, 6.0 Hz), 1.04 (s, 18H), 0.77 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, observed rotamer peaks are given in parentheses) δ 173.5, 172.3, 170.3, 136.4, 134.4, 134.3, 129.9(129.6), 128.4(128.7), 126.9, 80.5, 68.2, 58.9, 52.3, 51.7, 47.3, 46.9, 39.1, 37.3, 33.3, 32.1, 29.2, 24.9, 23.7, 20.6, 18.4, 18.3, 14.3, 12.7, 12.4 ppm; IR(neat): ν_{max} 3327, 2945, 1749, 1634, 1643, 1445 cm^{-1}; HRMS (ESI) m/z calculated for $C_{37}H_{62}N_2O_6SiNa$ $[M + Na]^+$ 681.4275, found 681.4278.

Macrocycle 28. The same experimental procedure as that adopted in the synthesis of macrocycle **16** using the Shiina macrolactonization protocol. Compound **27** (87 mg, 0.13 mmol) was treated with LiOH·H_2O (17 mg, 0.40 mmol) in THF:H_2O (3:1, 4 mL) in 1 h to provide the corresponding seco acid [85 mg, purification SiO_2, 60−120 mesh, EtOAc as eluant, viscous colorless oil, R_f = 0.32 (EtOAc)] in quantitative yield, which was confirmed by mass spectroscopy {HRMS (ESI) m/z calculated for $C_{36}H_{60}N_2O_6SiNa$ $[M + Na]^+$ 667.4118, found 667.4116} and taken into the next reaction without any more characterizations.

The seco acid (85 mg, 0.13 mmol) was then treated in the presence of MNBA (72 mg, 0.21 mmol) and DMAP (40 mg, 0.33 mmol) in dry CH_2Cl_2 (100 mL) to yield macro cycle **28** (53 mg, 64%, purification SiO_2, 100−200 mesh, 20% EtOAc in hexane as eluant) as a colorless oil: R_f = 0.43 (20% EtOAc in hexane); $[\alpha]_D^{29}$ = −58.9 (c 1.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, J = 8.0 Hz, 1H), 7.29−7.26 (m, 3H), 7.24−7.23 (m, 2H), 5.45−5.43 (m, 2H), 4.64−4.62 (m, 1H), 4.26 (d, J = 3.5 Hz, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.45−3.41 (m, 1H), 3.37−3.34 (m, 1H), 3.06 (dd, J = 12.8, 5.0 Hz, 1H), 2.92−2.90 (m, 1H), 2.82−2.78 (m, 1H), 2.21−2.18 (m, 1H), 2.06−2.03 (m, 1H), 1.73−1.69 (m, 2H), 1.62 (s, 3H), 1.50−1.43 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.5 Hz, 3H), 1.15−1.13 (m, 18H), 0.90 (d, J = 6.0 Hz, 3H), 0.84−0.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.7, 170.4, 137.1, 133.6, 132.6, 129.7, 128.7, 127.1, 78.9, 73.3, 59.2, 51.9, 47.9, 45.5, 42.3, 34.4, 34.1, 32.6, 27.9, 22.1, 21.6, 20.6, 18.2, 18.2,18.1, 14.7, 12.4 ppm; IR(neat): ν_{max} 2926, 1732, 1645, 1445 cm^{-1}; HRMS (ESI) m/z calculated for $C_{36}H_{59}N_2O_5Si$ $[M + H]^+$ 627.4193, found 627.4186.

Calcaripeptide A (1). Same experimental protocol as that adopted in the synthesis of Calcaripeptide C (**3**). Macrocycle **28** (49 mg, 0.08 mmol) was first subjected to TIPS ether cleavage using TBAF (1 M solution in THF, 0.11 mL, 0.11 mmol) to provide the corresponding desilylated product (34 mg, 92%, purification SiO_2, 100−200 mesh, 45% EtOAc in hexane as eluant) as a white solid, which, on crystallization from EtOAc/hexane, provided needle-shaped crystals, mp 141−142 °C: R_f = 0.21 (60% EtOAc in hexane); $[\alpha]_D^{29}$ = −96.0 (c 0.27 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.19 (m, 5H), 5.36−5.28 (m, 1H), 5.14 (d, J = 9.9 Hz, 1H), 4.67−4.62 (m, 1H), 4.13 (d, J = 6.9 Hz, 1H), 3.58 (d, J = 6.9 Hz, 1H), 3.45−3.38 (m, 2H), 3.10 (dd, J = 13.1, 4.8 Hz, 1H), 2.85−2.73 (m, 2H), 2.31−2.17 (m, 1H), 2.09−2.02 (m, 1H), 1.83−1.74 (m, 2H), 1.70 (s, 3H), 1.53−1.44 (m, 1H), 1.29 (d, J = 7.5 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.08−0.94 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.85−0.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 170.9, 170.2, 136.7, 135.5, 131.4, 129.6, 128.8, 127.2, 73.8, 59.1, 52.0, 45.8, 45.7, 41.5, 34.6, 34.5, 32.4, 28.0, 21.9, 21.7, 20.8, 17.8, 15.5 ppm; IR(KBr): ν_{max} 3420, 3302, 2978, 1734, 1626, 1456 cm^{-1}; HRMS (ESI) m/z calculated for $C_{27}H_{38}N_2O_5Na$ $[M + Na]^+$ 493.2678, found 493.2677.

The compound (32 mg, 0.07 mmol) from the above step was oxidized by DMP (52 mg, 0.12 mmol) in the presence of $NaHCO_3$ (6 mg, 0.07 mmol) in dry CH_2Cl_2 (3 mL) to yield calcaripeptide A (**1**) (30 mg, 94%, purification SiO_2, 100−200 mesh, 30% EtOAc in hexane as eluant) as a white solid. Crystallization from MeOH provided a white crystalline solid, mp 204−205 °C: R_f = 0.27 (30% EtOAc in hexane); $[\alpha]_D^{27}$ = −138.1 (c 0.23 MeOH); ^{1}H NMR (MeOH-d_4, 300 MHz) δ 7.31−7.18 (m, 5H), 6.38 (d, J = 10.5 Hz, 1H), 5.22 (dd, J = 9.2, 5.7 Hz, 1H), 4.65 (m, 1H, merged in water peak, confirmed by HSQC NMR study), 4.18 (q, J = 6.9 Hz, 1H), 3.87 (d, J = 6.9 Hz, 1H), 3.42−3.21 (m, 2H), 3.01 (dd, J = 12.9, 5.7 Hz, 1H), 2.82 (dd, J = 12.9, 9.0 Hz, 1H), 2.56−2.48 (m, 1H), 2.04−1.98 (m, 1H), 1.81−1.73 (m, 2H), 1.69 (d, J = 0.9 Hz, 3H), 1.39−1.29 (m, 3H), 1.24 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.14−1.03 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 198.9, 174.4, 171.9, 171.5, 149.9, 137.5, 136.7, 130.8, 129.9, 128.5, 75.2, 60.6, 53.9, 49.8, 46.9, 41.5, 36.0, 35.7, 35.3, 28.9, 22.8, 21.1, 20.8, 14.3, 12.4 ppm; IR(KBr): ν_{max} 3312, 2930, 1734, 1682,1620,1452 cm^{-1}; HRMS (ESI) m/z calculated for $C_{27}H_{37}N_2O_5$ $[M + H]^+$ 469.2702, found 469.2699.

(6*R*,9*R*,*E*)-Methyl 9-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4,6-dimethyldec-4-enoate (21, 21a). Alcohol **18** (201 mg, 0.70 mmol) was oxidized by IBX (314 mg, 1.12 mmol) in distilled EtOAc (8 mL) according to the procedure described in the preparation of compound **19** to produce the corresponding aldehyde (200 mg) in quantitative yield, which was directly taken into the next reaction without further characterizations.

To a cooled solution (−78 °C) of anhydrous MeOAc (0.56 mL, 7.0 mmol) in dry THF (8 mL) under argon, LiHMDS (1 M solution in THF, 3.5 mL, 3.5 mmol) was added, and the mixture was stirred for 30 min. The aldehyde from the above step (dissolved in 5 mL dry THF) was cannulated into it. The resulting mixture was stirred for 2 h at the same temperature and continued further 2 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) to afford a mixture of diastereomeric **21** and **21a** (153 mg, 61%) as a clear liquid: R_f = 0.13 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.23 (J = 9.6 Hz, 1H), 4.45−4.39 (m, 1H), 3.74−3.73 (m, 1H), 3.70 (s, 3H), 2.64−2.50 (m, 2H), 2.36−2.27 (m, 1H), 1.62 (d, J = 1.2 Hz, 3H), 1.41−1.27 (m, 4H), 1.09 (d, J = 5.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 134.1, 133.7, 133.2, 73.8, 73.5, 68.8, 68.7, 51.9, 40.4, 37.6, 33.5, 33.4, 32.2, 32.1, 29.8, 26.0, 23.9, 21.0, 18.3, 12.3, 11.9, −4.2, −4.6 ppm; IR(neat): ν_{max} 3485, 2928, 1742, 1254 cm^{-1}; HRMS (ESI) m/z calculated for $C_{19}H_{38}O_4SiNa$ $[M + Na]^+$ 381.2437, found 381.2435.

(6*R*,9*R*,*E*)-Methyl 9-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-3-(triisopropylsilyloxy)dec-4-enoate (22, 22a). The same experimental procedure as that adopted in TIPS protection of compound **14**. The mixture of methyl esters **21** and **21a** (149 mg, 0.42 mmol) was reacted with TIPSOTf (0.17 mL, 0.62 mmol) and 2,6-lutidine (0.22 mL, 1.26 mmol) in dry CH_2Cl_2 (4 mL) to yield TIPS protected compounds **22** and **22a** (175 mg, 82%) as a colorless oil: R_f = 0.51 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.11 (br d, J = 9.0 Hz, 1H), 4.61−4.49 (m, 1H), 3.73−3.72 (m, 1H), 3.65−3.62 (m, 3H), 2.65−2.38 (m, 2H), 2.31−2.25 (m, 1H), 1.60−1.59 (m, 3H), 1.41−1.25 (m, 4H), 1.08 (d, J = 6.0 Hz, 3H), 1.04 (m, 13H), 1.00−0.93 (m, 11H), 0.88−0.87 (m, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 171.7, 135.0, 134.9, 133.5, 133.3, 76.0, 75.8, 68.6, 51.6, 51.5, 43.0, 42.8, 37.6, 37.5, 33.4, 33.3, 32.0, 31.9, 26.0, 24.1, 19.0, 18.3, 18.2, 18.1, 17.8, 17.1, 12.9, 12.5, −4.2, −4.6 ppm; IR(neat): ν_{max} 2955, 1745, 1254 cm^{-1}; HRMS (ESI) m/z calculated for $C_{28}H_{58}O_4Si_2Na$ $[M + Na]^+$ 537.3771, found 537.3773.

(3*R*,6*R*,9*R*,*E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-4,6-dimethyldec-4-en-1-one (24). Alcohol **18** (318 mg, 1.10 mmol) was oxidized by IBX (497 mg, 1.78 mmol) in distilled EtOAc (8 mL) in 2.5 h according to the procedure described in the synthesis of compound **19** to produce the corresponding aldehyde (314 mg) in quantitative yield, which was taken directly into the next reaction without further characterizations.

To a solution of thiazolidinethione **23** (427 mg, 1.87 mmol) in anhydrous CH_2Cl_2 (8 mL) at −40 °C under argon, freshly distilled $TiCl_4$ (0.22 mL, 1.98 mmol) was added dropwise. The yellowish slurry was stirred for 5 min at the same temperature, and DIPEA (0.34 mL, 1.98 mmol) was added. The resulting deep reddish solution was stirred for another 40 min at the same temperature before cooling it to −78 °C. A solution of the above aldehyde (314 mg, 1.10 mmol, dissolved in 5 mL of CH_2Cl_2) was cannulated into it and stirred further for 15 min prior to quenching with saturated NH_4Cl solution (5 mL). The resulting mixture was extracted with EtOAc (2 × 20 mL), washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane as eluant) provided the corresponding aldol adduct

dx.doi.org/10.1021/jo5019798 | J. Org. Chem. XXXX, XXX, XXX−XXX

24 (434 mg, 73%, *dr* > 8:1) as a yellow liquid: R_f = 0.53 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = +153.5 (*c* 1.65 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.26 (m, 5H), 5.39 (m, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 4.59 (dd, *J* = 8.9, 3.3 Hz, 1H), 3.77−3.72 (m, 1H), 3.49−3.37 (m, 3H), 3.24 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.05 (dd, *J* = 12.9, 10.5 Hz, 1H), 2.90 (d, *J* = 11.7 Hz, 1H), 2.39−2.29 (m, 1H), 1.66 (d, *J* = 0.9 Hz, 1H), 1.41−1.28 (m, 4H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 173.1, 136.6, 134.2, 133.7, 129.6, 129.1, 127.4, 73.4, 68.6, 44.8, 37.6, 36.9, 33.5, 32.3, 32.1, 26.1, 24.0, 21.0, 18.3, 12.3, −4.2, −4.5 ppm; IR(neat): ν_{max} 3444, 2928, 1693 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{28}H_{45}NO_3S_2SiNa$ $[M + Na]^+$ 558.2508, found 558.2506.

(3*R*,6*R*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-3-(triisopropylsilyloxy)dec-4-enoic acid (25). Same as acid **9**. Compound **24** (428 mg, 0.80 mmol) was treated with TIPS-OTf (0.32 mL, 1.20 mmol) and 2,6-lutidine (0.28 mL, 2.40 mmol) in dry CH_2Cl_2 (3 mL) to get the corresponding TIPS ether {514 mg, 93%, yellow liquid, purification SiO_2, 100−200 mesh, 2% EtOAc in hexane as eluant}: R_f = 0.58 (10% EtOAc in hexane), HRMS (ESI) *m*/*z* calculated for $C_{37}H_{65}NO_3S_2Si_2Na$ $[M + Na]^+$ 714.3842, found 714.3844}, which next was treated with LiOH·H_2O (94 mg, 2.23 mmol) and 30% aqueous H_2O_2 (0.3 mL) in THF:H_2O (3:1, 4 mL) to provide acid **25** (316 mg, 85%, purification SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) as a colorless oil: R_f = 0.68 (15% EtOAc in hexane); $[\alpha]_D^{27}$ = −11.6 (*c* 1.22 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.13 (d, *J* = 9.6 Hz, 1H), 4.56 (t, *J* = 6.6 Hz, 1H), 3.76−3.70 (m, 1H), 2.66−2.51 (m, 2H), 2.33−2.23 (m, 1H), 1.61 (d, *J* = 1.2 Hz, 3H), 1.36−1.23 (m, 4H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.05−1.04 (m, 21H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 134.2, 134.1, 75.9, 69.2, 42.3, 37.3, 33.6, 32.2, 26.1, 24.1, 20.9, 18.3, 18.2, 18.1, 12.4, 11.1,-4.3, −4.5 ppm; IR(neat): ν_{max} 2930, 1713 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{27}H_{56}O_4Si_2Na$ $[M + Na]^+$ 523.3615, found 523.3614.

(*S*)-Methyl 1-((*S*)-2-((3*R*,6*R*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-3-(triisopropylsilyloxy)dec-4-enamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (29). Same as compound **8**. Dipeptide **6c** (215 mg, 0.57 mmol) in dry CH_2Cl_2 (3 mL) was treated with 30% TFA (0.9 mL) to afford the corresponding Boc deprotected product, which was subsequently reacted with acid **25** (237 mg, 0.47 mmol) in the presence of DIPEA (0.16 mL, 0.94 mmol), EDCI (109 mg, 0.57 mmol), and HOBt (77 mg, 0.57 mmol) in dry DMF(5 mL) to yield compound **29** (298 mg, 83% from **25**, purification SiO_2, 100−200 mesh, 25% EtOAc in hexane as eluant) as a thick liquid: R_f = 0.45 (15% EtOAc in hexane); $[\alpha]_D^{28}$ = −20.0 (*c* 3.3 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.20 (m, 5H), 6.55 (d, *J* = 7.9 Hz, 1H), 5.24 (d, *J* = 9.5 Hz, 1H), 4.94−4.88 (m, 1H), 4.58−4.55 (m, 1H), 4.42 (dd, *J* = 8.5 Hz, 4.5 Hz, 1H), 3.74 (s, 3H), 3.72−3.68 (m, 1H), 3.52−3.48 (m, 1H), 3.06 (d, *J* = 8.5 Hz, 1H), 2.98 (d, *J* = 5.0 Hz, 1H), 2.94−2.90 (m, 1H), 2.41−2.35 (m, 1H), 2.32−2.26 (m, 1H), 2.14−2.07 (m, 1H), 1.94−1.90 (m, 1H), 1.87−1.81 (m, 2H), 1.57 (s, 3H), 1.37−1.22 (m, 5H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.01 (s, 21H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, rotamer peaks are given in parentheses) δ 172.3, 170.2, 169.9, 136.3, 134.7, 133.0, 129.9(129.5), 128.4(128.6), 126.9, 75.3, 68.6, 59.0, 52.3(52.8), 52.1, 46.9, 44.6, 39.4, 37.5, 33.3(34.1), 32.0, 29.2(30.6), 26.0, 24.9, 23.9(24.1), 20.7(20.9), 18.2, 12.5, 12.4, 11.9, −4.3, −4.6 ppm; IR(neat): ν_{max} 3314, 2928, 1751, 1634, 1448 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{42}H_{74}N_2O_6Si_2Na$ $[M + Na]^+$ 781.4983, found 781.4985.

Macrocycle 30. The same procedure as described in the preparation of compound **16**. Compound **29** (272 mg, 0.36 mmol) was first treated with CSA (8.3 mg, 0.04 mmol) in CH_2Cl_2:MeOH (4:1, 4 mL) under argon to yield the corresponding TBS deprotected compound (199 mg, 86%, purification SiO_2, 100−200 mesh, 35% EtOAc in hexane as eluant) as a thick liquid: R_f = 0.29 (40% EtOAc in hexane); $[\alpha]_D^{29}$ = −29.4 (*c* 4.69 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.19 (m, 5H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 4.93−4.89 (m, 1H), 4.48 (m, 1H), 4.46−4.40 (m, 2H), 3.73 (s, 3H), 3.56−3.53 (m, 1H), 3.10−3.01 (m, 1H), 2.99−2.91 (m, 1H), 2.41 (d, *J* = 6 Hz, 2H), 2.32−2.29 (m, 1H), 2.10−2.08 (m, 1H), 1.93−1.79 (m, 5H), 1.57 (s, 3H), 1.41−1.27 (m, 4H), 1.13 (d, *J* = 6.0 Hz, 3H), 1.07−1.04 (m, 3H), 1.00 (s, 18H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 170.3, 169.9, 136.2, 135.2, 133.5, 129.9, 128.5, 127.0, 75.7, 68.3, 59.1, 52.3, 52.0, 47.0, 44.6, 39.1, 37.5, 33.7, 32.3, 29.2, 24.9, 23.5, 20.9, 18.2, 18.2, 12.4, 11.4 ppm; IR(neat): ν_{max} 3398, 2974, 1637, 1629 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{36}H_{60}N_2O_6SiNa$ $[M + Na]^+$ 667.4118, found 667.4117.

The above compound (79 mg, 0.12 mmol) was hydrolyzed by LiOH·H_2O (15 mg, 0.36 mmol) in THF:H_2O (3:1, 3 mL) in 1 h to produce the corresponding seco acid {77 mg, quantitative, purification SiO_2, 60−120 mesh, EtOAc as eluant, thick oil, R_f = 0.36 (EtOAc)} in quantitative yield, which was confirmed by mass spectroscopy {HRMS (ESI) *m*/*z* calculated for $C_{35}H_{58}N_2O_6SiNa$ $[M + Na]^+$ 653.3962, found 653.3965} and taken into the next reaction without any more characterizations.

The seco acid (77 mg, 0.012 mmol) was subsequently treated with MNBA (67 mg, 0.20 mmol) and DMAP (37 mg, 0.31 mmol) in CH_2Cl_2 (100 mL) to yield macrocycle **30** (46 mg, 61%, purification SiO_2, 100−200 mesh, 15% EtOAc in hexane as eluant) as a colorless liquid: R_f = 0.53 (25% EtOAc in hexane); $[\alpha]_D^{28}$ = −3.3 (*c* 0.40 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.20 (m, 5H), 6.30 (d, *J* = 7.6 Hz, 1H), 5.02−4.99 (m, 1H), 4.89 (d, *J* = 9.6 Hz, 1H), 4.60 (m, 1H), 4.37 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.49−3.47 (m, 2H), 3.37 (m, 1H), 3.11 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.79 (dd, *J* = 12.8, 10.0 Hz, 1H), 2.61−2.59 (m, 2H), 2.21 (m, 1H), 2.00−1.99 (m, 1H), 1.75−1.70 (m, 2H), 1.61 (s, 3H), 1.47 (m, 1H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.31−1.17 (m, 3H), 1.06−1.02 (m, 21H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.83−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 170.5, 168.0, 136.4, 135.1, 133.9, 129.6, 128.7, 127.3, 74.2, 59.1, 52.4, 45.9, 44.8, 41.1, 34.6, 34.4, 32.2, 28.9, 22.1, 21.4, 20.2, 18.2, 18.1, 12.3, 10.3 ppm; IR(neat): ν_{max} 3331, 2926, 1737, 1632, 1447 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{35}H_{56}N_2O_5SiNa$ $[M + Na]^+$ 635.3856, found 635.3854.

Calcaripeptide B (2). Following the same protocols as those adopted for the synthesis of calcaripeptide C, macrocycle **30** (43 mg, 0.07 mmol) was treated with TBAF (1 M solution in THF, 0.10 mL, 0.10 mmol) in dry THF to produce the corresponding desilylated compound (29 mg, 90%, purification SiO_2, 100−200 mesh, 45% EtOAc in hexane as eluant) in 2 h as a colorless oil; R_f = 0.13 (40% EtOAc in hexane); $[\alpha]_D^{28}$ = −56.7 (*c* 0.91 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.20 (m, 5H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.06−4.99 (m, 1H), 4.94 (d, *J* = 9.6 Hz, 1H), 4.62−4.56 (m, 1H), 4.35−4.31 (m, 1H), 3.50−3.42 (m, 2H), 3.39−3.35 (m, 1H), 3.15 (dd, *J* = 12.2, 5.1 Hz, 1H), 2.80 (dd, *J* = 12.2, 10.2 Hz, 1H), 2.68−2.66 (m, 2H), 2.26−2.20 (m, 1H), 1.99−1.93 (m, 1H), 1.78 (m, 4H), 1.52−1.44 (m, 1H), 1.34−1.28 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.19−1.09 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 170.5, 169.2, 136.4, 135.2, 133.8, 129.6, 128.8, 127.3, 75.5, 74.4, 59.1, 52.5, 45.9, 41.5, 41.2, 34.7, 34.6, 32.3, 28.9, 22.1, 21.6, 20.4, 11.5 ppm; IR(neat): ν_{max} 3315, 2924, 1731, 1626, 1454 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{26}H_{37}N_2O_5$ $[M + H]^+$ 457.2702, found 457.2694.

The aforementioned compound (25 mg, 0.05 mmol) was oxidized by DMP (36 mg, 0.09 mmol) in 2 h in the presence of $NaHCO_3$ (4.6 mg, 0.05 mmol) in dry CH_2Cl_2 to provide calcaripeptide B (**2**) (22 mg, 89%, purification SiO_2, 100−200 mesh, 35% EtOAc in hexane as eluant) as a colorless liquid: R_f = 0.35 (40% EtOAc in hexane); $[\alpha]_D^{20}$ = −117.6 (*c* 0.35 MeOH); ^1H NMR (acetone-d_6, 300 MHz) δ 7.51 (d, *J* = 8.4 Hz, 1H), 7.34−7.20 (m, 5H), 6.41 (dd, *J* = 10.2, 1H), 5.23−5.15 (m, 1H), 4.66−4.62 (m, 1H), 4.35 (d, *J* = 15.0 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 3.43−3.35 (m, 2H), 3.18 (d, *J* = 15.0 Hz, 1H), 3.09 (dd, *J* = 12.6, 10.2 Hz, 1H), 2.81 (dd, *J* = 12.6, 5.1 Hz, 1H), 2.59−2.50 (m, 1H), 2.01 (m, 1H), 1.85−1.76 (m, 2H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.51−1.45 (m, 2H), 1.36−1.26 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.17−1.13 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (Acetone-d_6, 75 MHz) δ 196.4, 171.3, 170.7, 167.6, 149.4, 137.8, 136.1, 130.4, 129.4, 127.8, 74.3, 59.8, 53.5, 48.5, 46.4, 41.3, 35.7, 35.5, 34.7, 29.0, 22.6, 21.0, 20.7, 11.8 ppm; IR(neat): ν_{max} 3313, 2926, 1734, 1680, 1620, 1452 cm^{-1}; HRMS (ESI) *m*/*z* calculated for $C_{26}H_{35}N_2O_5$ $[M + H]^+$ 455.2546, found 455.2540.

dx.doi.org/10.1021/jo5019798 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, copies of NMR (^{1}H and ^{13}C) and HRMS of representative compounds, X-ray crystallographic data for compound **1**, and 2D NMR data for both compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.D. thanks the Council of Scientific and Industrial Research, New Delhi, for a research fellowship. The financial support from the Department of Science and Technology (Project no. SB/S5/GC-03/2013) and the Board of Research in Nuclear Science (Project no. 2012/37C/7/BRNS), India, to carry out this work is gratefully acknowledged.

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dx.doi.org/10.1021/jo5019798 | *J. Org. Chem.* XXXX, XXX, XXX−XXX