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Expedient Synthesis of a Stereoisomer of Acremolide B[§]

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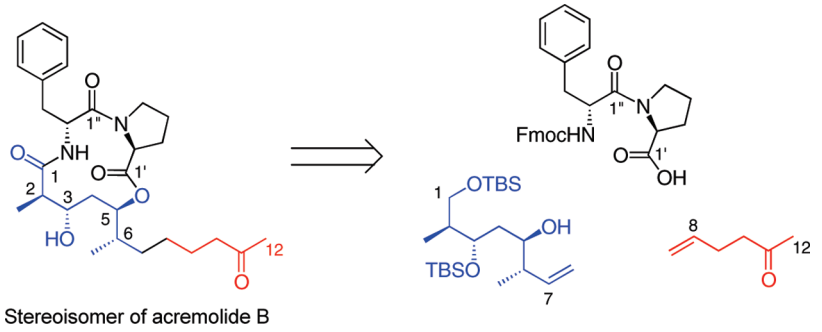

A highly straightforward strategy for the synthesis of the acremolide class of lipodepsipeptides has been developed. Synthetic highlights include a cross-metathesis to couple the C1−C7 and the C8−C12 fragments, an esterification to introduce the dipeptide unit, a macrolactamization to build the macrolide core, and two stereoselective allylations/crotylations to control all four stereogenic centers of the C1−C12 polypropionate segment.

Introduction

In 2008, Capon et al. reported the isolation of four members of a new family of lipodepsipeptides from an Australian estuarine isolate of an *Acremonium* sp. (MST-MF588a), namely acremolides A−D (Figure 1).[1] While the *Acremonium* sp. extract, which contained several mycotoxins such as 19-*O*-acetylchaetoglobosin B and D[2] as well as a known aromatic metabolite RKB 3564S,[3] exhibited significant cytotoxic activity against NS-1 cells (LD_{99} 16 μg/mL), the biological properties pertaining to the acremolides still remain unknown.

On the basis of extensive spectroscopic and degradation studies, the structures of acremolides A−D were proposed to display a 12-membered-ring lactam constituted of a C1−C12 polypropionate unit linked to a dipeptide. In addition, while the three-dimensional structure of the acremolides remains unknown, Capon et al. were able to identify unambiguously the amino acid content as L-proline (L-Pro) and D-phenylalanine (D-Phe) by applying a new C_3 Marfey's method[4] specially developed for amino acid analysis.

Due to the lack of both the relative and the absolute configuration of the acremolides, and to the structural similarities with the known histone deacetylase inhibitors FR235222,[5] apicidin A,[6] and trapoxin,[7] which exhibit promising biological properties, we became particularly interested in developing a concise and flexible synthesis that would allow a straightforward access to these natural products and to various analogues thereof. We report here the results of our endeavor that eventually led to the synthesis of an isomer of acremolide B.

Results and Discussion

First Strategy. In order to guarantee a high level of flexibility, our initial strategy relied on four key disconnections: a

[§] Dedicated to the memory of Marc Julia.

(1) Ratnayake, R.; Fremlin, L. J.; Lacey, E.; Gill, J. H.; Capon, R. J. *J. Nat. Prod.* **2008**, *71*, 403–408.
(2) Probst, A.; Tamm, C. *Helv. Chim. Acta* **1981**, *64*, 2056–2064.
(3) Osada, H.; Kakeya, H.; Konno, H.; Kanazawa, S. Japanese Patent 051804, 2003.
(4) Fujii, K.; Ikai, Y.; Oka, H.; Suzuki, M.; Harada, K. A. *Anal. Chem.* **1997**, *69*, 5146–5151.
(5) Mori, H.; Urano, Y.; Kinoshita, T.; Yoshimura, S.; Takase, S.; Hino, M. *J. Antibiot.* **2003**, *56*, 181–185.
(6) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Mosley, R. T.; Dombrowski, A. W.; Bills, G. F.; Darkin-Rattray, S. J.; Schmatz, D. M.; Goetz, M. A. *J. Org. Chem.* **2002**, *67*, 815–825.
(7) Kijima, M.; Yoshida, M.; Sugita, K.; Horinouchi, S.; Beppu, T. *J. Biol. Chem.* **1993**, *268*, 22429–22435.

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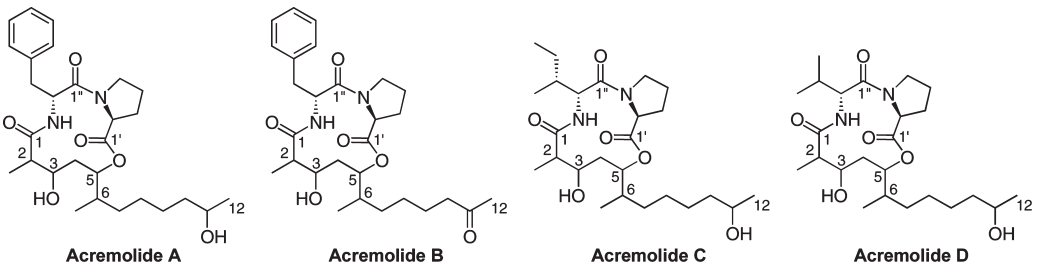
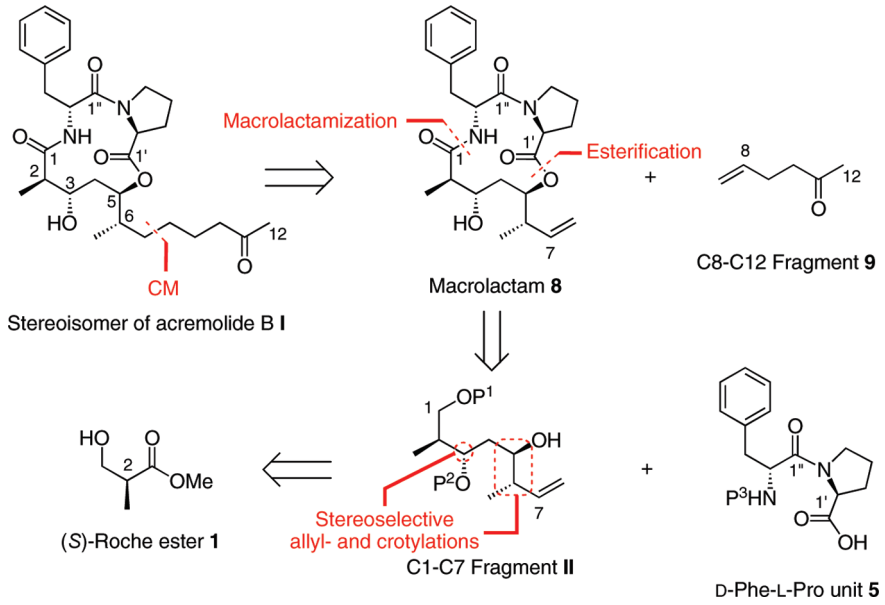


FIGURE 1. Structures of acremolides A−D.

SCHEME 1. Initial Retrosynthetic Analysis



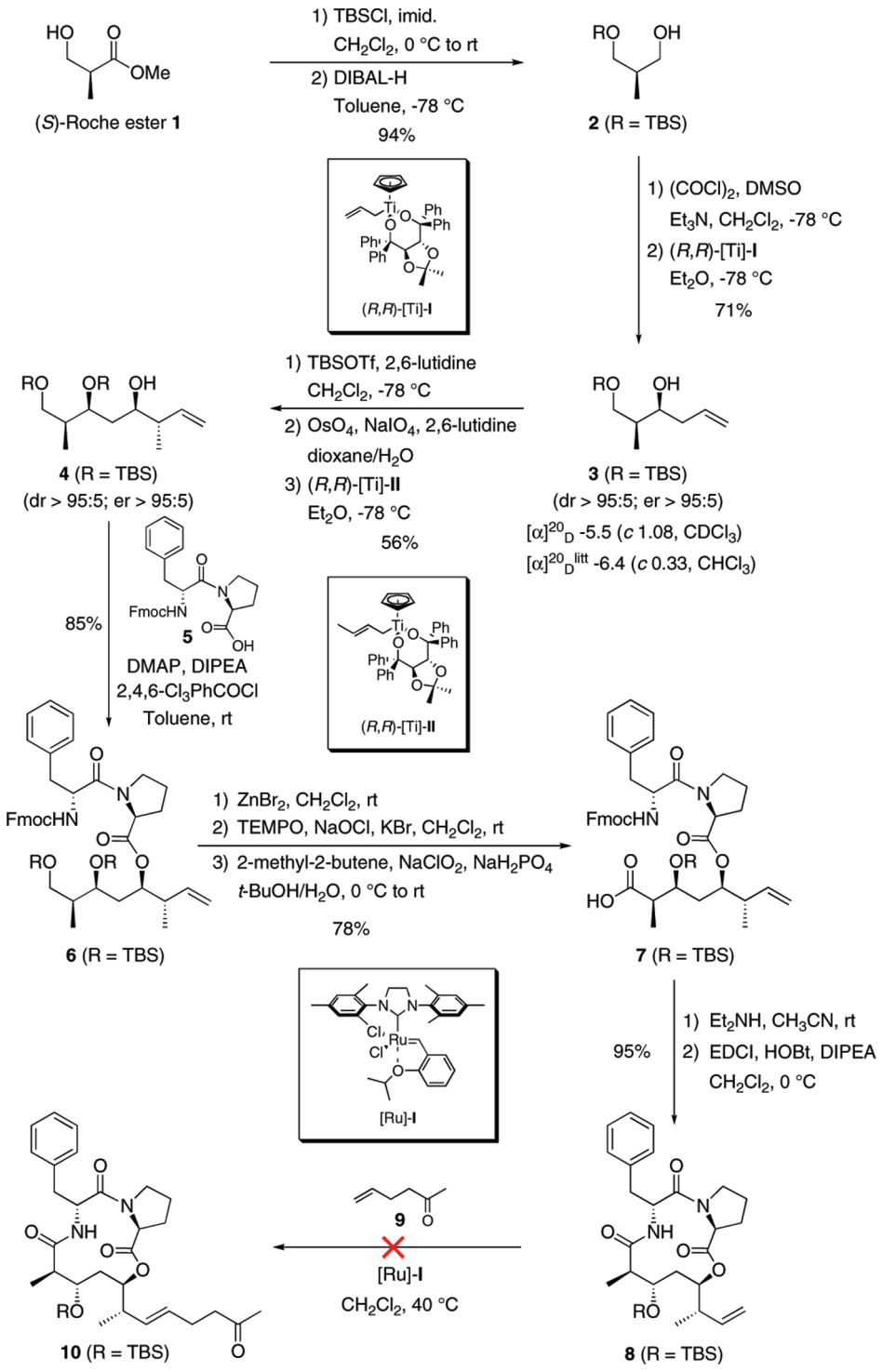
cross-metathesis (CM) to introduce the fatty-acid side chain, an esterification to link the dipeptide unit to the C1−C12 polypropionate fragment, a macrolactamization to build the 12-membered ring, and two stereoselective allylations/crotylations to control the three stereogenic centers at C3, C5, and C6 (Scheme 1). Two key compounds, **8** and **9**, were therefore identified.

The synthesis of macrolactam **8** started from the commercially available (*S*)-Roche ester **1** and proceeded through an initial protection of the primary alcohol as a *tert*-butyldimethylsilyl (TBS) ether (TBSCl, imid., CH_2Cl_2, 0 °C to rt, 99%) and the reduction of the ester moiety (DIBAL-H, toluene, −78 °C, 95%) (Scheme 2). Oxidation of the resulting alcohol using standard Swern[8] conditions [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C) followed by a diastereoselective allylation using the highly face-selective titanium complex (*R*,*R*)-[Ti]-**I** (THF, −78 °C)[9] then afford the corresponding homoallylic alcohol **3** (71% yield from **2**, dr >95/5, er >95/5, $[\alpha]^{20}_D$ −5.5 (*c* 1.08, $CDCl_3$); lit. $[\alpha]^{22}_D$ −6.4 (*c* 0.33, $CHCl_3$)),[10,11] which was later protected as a TBS ether (TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 80%) and engaged in an OsO_4-catalyzed oxidative cleavage[12] (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O). The aldehyde thus formed was then subjected to the (*R*,*R*)-[Ti]-**II** (Et_2O, −78 °C) complex to provide the corresponding homoallylic alcohol **4** as a single stereoisomer in 70% yield (dr >95/5). The next step concerned the esterification of alcohol **4** with the dipeptide unit **5**. The latter was prepared in three steps and 70% overall yield following a reported procedure[13] which involved converting L-Pro to the corresponding methyl ester ($SOCl_2$, MeOH, reflux), coupling the resulting amino ester with Fmoc-D-Phe-OH (EDCI, HOBt, DIPEA, CH_2Cl_2, rt), and ultimately saponifying the ester moiety (LiOH, THF/H_2O, 0 °C).

With the two coupling partners **4** and **5** in hand, our attention was then turned to the key esterification step. As various attempts to link alcohol **4** to the dipeptide unit **5** using either DCC or EDCI proved low-yielding, we finally opted for a Yamaguchi esterification.[14] To our delight, the Yamaguchi

(8) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
(9) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832.
(10) The diastereomeric ratio was determined by crude ^{1}H NMR analysis, while the absolute configuration of the C3 stereogenic center was determined as (3*S*) by comparing the optical rotation of the synthesized compound with the one reported in the literature {$[\alpha]^{25}_D$ −5.5 (*c* 1.08, $CDCl_3$); lit. $[\alpha]^{22}_D$ −6.4 (*c* 0.33, $CDCl_3$)}.
(11) See: Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117–4126.
(12) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
(13) Stüber, W.; Kosina, H.; Heimburger, N. *Int. J. Pept. Protein Res.* **1988**, *31*, 63–70.
(14) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. (b) Kawanami, Y.; Dainobu, Y.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 943–944.

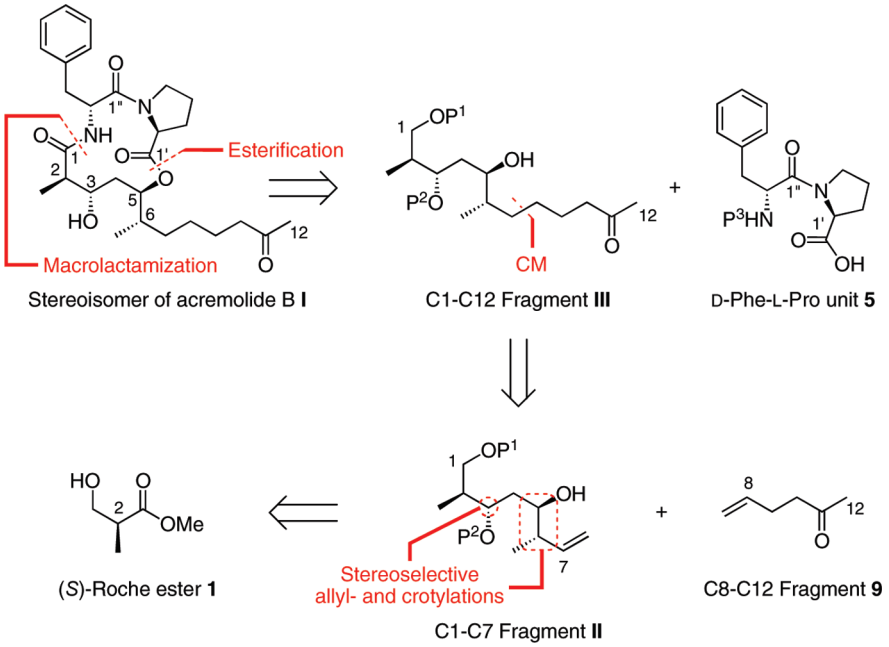
SCHEME 2. First Attempt To Synthesize Acremolide B



conditions (2,4,6-trichlorobenzoyl chloride, DMAP, toluene, rt) afforded the corresponding ester **6** in 85% yield. The primary TBS ether was then selectively cleaved using $ZnBr_2$ (CH_2Cl_2, rt, 94%),[15] and the resulting alcohol was subsequently oxidized,[16] first to the aldehyde (TEMPO, NaOCl, KBr, CH_2Cl_2, rt) and then to the carboxylic acid (2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O), to provide the lactam precursor **7** in 78% yield over three steps. The Fmoc protecting group was eventually removed under mild conditions (Et_2NH, CH_3CN), and the resulting amino acid was engaged in a macrolactamization (EDCI, HOBt, DIPEA, CH_2Cl_2, 0 °C), to afford the desired 12-membered-ring macrolactam **8** in 95% yield. Finally, in order to introduce the fatty-acid side chain and complete the synthesis of acremolide B,

(15) Crouch, R. D.; Polizzi, J. M.; Cleiman, R. A.; Yi, J.; Romany, C. A. *Tetrahedron. Lett.* **2002**, *43*, 7151–7153.
(16) Kurosawa, K.; Matsuura, K.; Nagase, T.; Chida, N. *Bull. Chem. Soc. Jpn.* **2006**, *6*, 921–937.

SCHEME 3. Second Synthetic Strategy



we envisioned a three-step sequence involving a CM with 5-hexen-2-one (**9**), a hydrogenation of the newly formed C7−C8 double bond, and a final cleavage of the silyl ether. Unfortunately, after multiple attempts to couple olefins **8** and **9** using various reaction conditions, we were unable to isolate any of the desired product **10**. This unfortunate outcome is believed to be due either to coordination between the ruthenium and the carbonyl of the lactone, which leads to an inactive catalytic species, or to sequestration of the ruthenium in the marocycle, which could poison the catalyst. In order to circumvent this dramatic issue, we therefore decided to slightly modify the current synthesis.

Second Strategy. Our second strategy relied on the same four disconnections as before but implied the introduction of the fatty-acid side chain prior to the dipeptide unit (Scheme 3).

Hence, instead of coupling **4** and **5** using a Yamaguchi esterification, the former was directly engaged in a CM with 5-hexen-2-one (**9**) using the Hoveyda−Grubbs catalyst, [Ru]-**I** (CH_2Cl_2, 40 °C) (Scheme 4). Fortunately, we were able to isolate the desired disubstituted olefin in 71% yield. The latter was then hydrogenated using AcOEt as the solvent (H_2, 10% Pd/C, rt, 90%) in order to avoid complete silyl ether deprotection which occurred under standard hydrogenation conditions.[17] Next, introduction of the dipeptide unit **5** using the Yamaguchi esterification conditions afforded the desired coupled product **14** in 75% yield. The primary TBS ether was then selectively cleaved using $SnCl_2$ ($EtOH/H_2O$, rt, 79%),[18,19] and the resulting alcohol was subsequently oxidized to the carboxylic acid using, once again, the same two-step sequence as the one used previously. This allowed us to isolate the lactam precursor **16** in 90% yield over two steps. Cleavage of the Fmoc protecting group followed by macrolactamization eventually afforded the desired 12-membered-ring lactam **17** (60% yield over two steps), which was ultimately deprotected (TBAF, THF, 0 °C, quant.) in order to complete the synthesis of what we hoped would be acremolide B. Unfortunately, analysis of the spectroscopic and physical data of **18** and comparison with the ones reported in the literature for the natural product[1] showed that we had synthesized a stereoisomer of acremolide B.[20]

Conclusion

In summary, we have completed the synthesis of a stereoisomer of acremolide B in 16 steps and 7.6% overall yield starting from (*S*)-Roche ester **1**. The strategy is particularly appealing as all the configurations of the stereogenic centers can be readily controlled by either starting the synthesis from the (*R*)-Roche ester, changing the chiral auxiliaries in the allylations/crotylations, or switching from a titanium- to a boron-mediated crotylation. As such, this straightforward approach should allow an easy access to any of the various stereoisomers of acremolide B as well as to all the other members of the acremolides.

Experimental Section

The reactions were run under argon atmosphere in oven-dried glassware unless otherwise specified. 5-Hexen-2-one (**9**) and other reagents were obtained from commercial suppliers and used as received. Fmoc-D-Phe-L-Pro-OH (**5**)[12] was prepared according to a reported procedure. Its spectroscopic and physical data

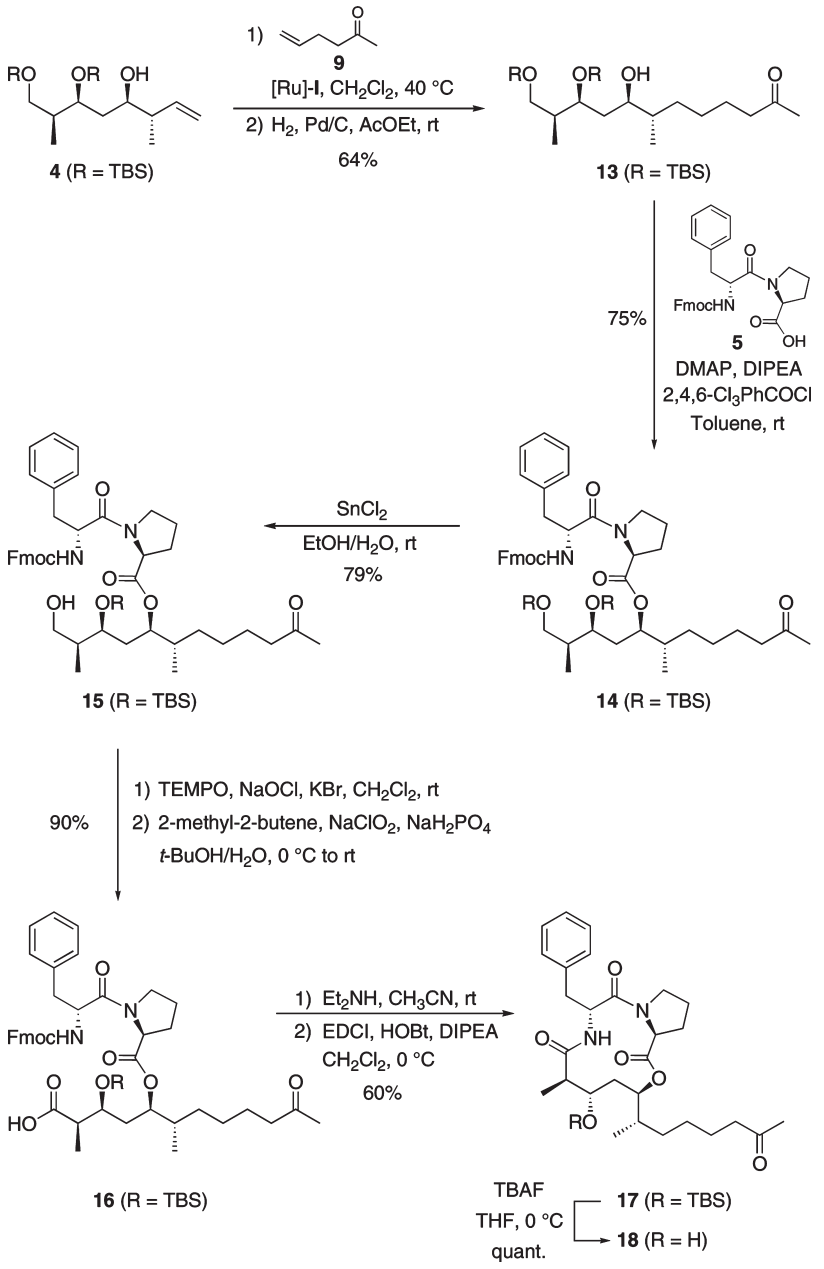
(17) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901–6911.

(18) Deprotection of the primary TBS ether in **14** using $ZnBr_2$ afforded the desired compound in a slightly lower yield (60%).

(19) Hua, J.; Jiang, Z. Y.; Wang, Y. G. *Chin. Chem. Lett.* **2004**, *15*, 1430–1432.

(20) After closely examining the discrepancies in the ^1H and ^{13}C NMR spectra of both the natural and the synthetic acremolide B, it is particularly difficult to speculate on the relative and absolute configuration of the C2, C3, C5, and C6 stereogenic centers (see Supporting Information for comparative Table), not to mention that, due to the cyclic nature of the natural product, a slight modification of one of the stereogenic centers could have a tremendous impact on the overall configuration of the molecule and therefore on all the chemical shifts.

SCHEME 4. Synthesis of a Stereoisomer of Acremolide B



were identical with those reported in the literature. Analytical thin-layer chromatography (TLC) was performed on silica gel plates visualized either with a UV lamp (254 nm) or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH, phosphomolybdic acid in EtOH, or $KMnO_4/K_2CO_3$/AcOH in water followed by heating. Flash chromatography was performed on silica gel (60−230 mesh mesh). Organic extracts were dried over anhydrous $MgSO_4$. Infrared spectra were recorded on a Bruker instrument, and wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$, and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non equivalent resonances), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ (unless otherwise specified), and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments). Mass spectra (MS) were recorded using a tandem gas chromatograph/mass spectrometer (70 eV). High-resolution mass spectra were performed by "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)".

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropionic Acid Methyl Ester.[21] To a solution of (*S*)-3-hydroxy-2-methylpropionic acid methyl ester (**1**, 5 g, 42.3 mmol) in CH_2Cl_2 (170 mL) at 0 °C was added imidazole (3.5 g, 50.8 mmol) followed by *tert*-butyldimethylsilyl chloride (7.5 g, 46.6 mmol), and the reaction mixture was then stirred at room temperature for 22 h until complete conversion of the starting material (reaction monitored by TLC analysis). The reaction mixture was then filtered and concentrated under reduced pressure, and the crude residue was purified by flash chromatography (petroleum ether/Et_2O: 99/1) to afford 3-(*tert*-butyldimethylsilyloxy)-2-methylpropionic acid methyl ester (9.8 g,

(21) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1990**, *55*, 1540–1547.

99%) as a colorless oil. Its spectroscopic and physical data matched the ones reported in the literature.[19]

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-1-ol (2).[22] To a solution of 3-(*tert*-butyldimethylsilyloxy)-2-methylpropionic acid methyl ester (9.5 g, 40.8 mmol) in toluene (150 mL) at −78 °C was slowly added DIBAL-H (98.5 mL of a 1 M solution in toluene, 98.5 mmol). The resulting reaction mixture was stirred for 20 min, time after which it was quenched with a 1:1 mixture of AcOEt/saturated aqueous solution of sodium potassium tartrate (200 mL). Stirring was continued at room temperature overnight before the organic layer was separated. The aqueous layer was then extracted with AcOEt (2 × 100 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/AcOEt: 99/1) to afford (*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropan-1-ol (**2**) as a colorless oil (7.9 g, 95%). The spectroscopic and physical data of **2** matched the ones reported in the literature.[20]

(2*S*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylhex-5-en-3-ol (3).[11] To a solution of oxalyl chloride (2.9 mL, 33.2 mmol) in CH_2Cl_2 (110 mL) at −78 °C was slowly added DMSO (5.1 mL, 66.4 mmol), and the reaction mixture was stirred for 30 min. (*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-1-ol (**2**, 3.36 g, 16.1 mmol) was then added dropwise, and stirring was continued for an additional 30 min at the same temperature. Et_3N (13.9 mL, 99.6 mmol) was then added, and the reaction mixture was warmed to room temperature and quenched with a saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Hexane was then added, and the precipitate was filtered over Celite. The solvent was removed under reduced pressure, and the resulting crude aldehyde was used in the next step without further purification. To a solution of the (*R*,*R*)-[Ti]-**I** complex (13.2 g, 21.9 mmol) in Et_2O (166 mL) at −78 °C was added allylmagnesium chloride (9.9 mL of a 2 M solution in THF, 19.9 mmol), and the reaction mixture was stirred for 2 h at 0 °C. The solution was then cooled to −78 °C, and the crude aldehyde (16.1 mmol) was added dropwise. The resulting reaction mixture was stirred for 4 h at the same temperature until complete conversion of the starting material (reaction monitored by TLC analysis), quenched with water (80 mL), and stirred overnight at room temperature. The reaction mixture was then filtered over Celite, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude residue was purified by flash chromatography (petroleum ether/AcOEt: 97/3) to afford (2*S*,3*S*)-1-(*tert*-butyldimethylsilyloxy)-2-methylhex-5-en-3-ol (**3**) (3.6 g, 71%) as a single stereoisomer and as a colorless oil. The spectroscopic and physical data of **3** matched the ones reported in the literature.[21]

(4*S*,5*S*)-4,6-Bis-(*tert*-butyldimethylsilyloxy)-5-methylhex-1-ene. To a solution of (2*S*,3*S*)-1-(*tert*-butyldimethylsilyloxy)-2-methylhex-5-en-3-ol (**3**, 3.6 g, 14.7 mmol) in CH_2Cl_2 (75 mL) at −78 °C were added 2,6-lutidine (3.4 mL, 29.5 mmol) and TBSOTf (5.8 g, 22.1 mmol). The resulting reaction mixture was stirred for 90 min at the same temperature before a saturated aqueous $NaHCO_3$ solution (40 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether/Et_2O: 99/1) to afford (4*S*,5*S*)-4,6-bis-(*tert*-butyldimethylsilyloxy)-5-methylhex-1-ene (4.2 g, 80%) as a colorless oil: R_f = 0.87 (petroleum ether/Et_2O: 99/1); $[\alpha]^{20}_D$ +7.55 (*c* 1.1, $CHCl_3$); IR (neat) 2929, 2858, 1472, 1253, 1095, 1039, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.08−4.94 (m, 2H), 3.81 (m, 1H), 3.50 (dd, *J* = 9.8, 6.8 Hz, 1H), 3.37 (dd, *J* = 9.8, 6.5 Hz, 1H), 2.29−2.12 (m, 2H), 1.66 (m, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 6H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (CH), 116.4 (CH_2), 71.5 (CH), 65.4 (CH_2), 39.8 (CH), 39.7 (CH_2), 26.0 ($3CH_3$), 25.9 ($3CH_3$), 18.2 (C), 18.1 (C), 10.2 (CH_3), −4.1 (CH_3), −4.7 (CH_3), −5.3 (CH_3), −5.4 (CH_3).

(3*S*,4*R*,6*S*,7*S*)-6,8-Bis-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-1-en-4-ol (4). To a solution of (4*S*,5*S*)-4,6-bis-(*tert*-butyldimethylsilyloxy)-5-methylhex-1-ene (2 g, 5.6 mmol) in a 3:1 dioxane/water mixture (56 mL) at 0 °C were added 2,6-lutidine (1.6 mL, 13.4 mmol), OsO_4 (3.5 mL of a 2.5% solution in water, 0.28 mmol), and $NaIO_4$ (4.75 g, 22.3 mmol). The resulting reaction mixture was stirred for 3.5 h at room temperature until complete conversion of the starting material (reaction monitored by TLC analysis). The reaction mixture was then quenched with a saturated aqueous $Na_2S_2O_3$ solution (20 mL) and stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was finally filtered over a small plug of silica, eluting with a petroleum ether/Et_2O (99/1) mixture. The solvent was removed under reduced pressure, and the resulting crude aldehyde was used in the next step without further purification. To a solution of the (*R*,*R*)-[Ti]-**II** complex (5.5 g, 8.9 mmol) in Et_2O (56 mL) at −78 °C was added 2-butenylmagnesium chloride (16.6 mL of a 2 M solution in THF, 8.3 mmol), and the resulting reaction mixture was stirred for 2 h at 0 °C. The solution was then cooled to −78 °C, and the crude aldehyde (5.6 mmol) was added dropwise. The resulting reaction mixture was stirred for 4 h at the same temperature until complete conversion of the starting material (reaction monitored by TLC analysis), quenched with water (80 mL), and stirred overnight at room temperature. The reaction mixture was then filtered over Celite, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford (3*S*,4*R*,6*S*,7*S*)-6,8-bis-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-1-en-4-ol (**4**, 1.6 g, 70%) as a colorless oil. R_f = 0.45 (petroleum ether/Et_2O: 95/5); $[\alpha]^{20}_D$ −6.37 (*c* 0.97, $CHCl_3$); IR (neat) 2929, 2858, 1472, 1389, 1255, 1096, 1047, 1005, 914, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.09−5.00 (m, 2H), 3.93 (td_{app}, *J* = 6.8, 3.0 Hz, 1H), 3.57 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.48 (m, 1H), 3.41 (dd, *J* = 9.5, 7.0 Hz, 1H), 2.39 (bs, 1H), 2.16 (m, 1H), 1.79 (m, 1H), 1.60 (m, 1H), 1.45 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (CH), 115.6 (CH_2), 73.2 (CH), 72.7 (CH), 64.8 (CH_2), 44.2 (CH), 40.5 (CH), 37.3 (CH_2), 26.0 ($3CH_3$), 25.9 ($3CH_3$), 18.3 (C), 18.0 (C), 15.7 (CH_3), 11.6 (CH_3), −4.3 (CH_3), −4.5 (CH_3), −5.3 (CH_3), −5.4 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{48}O_3NaSi_2$ $[M+Na]^+$ 439.3034, found 439.3031.

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic Acid (1*R*,3*S*,4*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-4-methyl-1-[(*S*)-1-methylallyl]-pentyl Ester (6). To a solution of (3*S*,4*R*,6*S*,7*S*)-6,8-bis-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-1-en-4-ol (**4**, 68 mg, 0.16 mmol) and Fmoc-D-Phe-L-Pro-OH (**5**, 87 mg, 0.18 mmol) in toluene (16 mL) was added DMAP (39 mg, 0.32 mmol). The reaction mixture was then cooled to −78 °C before DIPEA (98 μL, 0.60 mmol) was added, followed by 2,4,6-trichlorobenzoyl chloride (74 μL, 0.48 mmol). The resulting slurry was slowly warmed to room temperature over 2 h, stirred for an additional 6 h at the same

(22) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316–318.

temperature, and quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/EtOH: 97/3) to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*S*)-3,5-bis-(*tert*-butyldimethylsilyloxy)-4-methyl-1-[(*S*)-1-methylallyl]-pentyl ester (**6**, 120 mg, 85%) as a viscous oil. *Mixture of rotamers:* R_f = 0.67 (CH_2Cl_2/CH_3OH: 99/1); $[\alpha]^{20}_D$ −16.4 (*c* 0.45, $CHCl_3$); IR (neat) 2954, 2929, 2857, 1727, 1644, 1449, 1251, 1187, 1098, 1042, 836, 775 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d_{app}, *J* = 7.5 Hz, 2H), 7.60 (t_{app}, *J* = 8.2 Hz, 2H), 7.40 (t_{app}, *J* = 7.9 Hz, 2H), 7.36−7.29 (m, 2H), 7.28−7.16 (m, 5H), 5.81−5.64 (m, 2H), 5.12−4.98 (m, 2H), 4.88 (m, 1H), 4.69 (m, 1H), 4.38 (dd, *J* = 10.2, 7.9 Hz, 1H), 4.37−4.24 (m, 2H), 4.21 (t_{app}, *J* = 7.5 Hz, 1H), 3.78 (m, 1H), 3.54−3.43 (m, 2H), 3.37 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.11 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.98 (dd, *J* = 13.0, 9.4 Hz, 1H), 2.63 (m, 1H), 2.51 (m, 1H), 1.96−1.76 (m, 3H), 1.75−1.59 (m, 3H), 1.50 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C), 169.6 (C), 155.5 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 138.8 (CH), 136.3 (C), 129.6 (2CH), 128.5 (2CH), 127.7 (2CH), 127.1 (2CH), 127.0 (CH), 125.3 (2CH), 120.0 (2CH), 116.0 (CH_2), 75.0 (CH), 68.5 (CH), 67.0 (CH_2), 65.5 (CH_2), 58.8 (CH), 54.1 (CH), 47.2 (CH), 46.8 (CH_2), 41.1 (CH), 40.4 (CH_2), 39.6 (CH), 35.9 (CH_2), 31.0 (CH_2), 26.0 ($3CH_3$), 25.9 ($3CH_3$), 24.3 (CH_2), 18.3 (C), 18.1 (C), 15.4 (CH_3), 9.8 (CH_3), −4.1 (CH_3), −4.7 (CH_3), −5.3 (CH_3), −5.4 (CH_3).

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic Acid (1*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4-methyl-1-[(*S*)-1-methylallyl]-pentyl Ester. To a solution of $ZnBr_2$ (110 mg, 0.73 mmol) in CH_2Cl_2 (8 mL) at room temperature was added a solution of (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*S*)-3,5-bis-(*tert*-butyldimethylsilyloxy)-4-methyl-1-((*S*)-1-methylallyl)-pentyl ester (**6**, 110 mg, 0.13 mmol) in CH_2Cl_2 (16 mL). The resulting reaction mixture was stirred for 4 h at the same temperature until complete conversion of the starting material (reaction monitored by TLC analysis) and then quenched with a saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography, eluting with $CHCl_3$, to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methyl-1-[(*S*)-1-methylallyl]-pentyl ester (83 mg, 83%) as a viscous oil. *Mixture of rotamers:* R_f = 0.21 (9.9/0.1: CH_2Cl_2/CH_3OH); $[\alpha]^{20}_D$ −12.65 (*c* 0.63, $CHCl_3$); IR (neat) 2956, 2928, 2856, 1722, 1639, 1524, 1450, 1251, 1188, 1086, 1041, 837, 775 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d_{app}, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 11.5, 7.5 Hz, 2H), 7.38 (t_{app}, *J* = 7.5 Hz, 2H), 7.30 (t_{app}, *J* = 7.2 Hz, 2H), 7.27−7.14 (m, 5H), 5.86 (d, *J* = 8.2 Hz, 1H), 5.72 (m, 1H), 5.10−4.98 (m, 2H), 4.99 (m, 1H), 4.70 (m, 1H), 4.41 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.35−4.22 (m, 2H), 4.19 (t_{app}, *J* = 7.2 Hz, 1H), 3.80 (td, *J* = 7.6, 1.6 Hz, 1H), 3.55−3.36 (m, 3H), 3.10 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.95 (dd, *J* = 12.9, 9.3 Hz, 1H), 2.63 (m, 1H), 2.41 (m, 1H), 1.98−1.74 (m, 4H), 1.72−1.62 (m, 3H), 1.49 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C), 169.9 (C), 155.6 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 138.9 (CH), 136.2 (C), 129.5 (2CH), 128.5 (2CH), 127.7 (2CH), 127.1 (3CH), 125.3 (2CH), 120.0 (2CH), 116.1 (CH_2), 74.8 (CH), 68.6 (CH), 67.0 (CH_2), 65.4 (CH_2), 59.1 (CH), 54.2 (CH), 47.2 (CH), 46.9 (CH_2), 41.9 (CH), 40.4 (CH_2), 38.4 (CH), 35.7 (CH_2), 29.0 (CH_2), 25.8 ($3CH_3$), 24.3 (CH_2), 18.0 (C), 15.8 (CH_3), 9.8 (CH_3), −4.3 (CH_3), −4.8 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{45}H_{60}O_7N_2NaSi$ $[M+Na]^+$ 791.4062, found 791.4057.

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic Acid (1*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-carboxy-1-[(*S*)-1-methylallyl]-pentyl Ester (7). To a solution of (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methyl-1-[(*S*)-1-methylallyl]-pentyl ester (77 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at 0 °C were added TEMPO (22 mg, 0.14 mmol), KBr (50 μL of a 0.2 M solution in water, 0.01 mmol), and NaOCl (52 μL of a 13% solution in water, 0.1 mmol). After the mixture was stirred for 30 min at the same temperature, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. The crude aldehyde (0.1 mmol), *t*-BuOH (5 mL), 2-methyl-2-butene (0.74 mL, 7.0 mmol), water (1 mL), $NaClO_2$ (68 mg, 0.6 mmol), and NaH_2PO_4 (36 mg, 0.3 mmol) were mixed at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. *t*-BuOH was then removed under reduced pressure, and AcOEt (15 mL) was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 × 15 mL). The combined organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (CH_2Cl_2/CH_3OH: 99/1) to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-carboxy-1-[(*S*)-1-methylallyl]-pentyl ester (**7**, 73 mg, 93%) as a viscous oil. *Mixture of rotamers:* R_f = 0.22 (CH_2Cl_2/CH_3OH: 98/2); $[\alpha]^{20}_D$ −24.0 (*c* 0.87, $CHCl_3$); IR (neat) 2928, 2856, 1713, 1618, 1451, 1251, 1186, 1095, 1033, 837, 776, 759, 741 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 9.6, 7.6 Hz, 2H), 7.38 (t_{app}, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 7.6, 0.8 Hz, 2H), 7.26−7.14 (m, 5H), 5.80 (d, *J* = 8.4 Hz, 1H), 5.72 (m, 1H), 5.11−4.96 (m, 2H), 4.91 (m, 1H), 4.71 (m, 1H), 4.40−4.32 (m, 2H), 4.29 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.19 (t_{app}, *J* = 7.3 Hz, 1H), 4.09 (m, 1H), 3.51 (m, 1H), 3.08 (dd, *J* = 12.8, 5.6 Hz, 1H), 2.96 (dd, *J* = 12.8, 9.2 Hz, 1H), 2.68−2.52 (m, 2H), 2.43 (m, 1H), 1.96−1.72 (m, 3H), 1.71−1.62 (m, 2H), 1.49 (m, 1H), 1.10−0.99 (2d, *J* = 7.0 Hz, 6H) 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8 (C), 171.3 (C), 170.0 (C), 155.6 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 138.6 (CH), 136.2 (C), 129.5 (2CH), 128.5 (2CH), 127.7 (2CH), 127.1 (3CH), 125.3 (2CH), 120.0 (2CH), 116.3 (CH_2), 74.1 (CH), 69.8 (CH), 67.1 (CH_2), 58.8 (CH), 54.1 (CH), 47.1 (CH), 46.9 (CH_2), 43.2 (CH), 41.8 (CH), 40.3 (CH_2), 35.9 (CH_2), 29.0 (CH_2), 25.7 ($3CH_3$), 24.2 (CH_2), 17.9 (C), 15.4 (CH_3), 9.3 (CH_3), −4.3 (CH_3), −4.9 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{45}H_{58}O_8N_2NaSi$ $[M+Na]^+$ 805.3855, found 805.3859.

(5*R*,8*R*,9*S*,11*R*,13a*R*)-5-Benzyl-9-(*tert*-butyldimethylsilyloxy)-8-methyl-11-[(*S*)-1-methylallyl]-decahydro-12-oxa-3a,6-diaza-cyclopentacyclododecene-4,7,13-trione (8). To a solution of (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-carboxy-1-[(*S*)-1-methylallyl]-pentyl ester (**7**, 70 mg, 0.09 mmol) in CH_3CN (3.2 mL) at room temperature was added Et_2NH (1.6 mL), and the reaction mixture was stirred at room temperature until complete conversion of the starting material (reaction monitored by TLC analysis). The solvent was then removed under reduced pressure, and the resulting crude amino acid was used in the next step without further purification. To a solution of the amino acid (0.09 mmol) in CH_2Cl_2 (13 mL) at 0 °C were added EDCl (33 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol), and DIPEA (64 μL, 0.39 mmol), and the resulting reaction mixture was stirred for 3 h at room temperature. The reaction was

then quenched with a saturated aqueous NH_4Cl solution (10 mL), and the organic phase was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography, eluting with $CHCl_3$, to afford (5*R*,8*R*,9*S*,11*R*,13a*R*)-5-benzyl-9-(*tert*-butyldimethylsilyloxy)-8-methyl-11-[(*S*)-1-methylallyl]-decahydro-12-oxa-3a,6-diaza-cyclopentacyclododecene-4,7,13-trione (**8**, 46 mg, 95%) as an amorphous solid. *Mixture of rotamers:* R_f = 0.66 (9.5/0.5: CH_2Cl_2/CH_3OH); $[\alpha]^{20}_D$ −12.7 (*c* 0.3, $CHCl_3$); IR (neat) 3675, 2987, 2972, 2901, 1733, 1665, 1621, 1542, 1452, 1406, 1394, 1382, 1252, 1229, 1075, 1066 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, acetone-d_6) δ 7.32−7.12 (m, 6H), 5.67 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1H), 5.21 (m, 1H), 5.08−4.96 (m, 2H), 4.72−4.62 (m, 2H), 3.76 (td, *J* = 9.4, 2.9 Hz, 1H), 3.56 (m, 1H), 3.33 (m, 1H), 3.16−2.98 (m, 2H), 2.30 (m, 1H), 2.26−2.02 (m, 3H), 1.85 (m, 1H), 1.69 (m, 1H), 1.57 (dd, *J* = 15.6, 3.3 Hz, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 179.9 (C), 177.4 (C), 175.6 (C), 144.6 (CH), 143.5 (C), 134.5 (2CH), 133.8 (2CH), 132.1 (CH), 121.0 (CH_2), 77.4 (CH), 65.4 (CH), 62.7 (CH), 52.9 (CH_2), 49.5 (CH), 48.8 (CH), 41.6 (CH_2), 41.0 (CH_2), 38.2 (CH_2), 35.0 (CH), 30.9 ($3CH_3$), 26.7 (CH_2), 23.1 (C), 22.6 (CH_3), 20.0 (CH_3), 0.9 (CH_3), 0.0 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{46}O_5N_2NaSi$ $[M+Na]^+$ 565.3068, found 565.3060.

(7*S*,8*R*,10*S*,11*S*)-10,12-bis-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-7,11-dimethyldodecan-2-one (13). To a stirred solution of (3*S*,4*R*,6*S*,7*S*)-6,8-bis-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-1-en-4-ol (**4**, 1.6 g, 3.84 mmol) and 5-hexen-2-one (**9**, 753 mg, 7.68 mmol) in CH_2Cl_2 (40 mL) was added the Hoveyda−Grubbs catalyst (480 mg, 0.77 mmol), and the resulting reaction mixture was refluxed for 24 h until complete conversion of the starting material (reaction monitored by TLC analysis). The solvent was then removed under reduced pressure, and the crude residue was filtered over a short plug of silica eluting with petroleum ether/Et_2O (90/10) and concentrated under reduced pressure. To a stirred solution of the resulting disubstituted olefin (3.84 mmol) in AcOEt (10 mL) at room temperature was added 10% Pd/C (120 mg). The resulting reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature until complete conversion of the starting material (reaction monitored by TLC analysis). The crude reaction mixture was then filtered over Celite, the solvent was removed under reduced pressure, and the residue was finally purified by column chromatography (petroleum ether/Et_2O: 80/20) to afford (7*S*,8*R*,10*S*,11*S*)-10,12-bis-(*tert*-butyldimethylsilyloxy)-8-hydroxy-7,11-dimethyldodecan-2-one (**13**, 1.08 g, 64% over two steps) as a colorless oil. R_f = 0.28 (petroleum ether/Et_2O: 80/20); $[\alpha]^{20}_D$ −4.73 (*c* 1.1, $CHCl_3$); IR (neat) 3481, 2955, 2928, 2857, 1716, 1463, 1361, 1253, 1094, 1045, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (m, 1H), 3.60 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.52−3.38 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.09 (s, 3H), 1.81 (m, 1H), 1.64−1.32 (m, 8H), 1.14−0.98 (m, 2H), 0.86 (s, 9H), 0.85−0.79 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (C), 74.6 (CH), 74.1 (CH), 64.4 (CH_2), 43.7 (CH_2), 40.9 (CH), 38.9 (CH), 35.9 (CH_2), 31.8 (CH_2), 29.9 (CH_3), 26.9 (CH_2), 26.0 ($3CH_3$), 25.9 ($3CH_3$), 24.1 (CH_2), 18.3 (C), 18.0 (C), 15.0 (CH_3), 12.2 (CH_3), −4.3 (CH_3), −4.4 (CH_3), −5.3 (CH_3), −5.4 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{56}O_4NaSi_2$ $[M+Na]^+$ 511.3609, found 511.3599.

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic Acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2,4-Bis-(*tert*-butyldimethylsilyloxy)-3-methylbutyl]-2-methyl-7-oxooctyl Ester (14). To a solution of (7*S*,8*R*,10*S*,11*S*)-10,12-bis-(*tert*-butyldimethylsilyloxy)-8-hydroxy-7,11-dimethyldodecan-2-one (**13**, 1.0 g, 2.0 mmol) and L-Pro-D-Phe (**5**, 1.09 g, 2.2 mmol) in toluene (40 mL) at room temperature was added DMAP (498 mg, 4.1 mmol). The reaction mixture was then cooled to −78 °C before DIPEA (1.2 mL, 7.4 mmol) was added, followed by 2,4,6-trichlorobenzoyl chloride (0.94 mL, 6.1 mmol). The resulting slurry was slowly warmed to room temperature over 2 h, stirred for an additional 6 h at the same temperature, and quenched with a saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/AcOEt: 80/20) to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2,4-bis-(*tert*-butyldimethylsilyloxy)-3-methylbutyl]-2-methyl-7-oxooctyl ester (**14**, 1.32 g, 75%) as a viscous oil. *Mixture of rotamers:* R_f = 0.33 (petroleum ether/AcOEt: 80/20); $[\alpha]^{20}_D$ −12.9 (*c* 0.83, $CHCl_3$); IR (neat) 3294, 2954, 2927, 2856, 1716, 1642, 1449, 1250, 1187, 1099, 1040, 835, 774, 739 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.71 (d, *J* = 7.5 Hz, 2H), 7.64−7.56 (t_{app}, *J* = 8.0 Hz, 2H), 7.44−7.36 (m, 2H), 7.35−7.26 (m, 2H), 7.25−7.14 (m, 5H), 5.77 (m, 1H), 4.78 (m, 1H), 4.70 (m, 1H), 4.39 (m, 1H), 4.35−4.25 (m, 2H), 4.21 (m, 1H), 3.75 (m, 1H), 3.54−3.42 (m, 2H), 3.37 (m, 1H), 3.10 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.96 (m, 1H), 2.54 (m, 1H), 2.46−2.30 (m, 2H), 2.09 (s, 3H), 1.99−1.62 (m, 8H), 1.60−1.47 (m, 2H), 1.43−1.08 (m, 4H), 0.92 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (C), 171.2 (C), 169.6 (C), 155.5 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 136.3 (C), 129.6 (2CH), 128.4 (2CH), 127.7 (CH), 127.1 (2CH), 127.0 (2CH), 125.2 (2CH), 119.9 (2CH), 75.6 (CH), 68.2 (CH), 67.0 (CH_2), 65.8 (CH_2), 58.7 (CH), 54.1 (CH), 47.2 (CH), 46.8 (CH_2), 43.7 (CH_2), 40.4 (CH_2), 38.9 (CH), 36.3 (CH), 34.9 (CH_2), 31.8 (CH_2), 29.9 (CH_3), 29.0 (CH_2), 26.7 (CH_2), 26.0 ($3CH_3$), 25.9 ($3CH_3$), 24.4 (CH_2), 24.1 (CH_2), 18.4 (C), 18.1 (C), 14.7 (CH_3), 9.4 (CH_3), −4.0 (CH_3), −4.8 (CH_3), −5.3 (CH_3), −5.4 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{55}H_{82}O_8N_2NaSi_2$ $[M+Na]^+$ 977.5502, found 977.5500.

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic Acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-3-methylbutyl]-2-methyl-7-oxooctyl Ester (15). $SnCl_2$ (60 mg, 0.3 mmol) was added to a 6:1 EtOH/water (7 mL) mixture at room temperature. Once the reaction mixture became homogeneous, (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2,4-bis-(*tert*-butyldimethylsilyloxy)-3-methylbutyl]-2-methyl-7-oxooctyl ester (**14**, 600 mg, 0.6 mmol) was added, and the resulting reaction mixture was stirred for 2 h at room temperature. CH_2Cl_2 (10 mL) and water (4 mL) were then added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/AcOEt: 80/20) to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3-methylbutyl]-2-methyl-7-oxooctyl ester (**15**, 418 mg, 79%). *Mixture of rotamers:* R_f = 0.27 (petroleum ether/AcOEt: 70/30); $[\alpha]^{20}_D$ −14.91 (*c* 1.63, $CHCl_3$); IR (neat) 3430, 2955, 2926, 2855, 1716, 1643, 1450, 1250, 1189, 1094, 1042, 837 cm^{-1}. *Major rotamer:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.79−7.68 (d, *J* = 7.6 Hz, 2H), 7.61−7.52 (dd, *J* = 7.6 Hz, 2H), 7.39−7.31 (t_{app}, *J* = 7.6 Hz, 2H), 7.30−7.24 (t_{app}, *J* = 7.3 Hz, 2H), 7.23−7.10 (m, 5H), 5.87 (m, 1H), 4.79 (m, 1H), 4.68 (m, 1H), 4.39 (m, 1H), 4.30−4.20 (m, 2H), 4.15 (m, 1H), 3.80 (t_{app}, *J* = 8.0 Hz, 2H), 3.52−3.44 (m, 2H), 3.41 (d_{app}, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 12.7, 5.1 Hz, 1H), 2.93 (dd, *J* = 12.7, 9.6 Hz, 1H), 2.65 (m, 1H), 2.41−2.32 (m, 2H), 2.08 (s, 3H), 1.93−1.62 (m, 8H), 1.61−1.43 (m, 2H), 1.39−1.08 (m, 4H), 0.92−0.73 (m, 12H), 0.72 (d, *J* = 7.1 Hz, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.0 (C), 171.6 (C), 169.8 (C), 155.6 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 136.3 (C), 129.5 (2CH), 128.4 (2CH), 127.7 (CH), 127.1 (2CH), 127.0 (2CH), 125.2 (2CH), 119.9 (2CH), 75.5 (CH), 68.1 (CH), 67.0 (CH_2),

65.4 (CH_2), 59.1 (CH), 54.2 (CH), 47.2 (CH), 46.9 (CH_2), 43.6 (CH_2), 40.3 (CH_2), 38.2 (CH), 36.6 (CH), 34.7 (CH_2), 31.9 (CH_2), 29.6 (CH_3), 29.0 (CH_2), 26.6 (CH_2), 25.8 ($3CH_3$), 24.3 (CH_2), 23.9 (CH_2), 18.0 (C), 14.7 (CH_3), 9.2 (CH_3), −4.2 (CH_3), −4.9 (CH_3); HRMS (ESI) m/z calcd for $C_{49}H_{68}O_8N_2NaSi_1$ $[M+Na]^+$ 863.4637, found 863.4623.

(*R*)-1-[(*R*)-2-(9*H*-Fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-carboxybutyl]-2-methyl-7-oxooctyl Ester (16). To a solution of (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3-methylbutyl]-2-methyl-7-oxooctyl ester (**15**, 420 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added TEMPO (117 mg, 0.7 mmol), KBr (0.25 mL of a 0.2 M solution in water, 0.05 mmol), and NaOCl (0.26 mL of a 13% solution in water, 0.5 mmol). After the mixture was stirred for 30 min at the same temperature, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. The crude aldehyde (0.5 mmol), *t*-BuOH (25 mL), 2-methyl-2-butene (3.7 mL, 35 mmol), water (5 mL), $NaClO_2$ (337 mg, 3 mmol), and NaH_2PO_4 (180 mg, 1.5 mmol) were combined at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. *t*-BuOH was then removed under reduced pressure, and AcOEt (35 mL) was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 × 15 mL). The combined organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/acetone: 90/10) to afford (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*R*)-2-(*tert*-butyldimethylsilyloxy)-3-carboxybutyl]-2-methyl-7-oxooctyl ester (**16**, 375 mg, 90%) as a viscous oil. *Mixture of rotamers:* R_f = 0.5 (petroleum ether/acetone: 7/3); $[\alpha]^{20}_D$ −25.2 (*c* 1.2, $CHCl_3$); IR (neat) 3292, 2930, 1712, 1650, 1616, 1450, 1250, 1186, 1094, 837 cm^{-1}. *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.73 (d, J = 7.5 Hz, 2H), 7.64−7.56 (t_{app}, J = 7.5 Hz, 2H), 7.44−7.35 (m, 2H), 7.34−7.28 (m, 2H), 7.27−7.16 (m, 5H), 5.84 (m, 1H), 4.81 (m, 1H), 4.73 (m, 1H), 4.46−4.27 (m, 3H), 4.26−4.05 (m, 2H), 3.55 (m, 1H), 3.10 (dd, J = 12.7, 5.3 Hz, 1H), 2.99 (m, 1H), 2.75−2.59 (m, 2H), 2.46−2.37 (m, 2H), 2.10 (s, 3H), 2.01−1.65 (m, 6H), 1.63−1.49 (m, 3H), 1.45−1.23 (m, 4H), 1.09 (d, J = 7.0 Hz, 3H), 1.00−0.88 (m, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.2 (C), 179.2 (C), 171.4 (C), 169.8 (C), 155.6 (C), 144.0 (C), 143.8 (C), 141.3 (2C), 136.3 (C), 129.5 (2CH), 128.4 (3CH), 127.7 (2CH), 127.1 (2CH), 125.2 (2CH), 119.9 (2CH), 74.9 (CH), 69.7 (CH), 67.0 (CH_2), 58.9 (CH), 54.1 (CH), 47.2 (CH), 46.8 (CH_2), 43.6 (CH_2), 42.8 (CH_2), 40.2 (CH), 36.7 (CH), 35.1 (CH_2), 31.8 (CH_2), 29.8 (CH_3), 28.9 (CH_2), 26.6 (CH_2), 25.7 ($3CH_3$), 24.2 (CH_2), 23.9 (CH_2), 17.9 (C), 14.7 (CH_3), 8.8 (CH_3), −4.2 (CH_3), −5.0 (CH_3); HRMS (ESI) m/z calcd for $C_{49}H_{66}O_9N_2NaSi$ $[M+Na]^+$ 877.4430, found 877.4418.

(5*R*,8*R*,9*S*,11*R*,13a*R*)-5-Benzyl-9-(*tert*-butyldimethylsilyloxy)-8-methyl-11-((*S*)-1-methyl-6-oxoheptyl)-decahydro-12-oxa-3a,6-diazacyclopentacyclododecene-4,7,13-trione (17). To a solution of (*R*)-1-[(*R*)-2-(9*H*-fluoren-9-yloxycarbonylamino)-3-phenylpropionyl]-pyrrolidine-2-carboxylic acid (1*R*,2*S*)-1-[(2*S*,3*R*)-2-(*tert*-butyldimethylsilyloxy)-3-carboxybutyl]-2-methyl-7-oxooctyl ester (**16**, 360 mg, 0.4 mmol) in CH_3CN (15 mL) at room temperature was added Et_2NH (7.6 mL), and the reaction mixture was stirred at room temperature until complete conversion of the starting material (reaction monitored by TLC analysis). The solvent was then removed under reduced pressure, and the resulting crude amino acid was used in the next step without further purification. To a solution of amino acid (0.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added EDCl (153 mg, 0.8 mmol), HOBt (108 mg, 0.8 mmol), and DIPEA (0.3 mL, 1.8 mmol), and the resulting reaction mixture was stirred for 3 h at room temperature. The reaction was then quenched with a saturated aqueous NH_4Cl solution (30 mL), and the organic phase was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash chromatography (petroleum ether/acetone: 90/10) to afford (5*R*,8*R*,9*S*,11*R*,13a*R*)-5-benzyl-9-(*tert*-butyldimethylsilyloxy)-8-methyl-11-[(*S*)-1-methyl-6-oxoheptyl]-decahydro-12-oxa-3a,6-diazacyclopentacyclododecene-4,7,13-trione (**17**, 150 mg, 60%). *Mixture of rotamers:* R_f = 0.7 (petroleum ether/acetone: 70/30); $[\alpha]^{20}_D$ −28.9 (*c* 1.25, $CHCl_3$); IR (neat) 3263, 2931, 1721, 1661, 1622, 1541, 1439, 1256, 1080, 1052, 835 cm^{-1}. *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.14 (m, 5H), 5.36 (m, 1H), 5.23 (dd, J = 8.5, 3.5 Hz, 1H), 4.89 (m, 1H), 4.04 (d_{app}, J = 8.0 Hz, 1H), 3.86 (m, 1H), 3.65 (m, 1H), 3.54 (m, 1H), 3.21 (dd, J = 14.5, 4.8 Hz, 1H), 2.95 (dd, J = 14.5, 10.5 Hz, 1H), 2.43−2.34 (m, 2H), 2.21 (m, 1H), 2.14−2.02 (m, 6H), 1.91 (m, 1H), 1.70 (m, 1H), 1.59−1.42 (m, 4H), 1.39−1.12 (m, 4H), 0.96 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7 (C), 174.8 (C), 172.3 (C), 170.5 (C), 135.9 (C), 129.0 (2CH), 128.7 (2CH), 127.4 (CH), 74.6 (CH), 71.3 (CH), 60.3 (CH), 55.9 (CH), 48.0 (CH_2), 43.9 (CH), 43.5 (CH_2), 38.7 (CH), 36.2 (CH_2), 35.3 (CH_2), 33.1 (CH_2), 31.8 (CH_2), 29.8 (CH_3), 26.8 (CH_2), 25.8 ($3CH_3$), 23.8 (CH_2), 21.5 (CH_2), 17.9 (C), 17.4 (CH_3), 14.4 (CH_3), −3.8 (CH_3), −4.8 (CH_3); HRMS (ESI) m/z calcd for $C_{34}H_{54}O_6N_2SiNa$ $[M+Na]^+$ 637.3643, found 637.3627.

(5*R*,8*R*,9*S*,11*R*,13a*R*)-5-Benzyl-9-hydroxy-8-methyl-11-((*S*)-1-methyl-6-oxo-heptyl)-decahydro-12-oxa-3a,6-diazacyclopentacyclododecene-4,7,13-trione (*epi*-Acremolide B, 18). To a solution of (5*R*,8*R*,9*S*,11*R*,13a*R*)-5-benzyl-9-(*tert*-butyldimethylsilyloxy)-8-methyl-11-((*S*)-1-methyl-6-oxoheptyl)-decahydro-12-oxa-3a,6-diazacyclopentacyclododecene-4,7,13-trione (**17**, 75 mg, 0.12 mmol) in THF (4.7 mL) at 0 °C was added TBAF (0.1 mL, 0.4 mmol), and the resulting reaction mixture was stirred at the same temperature until complete conversion of the starting material (reaction monitored by TLC analysis). The solvent was then removed under reduced pressure, and the resulting crude residue was purified by flash chromatography (petroleum ether/acetone: 70/30) to afford *epi*-acremolide B (**18**) as a colorless solid (46 mg, 75%). *Mixture of rotamers:* R_f = 0.4 (petroleum ether/acetone: 70/30); $[\alpha]^{20}_D$ −65.2 (*c* 0.02, MeOH); IR (neat) 3307, 2933, 1714, 1659, 1622, 1524, 1454, 1426, 1272, 733, 700 cm^{-1}. *Major isomer:* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 7.0 Hz, 1H), 7.35−7.15 (m, 5H), 5.11 (m, 1H), 4.81 (m, 1H), 4.72 (m, 1H), 4.35 (m, 1H), 3.58−3.41 (m, 2H), 3.23 (m, 1H), 2.97 (dd, J = 14.0, 10.3 Hz, 1H), 2.85 (dd, J = 14.0, 5.3 Hz, 1H), 2.41 (t_{app}, J = 7.3 Hz, 2H), 2.21−2.12 (m, 2H), 2.07 (s, 3H), 2.03−1.94 (m, 2H), 1.89 (m, 1H), 1.58−1.38 (m, 5H), 1.32−1.14 (m, 4H), 1.00 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.4 (C), 174.6 (C), 171.3 (C), 169.9 (C), 138.0 (C), 128.9 (2CH), 128.0 (2CH), 126.3 (CH), 73.3 (CH), 69.1 (CH), 59.4 (CH), 57.3 (CH), 46.9 (CH_2), 42.7 (CH), 42.6 (CH_2), 37.2 (CH), 35.2 (CH_2), 33.5 (CH_2), 32.4 (CH_2), 31.6 (CH_2), 29.6 (CH_3), 26.0 (CH_2), 23.3 (CH_2), 20.9 (CH_2), 17.1 (CH_3), 14.0 (CH_3); HRMS (ESI) m/z calcd for $C_{28}H_{40}O_6N_2Na$ $[M+Na]^+$ 523.2779, found 523.2758.

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Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.