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TOTAL SYNTHESIS OF SPIRUCHOSTATIN A—A POTENT HISTONE DEACETYLASE INHIBITOR

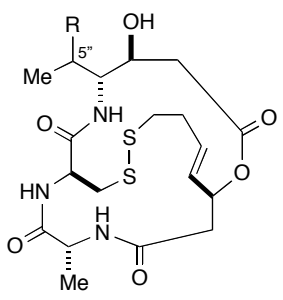
Toshiya Takizawa, Kazuhiro Watanabe, Koichi Narita, Kyosuke Kudo, Takamasa Oguchi, Hideki Abe, and Tadashi Katoh*

Laboratory of Medicinal Synthetic Chemistry, Department of Chemical Pharmaceutical Science, Tohoku Pharmaceutical University, Komatsushima, Aoba-ku, Sendai 981-8558, Japan. E-mail: katoh@tohoku-pharm.ac.jp

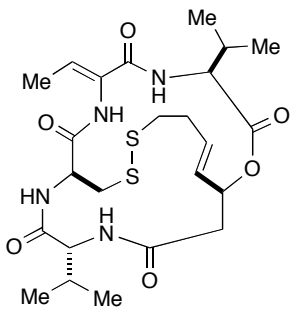
Abstract – Total synthesis of spiruchostatin A (**1**), a potent histone deacetylase inhibitor, was achieved; the method features (i) Julia–Kocienski olefination of sulfone **10** and aldehyde **11** to install the requisite (*E*)-olefin unit present in segment **6**, (ii) amide coupling of segment **5** with segment **6** to produce the key *seco*-acid **4**, and (iii) macrolactonization of **4** employing Shiina reagent to efficiently construct the desired 15-membered macrocyclic compound **32**.

INTRODUCTION

Spiruchostatins A (**1**) and B (**2**) (Figure 1), isolated from a culture broth of *Pseudomonas* sp. by Shin-ya *et al.*[1] in 2001, exhibit potent histone deacetylase (HDAC) inhibitory activity.[2] HDAC is the enzyme that catalyzes the hydrolysis of acetylated lysine residues on proteins, particularly on histones.[3] It has been



1 : spiruchostatin A (R = Me)
2 : spiruchostatin B (R = Et)



3 : FK228 (FR901228)

Figure 1. Structures of spiruchostatins A (**1**), B (**2**), and FK228 (FR901228) (**3**)

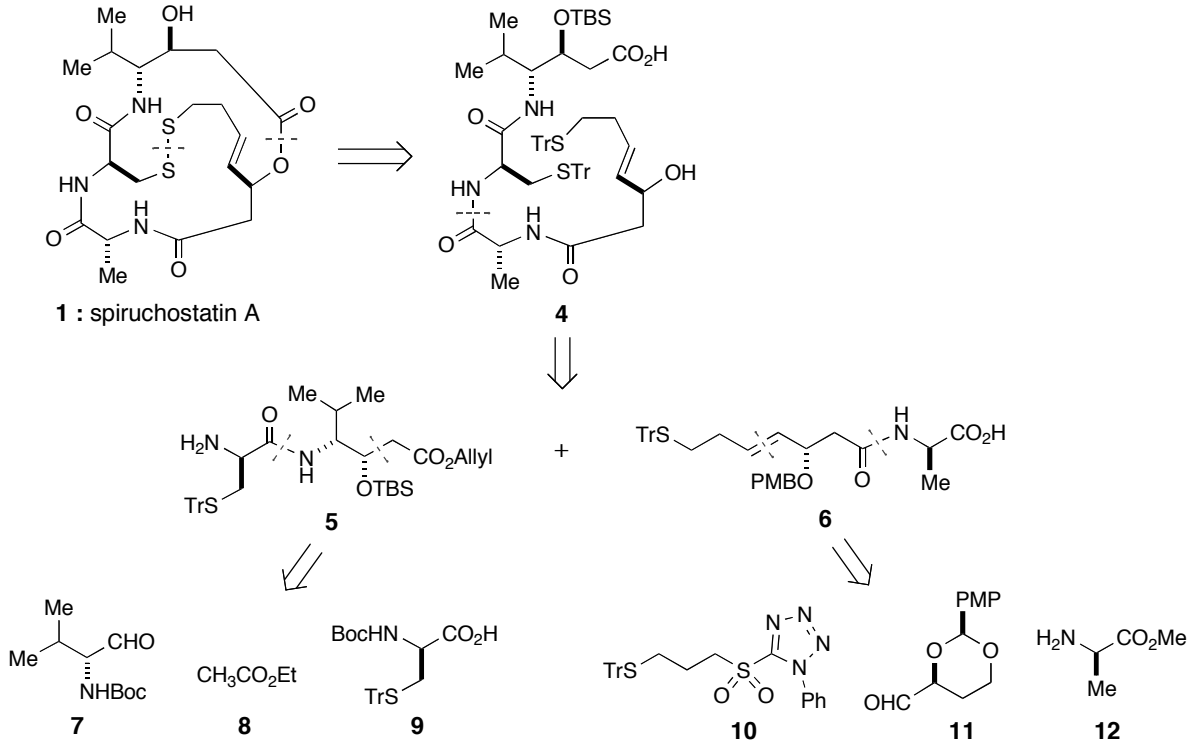
This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

reported that HDAC inhibitors can cause growth arrest in a wide range of transformed cells and can inhibit the growth of human tumor xenografts.[4] These natural products, therefore, are expected to be promising candidates for novel molecular-targeted anticancer agents. Structurally, **1** and **2** are 15-membered bicyclic depsipeptides consisting of (3*S*,4*R*)-statine, D-cysteine, D-alanine, (3*R*,4*E*)-3-hydroxy-7-mercapto-4-heptenoic acid, and characteristic disulfide bond linkage. The structurally closely related 16-membered bicyclic depsipeptide FK228 (FR901228) (**3**) is also a potent HDAC inhibitor isolated from the fermentation broth of *Chromobacterium violaceum* by Fujisawa Pharmaceutical Co. Ltd. (now Astellas Pharm Inc.).[5]

The attractive biological properties and intriguing structural features prompted us to undertake a project directed toward the total synthesis of **1**–**3**. To date, two total syntheses of **3** have been reported by Simon *et al.*[6] in 1996 and Williams *et al.*[7] in 2008, and two total syntheses of **1** have been reported by Ganesan *et al.*[8] in 2004 and Doi–Takahashi *et al.*[9] in 2006. Recently, we accomplished the first total synthesis of **2**,[10] which resulted in the establishment of the stereochemistry of **2** at C5" (spiruchostatin numbering). Herein, we report the total synthesis of **1** based on the same strategy developed in our laboratory.[10]

RESULTS AND DISCUSSION

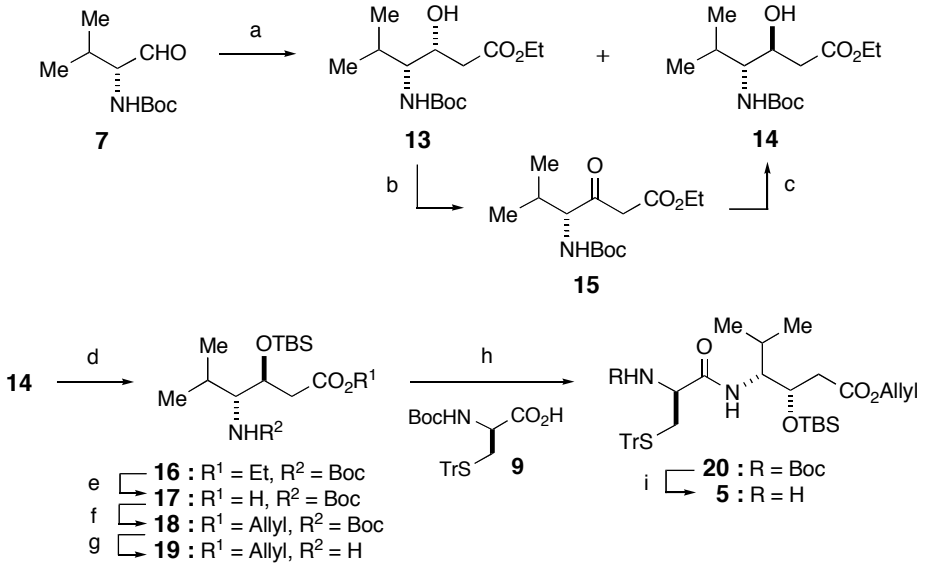
Our synthetic plan for spiruchostatin A (**1**) is outlined in Scheme 1. The targeted molecule **1** should be synthesized by macrolactonization of *seco*-acid **4** followed by a disulfide bond formation according to the



Scheme 1. Synthetic plan for spiruchostatin A (**1**). TBS = *tert*-butyldimethylsilyl, Tr (trityl) = triphenylmethyl, Boc = *tert*-butoxycarbonyl, PMB = 4-methoxybenzyl, PMP = 4-methoxyphenyl.

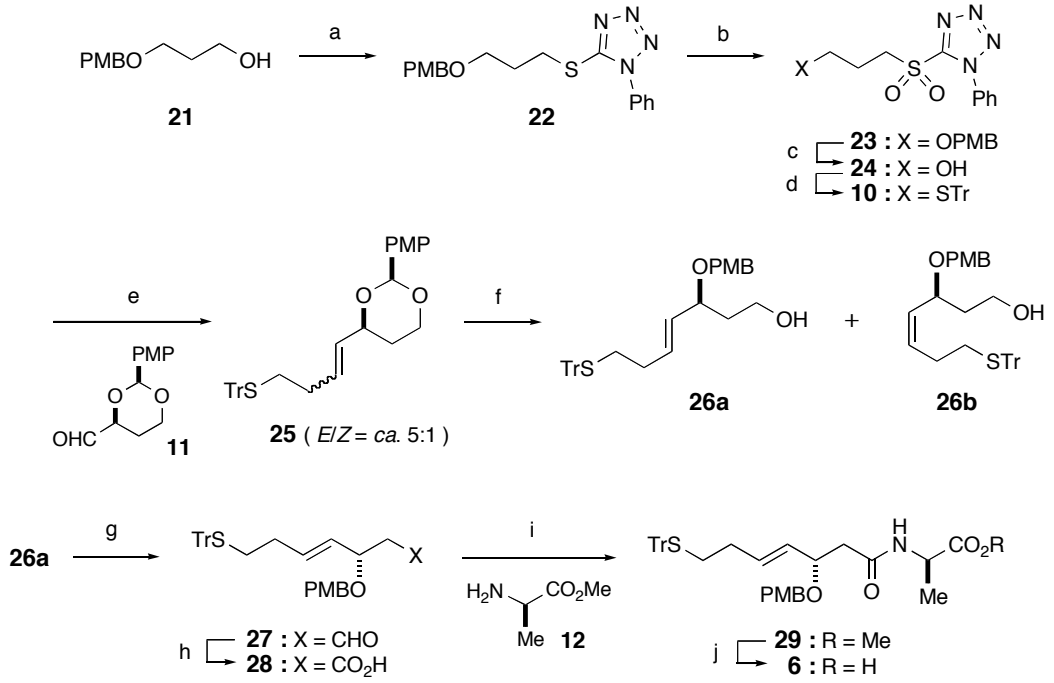
protocols reported previously.[8,9] The key feature of this scheme is expected to be a highly convergent assembly of **4** by direct coupling of segment **5** and segment **6** via amide bond formation. Segment **5** would be prepared via an aldol coupling of *N*-Boc-D-valinal (**7**)[11] with ethyl acetate (**8**) and subsequent condensation with D-cysteine derivative **9**.[12] On the other hand, segment **6** would be produced via Julia–Kocienski olefination[13] of sulfone **10** accessible from 1,3-propanediol with aldehyde **11**[14] available from L-malic acid, and subsequent condensation with D-alanine methyl ester (**12**).

We initially pursued the synthesis of segment **5** shown in Scheme 2. Aldol coupling of the known *N*-Boc-D-valinal (**7**)[11] with the lithium enolate of ethyl acetate (**8**) provided the desired coupling product **14** (30%) and the undesired stereoisomer **13** (63%). Conversion of **13** to **14** by inversion of the hydroxy group was then investigated; the sequence involved Jones oxidation[15] and subsequent stereoselective reduction of the resulting ketone **15**. After several experiments, the best result was obtained using KBH_4 at –40°C, which provided the desired product **14** with an 82% yield and high stereoselectivity (**14**/**13** = 16:1). When $LiBH_4$ or $NaBH_4$ was used as a reducing agent, a lower stereoselectivity of **14**/**13** was observed (4:1 to 7:1). To continue the synthesis, ethyl ester **14** was then transformed to allyl ester **19** via a four-step operation involving protection of the hydroxy group in **14** (84%), saponification of the ester moiety in the resulting TBS ether **16** (82%), formation of an allyl ester from the liberated carboxylic acid **17** (91%), and deprotection of the *N*-Boc group in **18** (90%). Condensation of amine **19** with *N*-Boc-*S*-trityl-L-cysteine (**9**)[12] furnished the desired coupling product **20** with an 88% yield. Finally, deprotection of the *N*-Boc group in **20** afforded the requisite segment **5** with a quantitative yield.

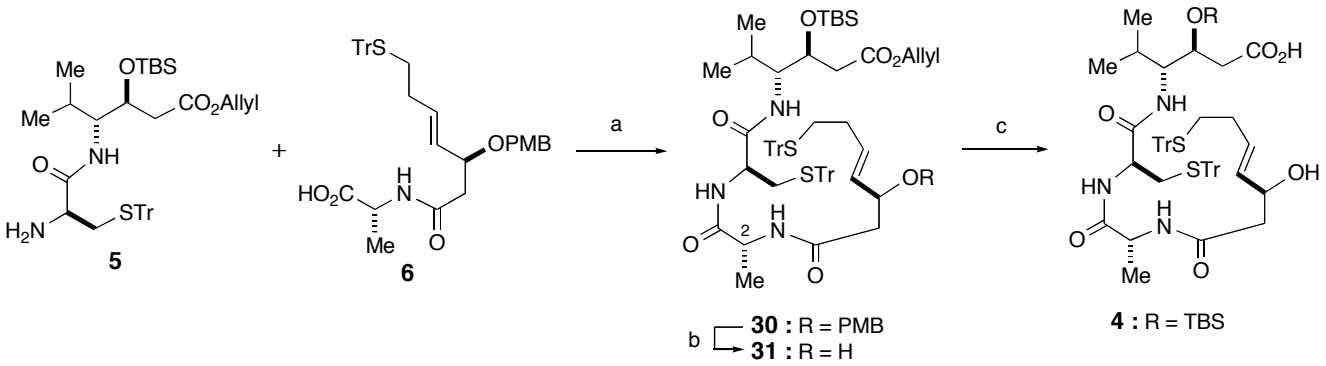


Scheme 2. Synthesis of segment **5**. *Reagents and conditions*: (a) LDA, $MeCO_2Et$ (**8**), THF, –78˚C; at –78˚C, add. **7**, 63% for **13**, 30% for **14** (**13**/**14** = *ca*. 2:1); (b) Jones reagent, acetone, 0˚C to rt, 80%; (c) KBH_4, MeOH, –40˚C, 82% for **14**, 6% for **13** (**14**/**13** = 16:1); (d) TBSCl, imidazole, DMF, rt, 84%; (e) 1 M NaOH, EtOH, rt, 82%; (f) allyl bromide, K_2CO_3, DMF, rt, 91%; (g) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt; MeOH, rt, 90%; (h) **9**, PyBOP, *i*-Pr_2NEt, MeCN, rt, 88%; (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 99%. LDA = lithium diisopropylamide, TMSOTf = trimethylsilyl trifluoromethanesulfonate, PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

We next synthesized segment **6**, the coupling partner of **5**, as shown in Scheme 3. Sulfone **10**, a substrate for the crucial Julia–Kocienski olefination,[13] was prepared with high efficiency from the known 3-(4-methoxybenzyloxy)propan-1-ol (**21**)[16] via a four-step sequence involving formation of the *S*-tetrazole **22** under Mitsunobu conditions[17] (95%), Molybdenum-mediated oxidation[18] of **22**, deprotection of the PMB group in sulfone **23** (94% in two steps), and substitution of the primary hydroxy group in **24** with a *S*-trityl group under Mitsunobu conditions[17] (96%). The crucial Julia–Kocienski olefination of **10** with the known aldehyde **11**,[14] readily prepared from L-malic acid, proceeded smoothly to form the desired coupling product **25** as an inseparable mixture of *E*/*Z*-stereoisomers (*E*/*Z* = 5:1 at 400 MHz ^{1}H NMR) in 66% yield. Reductive acetal opening of the *E*/*Z*-mixture **25** with DIBAL[19] at 0°C produced the desired *E*-olefinic primary alcohol **26a** as a major product (60%) along with the undesired *Z*-olefinic isomer **26b** (12%); at this stage, the *E*/*Z*-isomers could be separated by silica gel column chromatography. Dess–Martin oxidation[20] of **26a** followed by Pinnick oxidation[21] of the resulting aldehyde **27** produced the corresponding carboxylic acid **28** with a 66% yield in two steps. Compound **28** was finally converted to the requisite segment **6** (88% overall yield) by condensation with D-alanine methyl ester (**12**) followed by saponification of the methyl ester moiety of the resulting amide **29**.



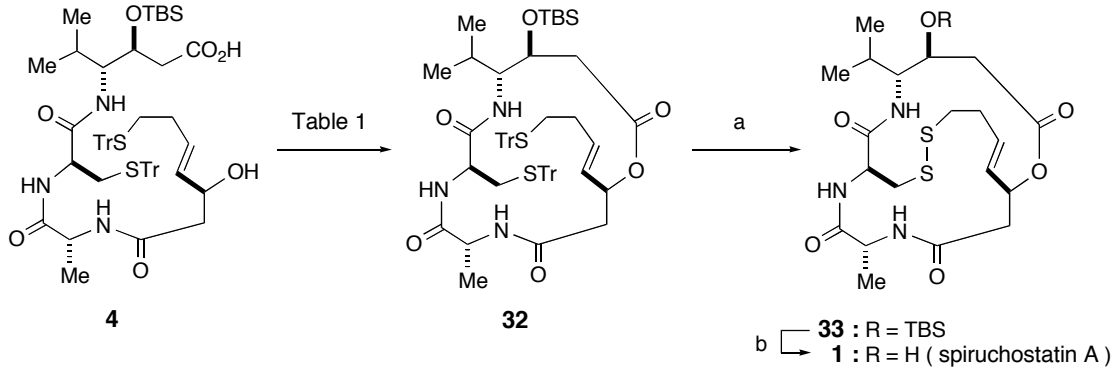
Scheme 3. Synthesis of segment **6**. *Reagents and conditions*: (a) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, rt, 95%; (b) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, 30% H_2O_2, EtOH, rt; (c) DDQ, CH_2Cl_2/H_2O, rt, 94% (2 steps); (d) TrSH, DEAD, PPh_3, CH_2Cl_2, reflux, 96%; (e) $LiN(SiMe_3)_2$, DMF, –60˚C; at –60˚C, add. **11**, –60 to 0˚C, 66% (*E*/*Z* = *ca.* 5:1); (f) DIBAL, toluene, 0˚C, 60% for **26a**, 12% for **26b**; (g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0˚C to rt, 88%; (h) $NaClO_2$, NaH_2PO_4, DMSO/H_2O, 0˚C to rt, 75%; (i) D-alanine methyl ester (**12**), PyBOP, *i*-Pr_2NEt, MeCN, 0˚C to rt, 90%; (j) 1 M LiOH, MeOH, rt, 98%. DEAD = diethyl azodicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL = diisobutylaluminium hydride.



Scheme 4. Synthesis of *seco*-acid **4**. *Reagents and conditions*: (a) HATU, HOAt, *i*-Pr_2NEt, CH_2Cl_2, –30°C, 94%; (b) DDQ, CH_2Cl_2/H_2O, rt, 89%; (c) $Pd(PPh_3)_4$, morpholine, THF, rt, 99%; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole,

After thus synthesizing the requisite segments **5** and **6**, we investigated the synthesis of *seco*-acid **4**, a substrate for the following crucial macrolactonization, by assembling the two segments as shown in Scheme 4. Initial attempts to achieve the pivotal amide coupling of **5** with **6** under conventional conditions[22] (e.g., PyBOP, EDCI/HOBt, or HATU, rt) resulted in failure; considerable epimerization was observed at the C2 stereogenic center (D-alanine part in **30**), while the coupling product **30** was produced with a good yield (~ 80%). After several experiments, we solved this epimerization problem using a combination of HATU and HOAt at low temperature. Treatment of **5** and **6** with HATU (1.3 equiv) and HOAt (1.3 equiv) in the presence of *i*-Pr_2NEt (2.5 equiv) in CH_2Cl_2 at –30°C for 2 h produced the desired coupling product **30** with a 94% yield without appreciable epimerization at C2. The coupling product **30** was then converted to the requisite *seco*-acid **4** with an overall yield of 88% via alcohol **31** by successive removal of both the PMB and allyl protecting groups.

Having synthesized *seco*-acid **4** in a highly convergent manner, the stage was set for the crucial macrolactonization event. In the previous two total syntheses of spiruchostatin A (**1**), Ganesan *et al.* successfully achieved macrolactonization of the *O*-triisopropylsilyl (TIPS) variant of **4** (R = TIPS) by the Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et_3N, MeCN/THF, 0 – 20°C; DMAP, toluene, 50°C, 53%);[8] furthermore, Doi–Takahashi *et al.* efficiently performed macrolactonization of the *O*-non-protected variant of **4** (R = H) by the Shiina method [2-methyl-6-nitrobenzoic anhydride (MNBA), DMAP, CH_2Cl_2, rt, 67%].[9] Given these results, we investigated macrolactonization of **4** under different conditions as shown in Scheme 5 (**4** → **32** in Scheme 5) and Table 1. As expected, the best result was obtained with the Shiina method[23] (entry 1). Thus, treatment of a dilute solution of **4** in CH_2Cl_2 (1.0 mM) with MNBA (1.3 equiv) and DMAP (3.0 equiv) at room temperature for 15 h produced the desired macrocyclic compound **32** with an 89% yield (entry 1). When macrolactonization was performed as per the Yamaguchi method[24] (entry 2) or the Mukaiyama–Corey–Nicolaou method[25] (entry 3), the yield of **32**



Scheme 5. Synthesis of spiruchostatin A (**1**) via the critical macrolactonization. *Reagents and conditions*: (a) I_2, MeOH/CH_2Cl_2, rt, 80%; (b) HF·pyridine, pyridine, rt, 92%.

Table 1. Macrolactonization of *seco*-acid **4** producing to macrocyclic compound **32**.

Entry	Reagents and Conditions	Yield of **32** [%]
1[a]	MNBA (1.3 equiv), DMAP (3.0 equiv), CH_2Cl_2, rt, 15 h	89
2[b]	2,4,6-trichlorobenzoyl chloride (5.0 equiv), Et_3N (5.0 equiv), THF, 0°C to rt; DMAP (3.0 equiv), toluene, 60°C, 16 h	67
3[c]	2,2-dipyridyl disulfide (3.0 equiv), Ph_3P (1.5 equiv), toluene, 80°C, 10 h	36

[a] Shiina method. [b] Yamaguchi method. [c] Mukaiyama–Corey–Nicolaou method.

was relatively lower (67% and 36%, respectively). Ultimately, simultaneous *S*-Tr deprotection and disulfide bond formation of **32** (80%) by brief exposure to iodine in dilute MeOH solution (0.5 mM) at ambient temperature[6–10,26] and subsequent deprotection of the TBS group of the resulting disulfide **33** (92%) with HF·pyridine, resulted in the completion of the total synthesis of spiruchostatin A (**1**), $[\alpha]_D^{24}$ –61.1 (c = 0.14, MeOH) {lit.[1] $[\alpha]_D$ –63.6 (c = 0.14, MeOH)}. The spectroscopic properties (IR, ^{1}H and ^{13}C NMR, and MS) of the synthetic sample **1** were identical with those reported for natural **1**.

CONCLUSION

We accomplished a total synthesis of spiruchostatin A (**1**) in a convergent manner starting from *N*-Boc-D-valinal (**7**), aldehyde **11** derived from L-malic acid, and sulfone **10** arising from 1,3-propanediol. The key elements of the synthesis are (i) Julia–Kocienski olefination of sulfone **10** and aldehyde **11** to install the requisite (*E*)-olefin unit present in the critical segment **6**, (ii) condensation of segment **5** with segment **6** under mild conditions to directly assemble the crucial *seco*-acid **4**, and (iii) macrolactonization of **4** using Shiina reagent (MNBA) to efficiently construct the desired 15-membered macrocyclic compound **32**. The explored synthetic route has a potential for producing various structural types of spiruchostatin analogs due to its generality and flexibility. These efforts are currently under way.

EXPERIMENTAL

General Procedures: All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated. All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran (THF) and Et_2O were freshly distilled from Na metal/benzophenone under argon. Toluene was distilled from Na metal under argon. *N*,*N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), CH_2Cl_2, MeCN, pyridine, and *N*,*N*-diisopropylamine were distilled from calcium hydride under argon. Measurements of optical rotations were performed with a JASCO DIP-370 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si ($\delta = 0$) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), sextet (sext), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and High-resolution mass (HRMS) spectra were measured on a JEOL JMS-DX 303/JMA-DA 5000 SYSTEM high resolution mass spectrometer.

(3*R*,4*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-3-hydroxy-5-methylhexanoate (13) and its (3*S*,4*R*)-isomer (14): A solution of EtOAc (**8**) (8.3 mL, 87 mmol) in THF (10 mL) was added slowly to a stirred solution of lithium diisopropylamide (LDA) (19 mmol) [prepared from *n*-BuLi in hexane (1.6 M solution, 54.4 mL, 87 mmol) and *i*-Pr_2NH (12.8 mL, 91 mmol)] in dry THF (50 mL) at –78°C. After 30 min, (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutylaldehyde (**7**)[11] (3.50 g, 17 mmol) in THF (50 mL) was added to the above mixture at –78°C. After 40 min, the reaction was quenched with 2 M HCl (20 mL) at –78°C, and the resulting mixture was extracted with AcOEt (2 x 80 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 40 mL) and brine (2 x 40 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 5:1→4:1) to **13** (3.17 g, 63%, less polar) and **14** (1.51 g, 30%, more polar).

13: colorless oil, $[\alpha]_D^{25}$ +43.8° (*c* 1.00, $CHCl_3$); IR (neat): 3363, 2967, 1696, 1526, 1466, 1391, 1173, 1071, 1038, 986, 868, 758, 611, 467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.28 (3H, t, *J* = 7.1 Hz), 1.44 (9H, s), 1.83–1.91 (1H, m), 2.45 (1H, A part of ABX, *J* = 2.7, 16.7 Hz), 2.55 (1H, B part of ABX, *J* = 9.8, 16.7 Hz), 3.15 (1H, t, *J* = 9.5 Hz), 3.39 (1H, d, *J* = 2.9 Hz), 4.16 and 4.19 (2H, ABq, *J* = 7.3 Hz), 4.24–4.28 (1H, m), 4.91 (1H, d, *J* = 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.5, 19.7, 28.3 (3C), 30.3, 39.1, 59.6, 60.8, 67.0, 79.0, 156.4, 173.6; HRMS (EI) calcd for $C_{14}H_{27}NO_5$ (M^+), 289.1889, found 289.1884.
14: colorless oil, $[\alpha]_D^{25}$ –9.0° (*c* 1.02, $CHCl_3$); IR (neat): 3445, 2978, 2876, 2361, 1715, 1505, 1367, 1175, 1024, 951, 916, 870, 758, 666, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 6.8 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 1.28 (3H, t, *J* = 7.1 Hz), 1.44 (9H, s), 2.09–2.17 (1H, m), 2.47 (1H, A part of ABX, *J* = 2.9, 16.6 Hz), 2.59 (1H, B part of ABX, *J* = 9.3, 16.6 Hz), 3.34 (1H, d, *J* = 4.9 Hz), 3.50–3.56 (1H, m), 3.90–3.96 (1H, m), 4.14–4.21 (2H, m), 4.45 (1H, br d, *J* = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 16.2, 20.1, 27.5, 28.3 (3C), 38.4, 58.7, 60.8,

69.2, 79.5, 156.4, 173.2; HRMS (EI) calcd for $C_{14}H_{27}NO_5$ (M^+), 289.1889, found 289.1903.

(*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-5-methyl-3-oxohexanoate (15): 2.6 M Jones reagent (5.99 mL, 15 mmol) was added dropwise to a stirred solution of **13** (3.00 g, 10 mmol) in acetone (80 mL) at 0°C. After stirring was continued at rt for 1 h, the mixture was diluted with Et_2O (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 80 mL) and brine (2 x 80 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 8:1→4:1) to give **15** (2.38g, 80%) as a colorless oil. $[\alpha]_D^{25}$ –16.5° (*c* 1.09, $CHCl_3$); IR (neat): 2974, 2936, 2878, 1715, 1653, 1505, 1393, 1368, 1314, 1242, 1173, 1034, 872, 779, 654, 594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, d, *J* = 0.9 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 1.28 (3H, t, *J* = 7.2 Hz), 1.45 (9H, s), 2.24 (1H, m), 3.53 (2H, s), 4.18 (1H, d, *J* = 7.1 Hz), 4.21 (1H, d, *J* = 7.1 Hz), 4.33 (1H, dd, *J* = 4.1, 8.9 Hz), 5.67 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.6, 28.1 (3 C), 29.4, 47.0, 61.3, 64.2, 79.8, 89.7, 155.7, 166.6, 202.1; HRMS (EI) calcd for $C_{14}H_{25}NO_5$ (M^+), 287.1733, found 287.1744.

Stereoselective reduction of 15 leading to 14: KBH_4 (1.94 g, 36 mmol) was added in small portions to a stirred solution of **15** (2.06 g, 7.2 mmol) in MeOH (70 mL) at –40°C. After 5 h, the reaction was quenched with 10% aqueous citric acid at 0°C (adjusted pH 3). After concentration of the solvent *in vacuo*, water (30 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (4 x 30 mL). The combined extracts were washed with brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 5:1→4:1) to give **14** (1.70 g, 82%) along with **13** (124 mg, 6%). The IR, ^1H and ^{13}C NMR, mass spectra of these samples were identical with those recorded for **13** and **14**.

(3*S*,4*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsiloxy)-5-methylhexanoate (16): *tert*-Butyldimethylsilyl chloride (TBSCl) (1.04 g, 6.9 mmol) was added to stirred solution of **14** (665 mg, 2.3 mmol) in DMF (10 mL) containing imidazole (940 mg, 14 mmol) at rt. After 24 h, the reaction mixture was diluted with Et_2O (120 mL), and the organic layer was washed successively with 3% aqueous HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 10:1→5:1) to give **16** (779 mg, 84%) as a colorless oil. $[\alpha]_D^{25}$ +3.0° (*c* 1.01, $CHCl_3$); IR (neat): 3389, 2961, 2361, 2340, 1559, 1507, 1474, 1175, 1084, 774, 434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0,09 (3H, s), 0.87–0.88 (12H, m), 0.92 (3H, d, *J* = 6.8 Hz), 1.27 (3H, t, *J* = 7.3 Hz), 1.43 (9H, s), 1.93–1.99 (1H, m), 2.44 (1H, A part of ABX, *J* = 6.3, 15.6 Hz), 2.53 (1H, B part of ABX, *J* = 5.4, 15.6 Hz), 3.47–3.53 (1H, m), 4.07–4.22 (3H, m), 4.46 (1H, br d, *J* = 10.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.9, –4.7, 14.1, 16.8, 17.9, 20.5, 25.7 (3C), 27.9, 28.4 (3C), 40.0, 59.5, 60.5, 70.1, 78.9, 155.9, 171.8; HRMS (EI) calcd for $C_{20}H_{41}NO_5Si$ (M^+), 403.2754, found 403.2750.

(3*S*,4*R*)-Allyl 4-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsiloxy)-5-methylhexanoate (18): 1 M NaOH (30.0 mL, 30 mmol) was added dropwise to a stirred solution of **16** (2.42 g, 6.0 mmol) in EtOH (60 mL) at rt. After 6 h, the reaction was diluted with 10% aqueous HCl (50 mL) at 0°C, and the resulting mixture was extracted with EtOAc (3 x 60 mL). The combined extracts were washed with brine (2 x 40 mL), then dried over Na_2SO_4.

Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 10:1→2:1) to give **17** (1.85 g, 82%) as a white amorphous solid.

Allyl bromide (0.72 mL, 8.6 mmol) was added to a stirred solution of **17** (1.85 g, 4.9 mmol) in DMF (50 mL) containing K_2CO_3 (2.06 g, 15 mmol) at rt. After 6 h, the reaction was diluted with water (20 mL) at rt, and the resulting mixture was extracted with Et_2O (4 x 40 mL). The combined extracts were washed successively with 3% aqueous HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 5:1) to give **18** (1.86 g, 91%) as a pale yellow oil. $[\alpha]_D^{25}$ +4.1° (*c* 1.03, $CHCl_3$); IR (neat): 3370, 2931, 1720, 1703, 1501, 1255, 1083, 990, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.10 (3H, s), 0.87–0.88 (12H, m), 0.93 (3H, d, *J* = 6.8 Hz), 1.43 (9H, s), 1.91–2.00 (1H, m), 2.48 (1H, dd, *J* = 6.8, 15.6 Hz), 2.57 (1H, dd, *J* = 5.8, 15.6 Hz), 3.51 (1H, ddd, *J* = 4.4, 6.3, 10.7 Hz), 4.21 (1H, dd, *J* = 6.3, 12.2 Hz), 4.44 (1H, d, *J* = 10.1 Hz), 4.56 (1H, A part of ABX, *J* = 1.5, 1.5, 5.9, 13.1 Hz) 4.60 (1H, B part of ABX, *J* = 1.0, 1.5, 5.9, 13.1 Hz), 5.24 (1H, ddd, *J* = 1.5, 2.9, 10.7 Hz), 5.33 (1H, ddd, *J* = 1.5, 2.9, 17.1 Hz), 5.88–5.97 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.9, –4.7, 16.7, 17.9, 20.5, 25.7 (3C), 27.9, 28.4 (3C), 40.0, 59.5, 65.3, 70.1, 79.0, 118.5, 132.0, 155.9, 171.5; HRMS (EI) calcd for $C_{21}H_{41}NO_5Si$ (M^+), 415.2754, found 415. 2758.

(3*S*,4*R*)-Allyl 4-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-(tritylthio)propanamido]-3-(*tert*-butyldimethylsiloxy)-5-methylhexanoate (20): Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.87 mL, 4.8 mmol) was added to a stirred solution of **18** (260 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) in the presence of 2,6-lutidine (0.70 mL, 6.0 mmol) at rt. After 30 min, MeOH (2.0 mL) was added to the reaction mixture at 0°C. After stirring at rt for 3 h, the reaction mixture was concentrated *in vacuo* to afford **19** (178 mg, 90%) as a colorless oil. This material was immediately used for the next reaction due to its instability (prone to form a γ-lactam ring).

N,*N*-Diisopropylethylamine (0.25 mL, 1.5 mmol) was added dropwise to a stirred solution of the crude amine **19** (178 mg, 0.57 mmol) and *N*-Boc-*S*-trityl-L-cysteine (**9**)[12] (314 mg, 0.68 mmol) in MeCN (10 mL) containing (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (382 mg, 0.73 mmol) at rt under argon. After 3 h, the mixture was diluted with Et_2O (80 mL), and the organic layer was washed successively with 3% aqueous HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* to afford a residue, which was purified by column chromatography (hexane/EtOAc, 1:1) to give **20** (378 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ +3.5° (*c* 1.03, $CHCl_3$); IR (neat): 3325, 2960, 2856, 1735, 1690, 1522, 1171, 1094, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.01 (3H, s), 0.06 (3H, s), 0.79–0.85 (15H, m), 1.77 (9H, s), 1.94–2.01 (1H, m), 2.42 (1H, dd, *J* = 6.8, 15.6 Hz), 2.51–2.56 (2H, m), 2.71 (1H, dd, *J* = 7.3, 13.2 Hz), 3.73–3.83 (2H, m), 3.80–3.86 (1H, m), 4.11–4.16 (1H, m), 4.46–4.56 (2H, m), 4.71 (1H, br d, *J* = 6.8 Hz), 5.21 (1H, dd, *J* = 1.0, 10.7 Hz), 5.29 (1H, dd, *J* = 1.5, 16.1 Hz), 5.82–5.92 (1H, m), 6.08 (1H, br d, *J* = 9.8 Hz), 7.19–7.43 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8, –4.6, 16.5, 17.9, 20.4, 25.7 (3C), 27.7, 28.2 (3C), 33.0, 39.9, 53.7, 57.9, 65.3, 67.2, 69.8, 80.2, 118.4, 126.8 (3C), 128.0 (6C), 129.6 (6C), 132.0, 144.5 (3C), 155.5, 170.6, 171.4; HRMS (EI) calcd for $C_{43}H_{61}N_2O_6SSi$ (M^++1), 761.4019, found 761.4037.

(3*S*,4*R*)-Allyl 4-[(*S*)-2-amino-3-(tritylthio)propanamido]-3-(*tert*-butyldimethylsiloxy)-5-methylhexanoate (5): Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.20 mL, 6.6 mmol) was added dropwise to a stirred solution

of **20** (630 mg, 0.83 mmol) in CH_2Cl_2 (18 mL) containing 2,6-lutidine (0.96 mL, 8.3 mmol) at rt. After 1 h, MeOH (2.0 mL) was added to the reaction mixture at 0°C. After 1 h, the mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane/EtOAc, 5:1) to give **5** (542 mg, 99%) as a white amorphous solid. $[\alpha]_D^{25}$ +1.6° (*c* 1.01, $CHCl_3$); IR (neat): 3365, 2929, 2856, 1753, 1673, 1509, 1255, 1174, 1092, 777, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.06 (3H, s), 0.08–0.88 (15H, m), 1.22 (2H, br s), 1.94–2.02 (1H, m), 2.43 (1H, dd, *J* = 6.3, 16.1 Hz), 2.50–2.57 (2H, m), 2.73 (1H, dd, *J* = 3.4, 12.7), 3.07 (1H, dd, *J* = 3.4, 8.3 Hz), 3.77 (1H, ddd, *J* = 4.4, 6.3, 10.7 Hz), 4.16 (1H, dt, *J* = 5.9, 6.3 Hz), 4.52 (2H, d, *J* = 5.9 Hz), 5.22 (1H, dd, *J* = 1.0, 9.3 Hz), 5.29 (1H, dd, *J* = 1.0, 16.8 Hz), 5.83–5.93 (1H, m), 7.17–7.45 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ–4.9, –4.6, 16.6, 17.9, 20.6, 25.7 (3C), 27.6, 37.3, 40.2, 53.9, 57.7, 65.1, 66.9, 69.9, 118.4, 126.7 (3C), 127.9 (6C), 129.5 (6C), 131.9, 144.6 (3C), 171.3, 172.8; HRMS (FAB$^+$) calcd for $C_{38}H_{53}N_2O_4SSi$ (M^++1), 661.3466, found 661.3478.

5-[3-(4-Methoxybenzyloxy)propylthio]-1-phenyl-1*H*-tetrazole (22): Diethyl azodicarboxylate (DEAD) in toluene (2.2 M in solution, 23.4 mL, 52 mmol) was added dropwise to a stirred solution of 3-(4-methoxybenzyloxy)propan-1-ol (**21**)[16] (9.18 g, 47 mmol) in THF (500 mL) containing Ph_3P (13.5 g, 52 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (9.17 g, 52 mmol) at rt under argon. After 5 h, the reaction mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane/EtOAc, 2:1) to give **22** (15.8 g, 95%) as a white amorphous solid. IR (KBr): 2857, 2546, 2347, 1596, 761, 694, 636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (2H, ddd, *J* = 5.8, 6.9, 13.2 Hz), 3.49 (2H, t, *J* = 6.9 Hz), 3.58 (2H, t, *J* = 5.8 Hz), 3.79 (3H, s), 4.43 (2H, s), 6.85–6.88 (2H, m), 7.23–7.26 (2H, m), 7.52–7.59 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 30.3, 55.2, 67.6, 72.6, 113.8, 123.8, 129.3 (3C), 129.7 (3C), 130.0, 130.2, 133.7, 154.3, 159.2; HRMS (EI) calcd for $C_{18}H_{20}N_4O_2S$ (M^+), 356.1307, found 356.1320.

1-Phenyl-5-[3-(tritylthio)propylsulfonyl]-1*H*-tetrazole (10): Hexaammonium heptamolybdate tetrahydrate $[Mo_7O_{24}(NH_4)_6{\cdot}4H_2O]$ (1.08 g, 0.87 mmol) in 30% aqueous H_2O_2 (9.38 mL, 83 mmol)] was added dropwise to a stirred solution of **22** (3.10 g, 8.7 mmol) in EtOH (90 mL) at 0°C, and the mixture was allowed to warm up to rt. After 18 h, the reaction was diluted with water (20 mL) at rt, and the resulting mixture was extracted with EtOAc (3 x 80 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (3 x 40 mL) and brine (2 x 40 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by short-pass column chromatography (hexane/EtOAc, 3:1) to give **23** (3.30 g), which was used for the next reaction without further purification.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (3.86 g, 17 mmol) was added in small portions to a stirred solution of **23** (3.30 g, 8.5 mmol) in CH_2Cl_2/H_2O 9:1 (150 mL) at rt. After 3 h, the mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 40 mL) and brine (2 x 40 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 2:1) to give **24** (2.33 g, 94%, two steps) as a colorless oil.

Diethyl azodicarboxylate (DEAD) in toluene (2.2 M in solution, 0.68 mL, 1.5 mmol) was added dropwise to a stirred solution of **24** (200 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) containing Ph_3P (391 mg, 1.5 mmol) and triphenylmethyl thiol (412 mg, 1.5 mmol) at rt under argon. The mixture was heated at reflux for 7 h under argon.

After cooling, the reaction mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane/EtOAc, 6:1) to give **10** (377 mg, 96%) as a white solid. Recrystallization from hexane/AcOEt afforded white needles, mp 117–119ºC. IR (KBr): 2360, 1593, 1339, 761, 744, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–1.89 (2H, m), 2.39 (2H, t, *J* = 6.8 Hz), 3.56 (2H, dd, *J* = 5.4, 10.2 Hz), 7.18–7.65 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 30.0, 54.9, 67.2, 125.1, 126.9 (3C), 128.0 (6C), 129.5 (6C), 129.7 (3C), 131.4, 132.9, 144.4 (3C), 153.3; HRMS (FAB$^+$) calcd for $C_{29}H_{27}N_4O_2S_2$ (M^++1), 527.1575, found 527.1578.

(2*S*,4*S*)-2-(4-Methoxyphenyl)-4-[(*E*/*Z*)-4-(tritylthio)but-1-enyl]-1,3-dioxane (25): Lithium bis(trimethylsilyl)-amide in THF (1.0 M solution, 8.90 mL, 8.9 mmol) was added dropwise to a stirred solution of **10** (4.26 g, 8.1 mmol) and (4*S*)-2-(4-methoxyphenyl)-1,3-dioxane-4-carbaldehyde (**11**)[14] (2.68 g, 12 mmol) in DMF (200 mL) at –60°C under argon. After 2 h, the mixture was gradually warmed up to 0°C over 2 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) at 0°C. The resulting mixture was extracted with Et_2O (3 x 150 mL), and the combined extracts were washed with brine (2 x 100 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 6:1) to give **25** (2.79 g, 66%) as a mixture of olefinic isomers (*E*/*Z* = 5:1) as a colorless oil. IR (neat): 2955, 2849, 2025, 1954, 1615, 1372, 1302, 747, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (1H, t, *J* = 12.1 Hz), 1.81–1.91 (1H, m), 2.09 (2H, t, *J* = 6.8 Hz), 2.19 (2H, d, *J* = 6.8 Hz), 3.78 (3H, s), 3.93 (1H, dt, *J* = 2.4, 12.1 Hz), 4.21–4.26 (2H, m), 5.45–5.50 (1H, m), 5.61 (1H, t, *J* = 6.8 Hz), 6.85 (1H, dd, *J* = 1.9, 4.8 Hz), 7.17–7.44 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.3, 55.3, 66.9, 77.3, 101.2, 113.5, 126.5 (3C), 127.4 (3C), 127.8 (7C), 129.6 (9C), 130.3, 131.1, 144.9 (3C), 159.9; HRMS (FAB$^+$) calcd for $C_{34}H_{35}O_3S$ (M^++1), 523.2306, found 523.2327.

(*S*,*E*)-3-(4-Methoxybenzyloxy)-7-(tritylthio)hept-4-en-1-ol (26a) and its (*S*,*Z*)-isomer (26b): Diisobutylaluminum hydride (DIBAL) in toluene (1.0 M solution, 6.74 mL, 6.7 mmol) was added dropwise to a stirred solution of **25** (*E*/Z = 5:1) (1.53 g, 2.9 mmol) in toluene (40 mL) at 0°C under argon. After 5 h, the reaction mixture was quenched with 10% aqueous NaOH (10 mL) at 0°C. The resulting mixture was extracted with Et_2O (3 x 60 mL), and the combined extracts were washed with brine (3 x 40 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 3:1) to give **26a** (921 mg, 60%, more polar) and **26b** (184 mg, 12%, less polar).

26a: colorless oil, $[\alpha]_D^{25}$ –33.1° (*c* 1.02, $CHCl_3$); IR (neat): 3418, 1666, 1612, 1034, 972, 767, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.66–1.74 (1H, m), 1.78–1.86 (1H, m), 2.14 (2H, t, *J* = 6.8 Hz), 2.22 (2H, d, *J* = 6.8 Hz), 3.66–3.76 (2H, m), 3.79 (3H, s), 3.89 (1H, dt, *J* = 4.4, 8.2 Hz), 4.23 (1H, d, *J* = 11.2 Hz), 4.51 (1H, d, *J* = 11.2 Hz), 5.33 (1H, dd, *J* = 8.2, 15.5 Hz), 5.53 (1H, dd, *J* = 6.8, 13.6 Hz), 6.84 (1H, dd, *J* = 1.9, 6.8 Hz), 7.18–7.43 (19H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2, 31.6, 37.9, 55.3, 60.8, 66.5, 69.6, 79.1, 113.8, 126.6 (3C), 127.8 (6C), 129.4 (3C), 129.6 (6C), 130.3, 131.5, 132.2, 144.9 (3C), 159.1; HRMS (FAB$^+$) calcd for $C_{34}H_{35}O_3S$ (M^+–1), 523.2307, found 523.2298.

26b: colorless oil, $[\alpha]_D^{25}$ –10.2° (*c* 0.94, $CHCl_3$); IR (neat) : 3397, 2865, 1716, 1612, 1443, 1034, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57–1.64 (1H, m), 1.76–1.85 (1H, m), 2.04–2.25 (4H, m), 2.46 (1H, d, *J* = 4.4 Hz), 3.64–3.76 (2H, m), 3.78 (3H, s), 4.17 (1H, d, *J* = 11.2 Hz), 4.23 (1H, d, *J* = 4.4 Hz), 4.45 (1H, d, *J* = 11.2 Hz), 5.37 (1H, dd, *J* = 9.2, 10.6 Hz), 5.46–5.52 (1H, m), 6.84 (2H, dd, *J* = 1.9, 6.3 Hz), 7.15–7.46 (17H, m); ^{13}C NMR (100

MHz, $CDCl_3$): δ 26.9, 31.8, 37.7, 55.2, 60.8, 66.6, 69.8, 73.6, 113.8 (2C), 126.6 (3C), 127.8 (6C), 129.3 (2C), 129.4 (3C), 129.5 (6C), 130.4, 131.2, 131.6, 144.8 (3C), 159.2; HRMS (FAB^+) calcd for $C_{34}H_{35}O_3S$ (M^+–1), 523.2307, found 523.2298.

(*S*,*E*)-3-(4-Methoxybenzyloxy)-7-(tritylthio)hept-4-enoic acid (28): Dess-Martin periodinane (1.07 g, 2.5 mmol) was added in small portions to a stirred solution of **26a** (660 mg, 1.3 mmol) in CH_2Cl_2 (60 mL) containing $NaHCO_3$ (1.06 g, 13 mmol) at rt. After 1 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) at 0°C, and the resulting mixture was extracted with $CHCl_3$ (3 x 50 mL). The combined extracts were washed with brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 3:1) to give **27** (578 mg, 88%) as a colorless oil.
A solution of $NaClO_2$ (80% purity, 635 mg, 5.6 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (876 mg, 5.6 mmol) in water (10 mL) were added dropwise to a stirred solution of **27** (578 mg, 1.1 mmol) in DMSO (40 mL) at 0°C, and stirring was continued for 1 h at rt. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL) at 0°C. The resulting mixture was extracted with Et_2O (3 x 100 mL), and the combined extracts were washed with brine (2 x 60 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded **28** (448 mg, 75%), which was used for the next reaction without further purification. $[\alpha]_D^{25}$ –17.8° (*c* 1.25, $CHCl_3$); IR (neat): 2835, 1738, 1713, 1668, 1644, 1594, 743, 700, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.12–2.19 (2H, m), 2.21–2.25 (2H, m), 2.48 (1H, dd, *J* = 4.8, 15.5 Hz), 2.61 (1H, dd, *J* = 8.2, 15.5 Hz), 3.78 (3H, s), 4.12 (1H, dt, *J* = 4.8, 8.2 Hz), 4.29 (1H, d, *J* = 11.2 Hz), 4.52 (1H, d, *J* = 11.2 Hz), 5.31 (1H, dd, *J* = 8.2, 15.0 Hz), 5.56–5.63 (1H, m), 6.82 (2H, d, *J* = 8.8 Hz), 7.13–7.45 (19H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2, 31.4, 40.9, 55.2, 66.6, 69.8, 75.5, 77.2, 113.8 (2C), 126.6 (3C), 127.8, 127.9 (8C), 129.4, 129.5 (3C), 129.8, 129.9, 133.3, 144.9 (3C), 159.2, 175.9; HRMS (FAB^+) calcd for $C_{34}H_{35}O_4S$ (M^++1), 539.2256, found 539.2273.

(*R*)-Methyl 2-[(*S*,*E*)-3-(4-methoxybenzyloxy)-7-(tritylthio)hept-4-enamido]propanoate (29): *N*,*N*-Diisopropylethylamine (1.12 mL, 6.6 mmol) was added dropwise to a stirred solution of **28** (507 mg, 0.94 mmol) in MeCN (20 mL) and D-alanine methyl ester (**12**) (261 mg, 1.9 mmol) containing (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (981 mg, 1.9 mmol) at rt under argon. After 2 h, the reaction mixture was diluted with EtOAc (120 mL). The organic layer was washed successively with 10% aqueous HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 20 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 1:1) to give **29** (528 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$ –7.9° (*c* 1.00, $CHCl_3$); IR (neat): 3318, 2867, 2836, 1745, 1659, 1513, 1247, 973, 744, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, d, *J* = 7.3 Hz), 2.09–2.17 (2H, m), 2.22 (2H, t, *J* = 6.7 Hz), 2.35 (1H, dd, *J* = 3.8, 15.3 Hz), 2.48 (1H, dd, *J* = 8.6, 15.3 Hz), 3.72 (3H, s), 3.79 (3H, s), 4.08 (1H, dt, *J* = 3.3, 8.2 Hz), 4.30 (1H, d, *J* = 10.6 Hz), 4.49–4.59 (2H, m), 5.30 (1H, q, *J* = 7.7 Hz), 5.54–5.61 (1H, m), 6.82 (2H, d, *J* = 8.6 Hz), 6.89 (1H, d, *J* = 7.7 Hz), 7.19–7.42 (17H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 31.2, 31.4, 42.7, 47.8, 52.2, 55.2, 66.5, 69.9, 76.5, 113.8, 126.6 (6C), 127.8 (6C), 129.5, 129.6 (4C), 129.9, 130.3, 132.8, 144.8 (4C), 159.2, 170.2, 173.3; HRMS (FAB^+) calcd for $C_{38}H_{42}NO_5S$ (M^++1), 624.2783, found 624.2776.

(*R*)-2-[(*S*,*E*)-3-(4-Methoxybenzyloxy)-7-(tritylthio)hept-4-enamido]propanoic acid (6): 1 M LiOH (3.00 mL, 3.0 mmol) was added dropwise to a stirred solution of **29** (470 mg, 0.75 mmol) in MeOH (15 mL) at rt. After 3 h, 10% aqueous HCl was added to the mixture at 0°C until pH was 6. The resulting mixture was extracted with EtOAc (3 x 30 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography ($CHCl_3$/MeOH, 9:1) to give **6** (450 mg, 98%) as a white amorphous solid. $[\alpha]_D^{25}$ –1.8° (*c* 1.00, $CHCl_3$); IR (KBr): 2931, 2868, 1730, 1632, 1614, 744, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, d, *J* = 6.8 Hz), 2.10–2.15 (2H, m), 2.21 (2H, d, *J* = 6.8 Hz), 2.40 (1H, dd, *J* = 3.4, 15.6 Hz), 2.49 (1H, dd, *J* = 8.8, 15.6 Hz), 3.78 (3H, s), 4.08 (1H, dt, *J* = 3.4, 8.2 Hz), 4.25 (1H, d, *J* = 10.7 Hz), 4.44 (1H, t, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 11.2 Hz), 5.29 (1H, dd, *J* = 8.2, 15.6 Hz), 5.59 (1H, dd, *J* = 6.8, 15.6 Hz), 6.82 (2H, d, *J* = 8.2 Hz), 7.00 (1H, d, *J* = 6.8 Hz), 7.17–7.42 (17H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 31.5, 31.7, 42.6, 48.5, 55.5, 66.9, 70.3, 77.6, 114.1, 126.9 (3C), 128.1 (6C), 129.8 (6C), 130.0 (3C), 130.4 (2C), 133.3, 145.1 (3C), 159.5, 171.7, 176.4; HRMS (FAB^+) calcd for $C_{37}H_{40}NO_5S$ (M^++1), 610.2627, found 610.2627.

(3*S*,4*R*)-Allyl 3-(*tert*-butyldimethylsiloxy)-4-[(*S*)-2-[(*R*)-2-[(*S*,*E*)-3-(4-methoxybenzyloxy)-7-(tritylthio)hept-4-enoylamino]propionylamino]-5-methylhexanoate (30): *N*,*N*-Diisopropylethylamine (37 μL, 0.22 mmol) was added dropwise to a stirred solution of **5** (56.0 mg, 85 μmol) and **6** (51.7 mg, 85 μmol) in CH_2Cl_2 (4.0 mL) containing *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) (41.9 mg, 0.11 mmol) and 1-hydroxy-7-azabenzotriazol (HOAt) (15.0 mg, 0.11 mmol) at –30°C under argon. After 2 h, the reaction mixture was diluted with $CHCl_3$ (60 mL). The organic layer was washed successively with 10% aqueous HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 1:1) to give **30** (99.8 mg, 94%) as a colorless viscous liquid. $[\alpha]_D^{25}$ +14.8° (*c* 1.03, $CHCl_3$); IR (neat): 3283, 3059, 2927, 1736, 1632, 1513, 1247, 1035, 988, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.01 (3H, s), 0.06 (3H, s), 0.79–0.84 (15H, m), 1.16 (3H, d, *J* = 6.8 Hz), 1.89–1.98 (1H, m), 2.06–2.13 (2H, m), 2.19–2.24 (2H, m), 2.29–2.34 (1H, dd, *J* = 3.4, 13.9 Hz), 2.34–2.54 (4H, m), 2.77 (1H, dd, *J* = 8.2, 13.0 Hz), 3.79 (3H, s), 3.90 (1H, q, *J* = 8.2 Hz), 4.01 (1H, dt, *J* = 3.4, 8.2 Hz), 4.13–4.18 (2H, m), 4.28 (1H, t, *J* = 10.6 Hz), 4.47–4.55 (2H, m), 5.19–5.32 (3H, m), 5.41 (1H, dt, *J* = 6.8, 15.5 Hz), 5.83–5.91 (1H, m), 6.10 (1H, d, *J* = 10.6 Hz), 6.54 (1H, d, *J* = 7.7 Hz), 6.82 (1H, d, *J* = 8.2 Hz), 6.95 (1H, d, *J* = 6.8 Hz), 7.14–7.44 (30H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.7, –4.6, 16.7, 17.2, 17.9, 20.4, 25.7, 27.8, 31.2, 31.4, 32.8, 39.6, 42.4 (4C), 48.7, 52.3, 55.3, 58.3, 65.2, 66.5, 67.0, 69.5, 70.0, 76.4, 77.2, 113.9, 118.4, 126.6 (3C), 126.8 (3C), 127.8 (6C), 128.0 (8C), 129.4 (6C), 129.5 (3C), 129.7 (4C), 129.8, 130.0, 132.0, 132.9, 144.3 (3C), 144.8, 159.3, 169.8, 171.1, 171.6, 172.2; HRMS (FAB^+) calcd for $C_{75}H_{89}N_3O_8S_2SiNa$ (M^++Na), 1274.5757, found 1274.5737.

(3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-[(*S*)-2-[(*R*)-2-[(*S*,*E*)-3-hydroxy-7-(tritylthio)hept-4-enoylamino]propionylamino]-5-methylhexanoic acid (4): 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (27.9 mg, 0.12 mmol) was added in small portions to a stirred solution of **30** (76.9 mg, 61 μmol) in CH_2Cl_2/H_2O 9:1 (1.5 mL) at rt. After 3 h, the mixture was diluted with $CHCl_3$ (30 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo*

afforded a residue, which was purified by column chromatography (hexane/EtOAc, 3:2) to give **31** (61.9 mg, 89%) as a colorless viscous liquid.

Morpholine (9.5 μL, 0.11 mmol) was added dropwise to a stirred solution of **31** (61.9 mg, 55 μmol) in dry THF (3.0 mL) containing $Pd(PPh_3)_4$ (6.3 mg, 54 μmol) at rt under argon. After 30 min, the reaction mixture diluted with EtOAc (70 mL), and the organic layer was washed successively with 10% aqueous HCl (2 x 15 mL) and brine (2 x 15 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography ($CHCl_3$/MeOH, 9:1) to give **4** (58.4 mg, 99%) as a white amorphous solid. $[\alpha]_D^{25}$ –1.6° (*c* 1.00, $CHCl_3$); IR (KBr): 3287, 2928, 2365, 1738, 1634, 1536, 1254, 1033, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.76–0.88 (15H, m), 1.28 (3H, d, *J* = 6.8 Hz), 1.92–2.08 (3H, m), 2.17–2.56 (7H, m), 2.72 (1H, dd, *J* = 7.3, 12.2 Hz), 3.79–3.82 (1H, m), 4.08–4.15 (2H, m), 4.35–4.41 (2H, m), 5.30 (1H, dd, *J* = 5.9, 15.1 Hz), 5.42 (1H, dt, *J* = 6.3, 15.1), 6.40 (1H, d, *J* = 10.2 Hz), 6.56 (1H, d, *J* = 6.8 Hz), 7.16–7.42 (30H, m); ^{13}C NMR (100 MHz, $CDCl_3$):δ −4.8, −4.5, 16.4, 17.7, 17.8, 20.3, 25.7, 27.7, 31.2, 31.3, 33.1, 43.9 (4C), 49.4, 53.0, 59.0, 66.6, 67.0, 69.0, 77.2, 126.6 (3C), 126.8 (3C), 126.7, 126.8, 127.8 (6C), 127.9, 128.0 (8C), 129.4 (6C), 129.5 (3C), 129.8, 132.3, 144.3 (3C), 144.8, 170.3, 171.7, 172.6, 174.4; HRMS (FAB^+) calcd for $C_{64}H_{77}N_3O_7S_2SiNa$ (M^++Na), 1114.4869, found 1114.4851.

(2*S*,6*R*,9*S*,12*R*,13*S*)-13-(*tert*-Butyldimethylsiloxy)-12-isopropyl-6-methyl-2-[(*E*)-4-(tritylthio)but-1-enyl]-9-(tritylthiomethyl)-1-oxa-5,8,11-triazacyclopentadecane-4,7,10,15-tetraone (32): A solution of **4** (36.0 mg, 33 μmol) in CH_2Cl_2 (33 mL, 1.0 mM concentration) was added very slowly to a stirred solution of 2-methyl-6-nitrobenzoic anhydride (MNBA) (14.9 mg, 43 μmol) in CH_2Cl_2 (4.0 mL) containing 4-(dimethylamino)pyridine (DMAP) (12.2 mg, 0.10 mmol) at toom temperature over 14 hours. After 1 h, the mixture was diluted with CH_2Cl_2 (40 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography ($CHCl_3$/MeOH, 20:1) to give **32** (31.8 mg, 89%) as a white amorphous solid. $[\alpha]_D^{25}$ −11.4° (*c* 1.00, $CHCl_3$); IR (KBr): 3296, 2957, 1650, 1595, 1537, 1258, 1034, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (3H, s), 0.02 (3H, s), 0.75–0.86 (15H, m), 1.34 (3H, d, *J* = 6.8 Hz), 2.00–2.08 (3H, m), 2.15 (2H, t, *J* = 6.8 Hz), 2.37–2.44 (4H, m), 2.64 (1H, d, *J* = 7.8 Hz), 3.30–3.35 (2H, m), 3.57 (1H, t, *J* = 8.8 Hz), 4.09–4.13 (2H, m), 5.29 (1H, dd, *J* = 6.8, 15.1 Hz), 5.52–5.58 (1H, m), 5.61 (1H, dt, *J* = 6.3, 15.1 Hz), 6.39 (1H, br s), 6.77 (1H, br s), 7.70 (1H, d, *J* = 9.8 Hz), 7.16–7.42 (30H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ−4.9, −4.1, 15.5, 16.5, 17.9, 20.6, 25.7, 27.4, 31.0, 31.3, 33.9, 41.9, 42.2 (4C), 49.9, 56.8, 59.2, 66.6, 66.8, 68.6, 71.2, 77.2, 126.6 (3C), 126.8 (2C), 127.9, 127.8 (6C), 128.0 (10C), 129.5 (9C), 132.9, 144.5 (3C), 144.8, 169.9, 170.1, 170.2, 172.3; HRMS (FAB^+) calcd for $C_{64}H_{75}N_3O_6S_2SiNa$ (M^++Na), 1096.4763, found 1096.4771.

(1*S*,5*S*,6*R*,9*S*,20*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-6-isopropyl-20-methyl-2-oxa-11,12-dithia-7,19,22-triazabicyclo[7.7.6]docos-15-ene-3,8,18,21-tetraone (33): A solution of **32** (30.0 mg, 28 μmol) in CH_2Cl_2/MeOH 9:1 (16 mL) was added dropwise to a vigorously stirring solution of I_2 (71.0 mg, 0.28 mmol) in CH_2Cl_2/MeOH 9:1 (56 mL, 0.5 mM concentration) over 10 min at rt. After 10 min, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (20 mL) at rt. The resulting mixture was diluted with CH_2Cl_2 (60 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), then dried over Na_2SO_4. Concentration of the

solvent *in vacuo* afforded a residue, which was purified by column chromatography ($CHCl_3$/MeOH, 20:1) to give **33** (13.2 mg, 80%) as a white amorphous solid. $[\alpha]_D^{25}$ −1.8° (*c* 1.02, $CHCl_3$); IR (KBr): 3334, 2930, 1746, 1667, 1538, 1257, 1034, 973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.10 (3H, s), 0.16 (3H, s), 0.88 (3H, d, *J* = 7.3 Hz), 0.92 (9H, s), 0.96 (3H, d, *J* = 7.3 Hz), 1.49 (3H, d, *J* = 7.3 Hz), 2.16–2.21 (1H, m), 2.50–2.61 (3H, m), 2.62-2.72 (3H, m), 2.95–3.12 (4H, m), 3.12 (2H, dd, *J* = 6.8, 13.1 Hz), 3.49–3.60 (1H, br m), 4.24–4.30 (1H, m), 4.82 (1H, dt, *J* = 3.4, 9.8 Hz), 4.96–5.00 (1H, m), 5.68–5.72 (2H, m), 6.19 (1H, s), 6.34 (1H,br s), 6.73 (1H, d, *J* = 9.8 Hz), 7.22 (1H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.9, –4.3, 16.8, 17.1, 17.9, 21.0, 25.7 (2C), 29.1 (2C), 34.3, 40.0, 40.6, 41.0, 52.1, 53.7, 62.8, 67.4 (2C), 68.9, 77.2, 129.2, 132.6, 168.9, 170.9, 171.2; HRMS (FAB^+) calcd for $C_{26}H_{46}N_3O_6S_2Si$ (M^++H), 588.2597, found 588.2609.

Spiruchostatin A (1): HF·pyridine (0.20 mL) was added to a stirring solution of **33** (13.0 mg, 22 μmol) in pyridine (1.0 mL) at rt. After 14 h, the reaction mixture was diluted with EtOAc (40 mL), and the organic layer was washed successively with 3% aqueous HCl (3 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography ($CHCl_3$/MeOH, 10:1) to give **1** (spiruchostatin A) (9.6 mg, 92%) as a white amorphous solid. $[\alpha]_D^{25}$ −69.9° (*c* 0.14, MeOH) {lit.[1] $[\alpha]_D$ –63.6° (*c* 0.14, MeOH)}; IR (neat): 3375, 2933, 1633, 1542, 1160, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 6.8 Hz), 1.51 (3H, d, *J* = 7.3 Hz), 2.38–2.47 (2H, m), 2.56 (1H, d, *J* = 13.2 Hz), 2.70–2.77 (5H, m), 3.15 (1H, d, *J* = 7.3, 13.2 Hz), 4.25 (1H, dq, *J* = 3.9, 7.3 Hz), 4.54–4.59 (1H, m), 4.89 (1H, dt, *J* = 3.9, 9.3 Hz), 5.50 (1H, s), 5.65 (1H, d, *J* = 15.1 Hz), 5.92 (1H, s), 6.39 (1H, s), 6.71 (1H, d, *J* = 9.3 Hz), 7.40 (1H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 19.6, 20.6, 29.6, 33.3, 39.6, 40.7, 40.9, 52.3, 54.3, 63.8, 69.3, 70.5, 77.2, 128.6, 133.6, 169.0, 170.6, 170.9, 171.9; HRMS (FAB^+) calcd for $C_{20}H_{32}N_3O_6S_2$ (M^++1), 474.1732, found 474.1750. The IR, ^1H and ^{13}C NMR, and HRMS spectrum are essentially identical with those reported for natural spiruchostatin A.[1]

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