Organozirconium Chemistry on Cyclosporin: A Novel Process for the Highly Stereoselective Synthesis of (*E*)-ISA247 (Voclosporin) and Close Analogues

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Received 3 October 2011; revised 27 October 2011

Abstract: Application of organozirconium chemistry to cyclosporin has led to the development of a novel process for the highly stereoselective synthesis of the *E*-isomer of ISA247 (voclosporin), which is a potent immunosuppressive agent currently in late stage human clinical trials for treatment of psoriasis, prevention of kidney transplant rejection, and ophthalmic indications. Synthesis of deuterated analogues of ISA247 and a cyclosporin triene analogue using the same methodology is also described.

Key words: cyclosporin A, ISA247, voclosporin, *E*-diene, organozirconium chemistry

ISA247 (**1**) is a novel semi-synthetic analogue of cyclosporin A (CsA, **2**) which was originally reported as a mixture of cyclosporin terminal *E*- and *Z*-dienes **1**, where the *E*/*Z* ratio varies depending on the synthetic method employed to construct the terminal diene[1] on the 1-amino acid side chain (Figure 1). The replacement of the terminal methyl of CsA with a vinyl group is the only structural difference between ISA247 (**1**) and CsA (**2**). CsA remains one of the major drugs used for the prevention of organ transplant rejection. Recent reports indicate that (*E*)-ISA247 (**1a**) exhibits greater immunosuppressive potency and an improved drug safety profile in human clinical trials compared with CsA.[2] CsA's poor therapeutic index is attributed largely to renal toxicity, which often occurs in patients undergoing chronic, long term treatment with this potent immunosuppressive agent. The drug name voclosporin was recently adopted for (*E*)-ISA247 (**1a**), which is currently in phase II clinical trials for the prevention of organ rejection after kidney transplantation, and phase III clinical trials for the treatment of psoriasis. It is also in phase III clinical trials for the ophthalmic indication, uveitis.[2g] The recent clinical findings and the potential pharmaceutical utility of voclosporin warrant the development of a highly stereoselective synthetic route for the preparation of this drug candidate.

In an effort to obtain (*E*)-ISA247 (**1a**) for benchmarking purposes in our biological assays, we developed a novel, highly stereoselective route for the synthesis of **1a**. Our synthetic method was also used to synthesize close analogues of **1a** to elucidate structure–activity relationships around this part of the molecule.[3]

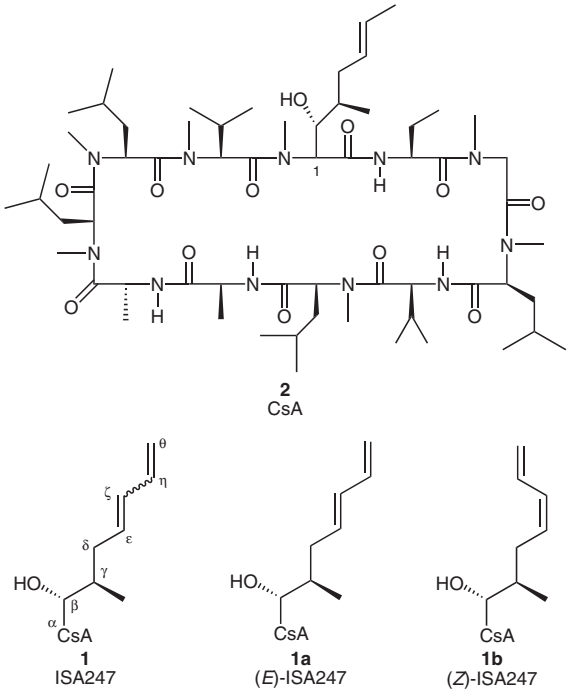


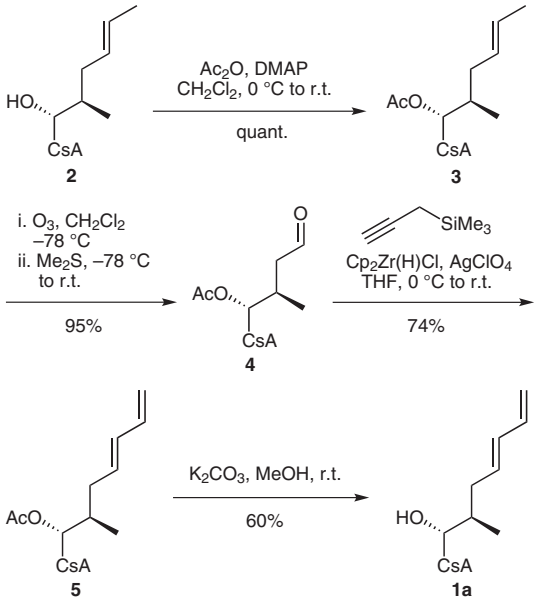
Figure 1 Structures of CsA and ISA247 (voclosporin) stereoisomers

Suzuki and co-workers developed a facile and highly *E*-selective method using an organozirconium reagent for the stereoselective synthesis of terminal 1,3-dienes directly from simple aromatic and aliphatic aldehydes.[4]

Our efforts toward the stereoselective synthesis of (*E*)-ISA247 (**1a**) are summarized in Scheme 1. The known intermediate aldehyde **4** was prepared in two steps from cyclosporin A following the procedure described in the literature.[1b] Protection of the secondary alcohol of CsA (**2**) with an acetyl group followed by ozonolysis of the resulting acetylcyclosporin A (**3**) provided aldehyde **4** in excellent yield that was satisfactory to carry forward without further purification. The subsequent treatment of aldehyde **4** with the γ-trimethylsilylpropenylzirconocene chloride complex, which was prepared in situ from bis(cyclopentadienyl)zirconium chloride hydride (Schwartz's reagent) and propargyltrimethylsilane, in the presence of silver perchlorate produced exclusively the desired *E*-di-

SYNTHESIS 2012, 44, 63–68
Advanced online publication: 22.11.2011
DOI: 10.1055/s-0031-1289616; Art ID: M94711SS

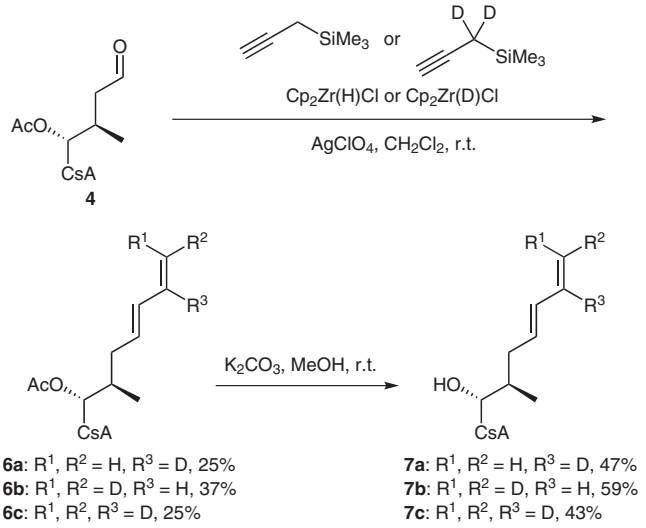
ene **5**. None of the *Z*-isomer of the diene was detected by either HPLC or ^{1}H NMR analyses (the coupling constant $J_{\varepsilon,\zeta}$ = 14.9 Hz).[5] Finally, (*E*)-ISA247 (**1a**) was obtained by the hydrolysis of acetate **5** using potassium carbonate in methanol.[6]



Scheme 1 Synthesis of (*E*)-ISA247 (voclosporin)

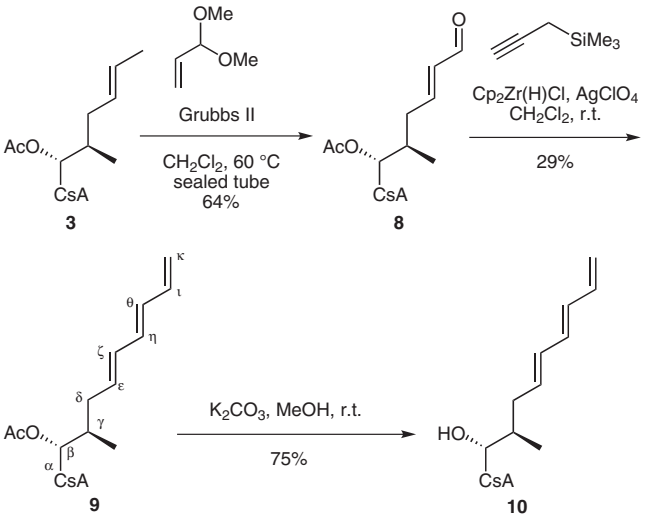
Interestingly, the corresponding deuterated diene analogues, which have been reported to change both the physicochemical and pharmacokinetic profile and improve the therapeutic index,[7] can be synthesized utilizing the same strategy by employing deuterated reagents (Scheme 2). Reaction of aldehyde **4** with the zirconium complex prepared in situ from the commercially available $Cp_2Zr(D)Cl$ and propargyltrimethylsilane in the presence of silver perchlorate provided exclusively the *E*-isomer of deuterated diene **6a** by ^{1}H NMR analyses (the coupling constant $J_{\varepsilon,\zeta}$ = 15.2 Hz). Similarly, deuterated *E*-dienes **6b** and **6c** were synthesized by employing deuterated propargyltrimethylsilane, which was prepared following a two-step literature procedure,[8] with either $Cp_2Zr(H)Cl$ (for **6b**) or $Cp_2Zr(D)Cl$ (for **6c**).[9] No corresponding *Z*-isomers of **6b** and **6c** were observed by ^{1}H NMR analyses (the coupling constants $J_{\varepsilon,\zeta}$ from **6b** and **6c** are 14.3 Hz and 15.2 Hz, respectively). Hydrolysis of the acetates **6a–c** with potassium carbonate in methanol provided *E*-dienes **7a–c** smoothly.

With these successes in hand, we next investigated the synthesis of a novel cyclosporin triene analogue[10] by utilizing the organozirconium chemistry (Scheme 3). The *E*-α,β-unsaturated aldehyde **8** ($J_{\varepsilon,\zeta}$ = 15.5 Hz) was prepared from acetylcyclosporin A (**3**) via olefin cross-metathesis using Grubbs' second-generation catalyst.[11] The resulting acetal from the reaction was hydrolyzed to provide the corresponding aldehyde in the course of the purification by semi-preparative HPLC on a C18 column at 70 °C using a solvent system of acetonitrile and water with 0.05%



Scheme 2 Synthesis of deuterated ISA247 analogues

TFA (v/v). Aldehyde **8** was treated with a mixture of Schwartz's reagent and propargyltrimethylsilane in the presence of silver perchlorate to produce acetyltriene **9** in 29% yield.[9] The structure of the triene **9** was confirmed to be an *E*,*E*-triene ($J_{\varepsilon,\zeta}$ = 14.6 Hz and $J_{\eta,\theta}$ = 14.8 Hz) by NMR studies. Hydrolysis of the acetyltriene **9** with potassium carbonate provided the final compound **10** in 75% yield.



Scheme 3 Synthesis of cyclosporin triene

In conclusion, we have successfully developed an efficient synthetic approach to the immunosuppressive drug candidate voclosporin (**1a**). The four-step novel process provides a highly stereocontrolled conversion from cyclosporin A to voclosporin (**1a**) in 42% overall yield. Utilizing this method, the corresponding deuterated ISA247 and triene analogues have also been prepared.

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Optical rotations were measured on a Perkin-Elmer 343 polarimeter at r.t. ^{1}H and ^{13}C NMR spectra

were recorded at 300 and 75 MHz or 500 and 125 MHz, respectively. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin-Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer or a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer. High-resolution mass spectrometry (HRMS) was performed in ESI positive mode on a Waters Q-Tof Micro mass spectrometer. HPLC analyses were obtained using a Dynamax C18 column (200 × 4.5 mm) or Phenomenex Luna C18(2) column (250 × 4.6 mm) with UV detection at 210 nm and oven temperature at 65 °C. Semi-preparative HPLC purifications were performed on a Luna C18(2) column (250 × 21.2 mm) with oven temperature at 70 °C using a solvent system of MeCN and H_2O with 0.05% TFA (v/v). Combi-Flash chromatography was performed using Combi-Flash Companion (Isco, Inc.) with either a silica gel column or a C18 column.

Acetylcyclosporin A (3)

A mixture of cyclosporin A (**2**; 40 g, 33.3 mmol), Ac_2O (31.3 mL, 332 mmol), pyridine (40.2 mL, 498 mmol), DMAP (0.405 g, 3.32 mmol), and anhyd CH_2Cl_2 (250 mL) was stirred under N_2 at 0 °C and allowed to warm to r.t. for 2 days. After this time, the mixture was poured slowly into sat. aq $NaHCO_3$ (1 L) and stirred for 1 h (**Caution**: there was vigorous production of CO_2 when the reaction was quenched). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with aq 1 M HCl (2 × 500 mL), sat. aq $NaHCO_3$ (500 mL), and brine (500 mL). The organics were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give acetylcyclosporin A (**3**); yield: 41.4 g (quant); off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 9.9 Hz, 1 H), 8.05 (d, *J* = 6.9 Hz, 1 H), 7.50 (d, *J* = 9.6 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 5.67 (dd, *J* = 10.8, 3.9 Hz, 1 H), 5.45–5.60 (m, 1 H), 5.38 (dd, *J* = 11.7, 3.6 Hz, 1 H), 5.10–5.35 (m, 6 H), 4.97 (d, *J* = 11.1 Hz, 2 H), 4.84 (t, *J* = 7.2 Hz, 1 H), 4.76 (t, *J* = 9.9 Hz, 1 H), 4.65 (d, *J* = 13.8 Hz, 1 H), 4.41 (t, *J* = 7.2 Hz, 1 H), 3.44 (s, 3 H), 3.26 (s, 3 H), 3.24 (s, 3 H), 3.21 (s, 3 H), 3.09 (s, 3 H), 2.67 (s, 3 H), 2.65 (s, 3 H), 2.33–2.48 (m, 1 H), 2.09–2.22 (m, 5 H), 2.02 (s, 3 H), 0.70–1.75 (m, 64 H).

ESI-MS: *m*/*z* = 1244 $[C_{64}H_{113}N_{11}O_{13} + H]^+$.

Acetylcyclosporin A Aldehyde (4)

A mixture of acetylcyclosporin A (**3**; 41.4 g, 33.2 mmol) and anhyd CH_2Cl_2 (200 mL) was cooled to –78 °C, and ozone was bubbled through the mixture until a light blue color appeared. N_2 was bubbled through the mixture for 10 min and then Me_2S (20 mL, 272 mmol) was added at –78 °C. The mixture was allowed to warm to r.t. and stirred overnight under N_2. The mixture was concentrated, and the residue was dissolved in Et_2O (2 L), washed with 10% aq Na_2CO_3 (2 × 500 mL) and brine (1 L), dried (Na_2SO_4), filtered, and concentrated to dryness to give aldehyde **4**; yield: 38.8 g (95%); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 3.3 Hz, 1 H), 8.56 (d, *J* = 9.6 Hz, 1 H), 7.97 (d, *J* = 6.9 Hz, 1 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 1 H), 5.66 (dd, *J* = 11.1, 3.6 Hz, 1 H), 5.45–5.60 (m, 3 H), 5.32 (dd, *J* = 12.6, 3.6 Hz, 1 H), 5.10–5.23 (m, 6 H), 4.83 (t, *J* = 7.2 Hz, 1 H), 4.73 (t, *J* = 9.6 Hz, 1 H), 4.65 (d, *J* = 13.8 Hz, 1 H), 4.41 (t, *J* = 6.9 Hz, 1 H), 3.46 (s, 3 H), 3.29 (s, 6 H), 3.21 (s, 3 H), 3.08 (s, 3 H), 2.67 (s, 3 H), 2.65 (s, 3 H), 2.33–2.48 (m, 1 H), 2.09–2.22 (m, 5 H), 2.01 (s, 3 H), 0.70–1.75 (m, 59 H).

ESI-MS: *m*/*z* = 1232 $[C_{62}H_{109}N_{11}O_{14} + H]^+$.

(*E*)-Acetyl-ISA 247 (5)

To a suspension of $Cp_2Zn(H)Cl$ (620 mg, 2.4 mmol) in THF (10 mL) at 0 °C was added propargyltrimethylsilane (280 mg, 2.5 mmol). The mixture was stirred at 0 °C for 30 min and then warmed to r.t. for 2 h. The mixture was cooled to 0 °C again, and a solution of aldehyde **4** (300 mg, 0.24 mmol) in THF (2 mL) was added. The mixture was stirred at 0 °C for 10 min and then warmed to r.t. $AgClO_4$ (10 mg, 0.05 mmol) was added and the resulting mixture was stirred at r.t. for 12 h. The mixture was poured into sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by Combi-Flash chromatography on a silica gel column (0 to 50% EtOAc–hexanes) to afford **5**; yield: 223 mg (74%); white solid; $[\alpha]_D^{25}$ –298.8 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 9.1 Hz, 1 H), 8.05 (d, *J* = 7.1 Hz, 1 H), 7.78 (d, *J* = 9.0 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 6.21 (dt, *J* = 16.8, 10.3 Hz, 1 H), 5.90 (dd, *J* = 14.9, 10.8 Hz, 1 H), 5.69 (dd, *J* = 10.7, 3.6 Hz, 1 H), 5.54 (s, 2 H), 5.40–4.75 (m, 7 H), 4.65 (d, *J* = 14.2 Hz, 1 H), 4.46 (t, *J* = 7.3 Hz, 1 H), 3.44 (s, 3 H), 3.25 (s, 3 H), 3.19 (s, 6 H), 3.11 (s, 3 H), 2.69 (s, 6 H), 2.48–2.33 (m, 1 H), 2.22–2.09 (m, 5 H), 2.02 (s, 3 H), 1.75–0.70 (m, 65 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 173.2, 173.0, 172.9, 171.6 (2 C), 171.4, 171.1, 170.6, 170.5, 170.2, 168.1, 136.8, 133.1, 132.3, 115.1, 73.1, 58.4, 57.5, 56.2, 55.4, 54.9, 54.4, 50.2, 48.9, 48.4, 48.0, 45.0, 40.9, 39.2, 39.1, 37.0, 35.7, 34.0, 33.3, 32.3, 31.7, 31.5, 31.4, 30.2, 30.1, 29.7, 29.5, 25.0, 24.8, 24.7 (2 C), 24.5, 24.1, 23.7, 23.4 (2 C), 22.5, 21.7, 21.2, 21.1, 20.6, 20.3, 19.4, 18.5, 18.1, 17.9, 17.5, 15.1, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{65}H_{114}N_{11}O_{13}$ $[M + H]^+$: 1256.8597; found: 1256.8447.

(*E*)-ISA 247 (1a)

To a stirred solution of *E*-acetyldiene **5** (75 mg, 0.06 mmol) in MeOH (8 mL) was added K_2CO_3 (205 mg, 1.48 mmol) at r.t. After stirring for 12 h at r.t., the reaction mixture was diluted with EtOAc (50 mL) and then washed with sat. aq NH_4Cl (15 mL). The aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by Combi-Flash chromatography on a C18 column (10 to 100% MeCN–H_2O) to afford **1a**; yield: 44 mg (60%); white solid; $[\alpha]_D^{25}$ –220.0 (*c* 0.3, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 10.2 Hz, 1 H), 7.60 (d, *J* = 6.2 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.16 (d, *J* = 7.9 Hz, 1 H), 6.30 (dt, *J* = 17.0, 10.3 Hz, 1 H), 5.99 (dd, *J* = 15.4, 10.3 Hz, 1 H), 5.53–5.73 (m, 2 H), 5.50 (d, *J* = 5.7 Hz, 1 H), 5.33 (dd, *J* = 11.6, 3.9 Hz, 1 H), 4.92–5.16 (m, 5 H), 4.82 (t, *J* = 7.3 Hz, 1 H), 4.77 (d, *J* = 13.3 Hz, 1 H), 4.65 (t, *J* = 8.7 Hz, 1 H), 4.53 (t, *J* = 7.2 Hz, 1 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.23 (s, 3 H), 3.11 (s, 3 H), 3.10 (s, 3 H), 2.70 (s, 3 H), 2.69 (s, 3 H), 1.98–2.52 (m, 8 H), 0.65–1.82 (m, 63 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8 (2 C), 173.6, 173.4, 171.5, 171.2, 171.1, 170.4, 170.3, 170.1, 170.0, 137.3, 133.5, 132.6, 114.5, 74.6, 58.8, 57.8, 57.5, 55.5, 55.4, 55.3, 50.3, 48.7, 48.5, 48.2, 45.1, 40.6, 39.4, 38.9, 37.3, 36.1, 35.9, 35.8, 34.0, 31.5, 31.3, 31.1, 29.8, 29.7, 29.5, 29.0, 25.4, 24.8 (2 C), 24.6, 24.4, 23.8, 23.7, 23.6, 23.4 (2 C), 21.9, 21.8, 21.0, 20.2, 19.8, 18.6, 18.3, 18.1, 16.8, 15.9, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{63}H_{112}N_{11}O_{12}$ $[M + H]^+$: 1214.8492; found: 1214.8394.

(*E*)-Acetyl-(η-*d*)-ISA247 (6a)

To a suspension of $Cp_2Zn(D)Cl$ (410 mg, 1.60 mmol) in CH_2Cl_2 (3 mL) at r.t. was added propargyltrimethylsilane (0.25 mL, 1.7 mmol). The mixture was stirred at r.t. for 10 min. A solution of al-

dehyde **4** (200 mg, 0.160 mmol) in CH_2Cl_2 (1 mL) was added, followed by $AgClO_4$ (7.0 mg, 0.03 mmol). The resulting mixture was stirred at r.t. for 12 h. The mixture was poured into sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by semi-preparative HPLC on a C18 column to afford **6a**; yield: 50 mg (25%); white solid; $[\alpha]_D^{25}$ –255.8 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 9.6 Hz, 1 H), 8.04 (d, *J* = 6.9 Hz, 1 H), 7.62 (d, *J* = 9.0 Hz, 1 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 5.90 (d, *J* = 15.2 Hz, 1 H), 5.69 (d, *J* = 6.8 Hz, 1 H), 5.53 (s, 2 H), 5.40–4.72 (m, 7 H), 4.64 (d, *J* = 13.3 Hz, 1 H), 4.43 (t, *J* = 6.6 Hz, 1 H), 3.45 (s, 3 H), 3.26 (s, 3 H), 3.21 (s, 3 H), 3.20 (s, 3 H), 3.10 (s, 3 H), 2.68 (s, 3 H), 2.66 (s, 3 H), 2.48–2.33 (m, 1 H), 2.22–2.09 (m, 5 H), 2.02 (s, 3 H), 1.92–0.70 (m, 65 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 173.2, 173.1, 172.9, 171.9, 171.8, 171.7, 171.4, 170.8, 170.7, 170.2, 168.2, 136.8, 133.4, 131.9, 115.0, 73.2, 58.5, 57.6, 56.2, 55.5, 55.0, 54.3, 50.3, 48.9, 48.4, 48.1, 45.0, 40.9, 39.2, 39.1, 37.0, 35.7, 34.0, 33.3, 32.3, 31.7, 31.5, 31.4, 30.2, 30.1, 29.7, 29.5, 25.0, 24.8, 24.7 (2 C), 24.5, 24.0, 23.6, 23.4 (2 C), 22.5, 21.7, 21.2, 21.1, 20.6, 20.3, 19.4, 18.5, 18.1, 17.8, 17.5, 15.1, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{65}H_{113}DN_{11}O_{13}$ $[M + H]^+$: 1257.8659; found: 1257.8561.

(*E*)-Acetyl-(θ,θ-*d*,*d*)-ISA247 (6b)

To a suspension of $Cp_2Zn(H)Cl$ (410 mg, 1.60 mmol) in CH_2Cl_2 (3 mL) at r.t. was added 1,1-*d*,*d*-propargyltrimethylsilane (190 mg, 1.70 mmol). The mixture was stirred at r.t. for 10 min. A solution of aldehyde **4** (200 mg, 0.160 mmol) in CH_2Cl_2 (1 mL) was added, followed by $AgClO_4$ (7.0 mg, 0.03 mmol). The resulting mixture was stirred at r.t. for 12 h. The mixture was poured into sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by semi-preparative HPLC on a C18 column to afford **6b**; yield: 75 mg (37%); white solid; $[\alpha]_D^{25}$ –300.4 (*c* 0.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 9.2 Hz, 1 H), 8.06 (d, *J* = 6.5 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.59 (d, *J* = 7.1 Hz, 1 H), 6.20 (d, *J* = 10.4 Hz, 1 H), 5.90 (dd, *J* = 14.3, 10.4 Hz, 1 H), 5.69 (d, *J* = 7.3 Hz, 1 H), 5.54 (s, 2 H), 5.40–4.75 (m, 5 H), 4.65 (d, *J* = 13.6 Hz, 1 H), 4.46 (t, *J* = 7.1 Hz, 1 H), 3.43 (s, 3 H), 3.25 (s, 3 H), 3.19 (s, 6 H), 3.12 (s, 3 H), 2.70 (s, 3 H), 2.68 (s, 3 H), 2.45–2.28 (m, 1 H), 2.22–2.05 (m, 5 H), 2.03 (s, 3 H), 1.75–0.70 (m, 65 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 173.3, 173.0, 172.9, 171.5, 171.4, 171.2, 171.0, 170.5, 170.3, 170.2, 168.1, 136.7, 133.0, 132.4, 115.0, 73.1, 58.3, 57.4, 56.2, 55.3, 54.8, 54.3, 50.1, 48.8, 48.3, 47.9, 44.8, 40.9, 39.2, 39.1, 37.0, 35.8, 34.0, 33.2, 32.3, 31.7, 31.5, 31.4, 30.2, 30.0, 29.7, 29.5, 25.0, 24.8, 24.7 (2 C), 24.5, 24.1, 23.7, 23.4 (2 C), 22.5, 21.8, 21.2, 21.1, 20.6, 20.3, 19.4, 18.5, 18.1, 18.0, 17.6, 15.0, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{65}H_{112}D_2N_{11}O_{13}$ $[M + H]^+$: 1258.8721; found: 1258.8801.

(*E*)-Acetyl-(η,θ,θ-*d*,*d*,*d*)-ISA247 (6c)

To a suspension of $Cp_2Zn(D)Cl$ (410 mg, 1.60 mmol) in CH_2Cl_2 (3 mL) at r.t. was added 1,1-*d*,*d*-propargyltrimethylsilane (190 mg, 1.70 mmol). The mixture was stirred at r.t. for 10 min. A solution of aldehyde **4** (200 mg, 0.160 mmol) in CH_2Cl_2 (1 mL) was added, followed by $AgClO_4$ (7.0 mg, 0.03 mmol). The resulting mixture was stirred at r.t. for 12 h. The mixture was poured into sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by semi-preparative HPLC on a C18 column to afford **6c**; yield: 51 mg (25%); white solid; $[\alpha]_D^{25}$ –258.7 (*c* 0.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 9.2 Hz, 1 H), 8.06 (d, *J* = 6.8 Hz, 1 H), 7.68 (d, *J* = 9.0 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 5.90 (d, *J* = 15.2 Hz, 1 H), 5.69 (dd, *J* = 11.2, 3.7 Hz, 1 H), 5.54 (s, 2 H), 5.42–4.75 (m, 5 H), 4.66 (d, *J* = 13.9 Hz, 1 H), 4.44 (t, *J* = 7.1 Hz, 1 H), 3.45 (s, 3 H), 3.26 (s, 3 H), 3.24 (s, 6 H), 3.11 (s, 3 H), 2.68 (s, 3 H), 2.67 (s, 3 H), 2.45–2.35 (m, 1 H), 2.28–2.05 (m, 5 H), 2.02 (s, 3 H), 1.95–0.65 (m, 65 H).

HRMS (ESI): *m*/*z* calcd for $C_{65}H_{111}D_3N_{11}O_{13}$ $[M + H]^+$: 1259.8783; found: 1259.8857.

(*E*)-(η-*d*)-ISA247 (7a)

To a stirred solution of *E*-acetyldiene **6a** (43 mg, 0.03 mmol) in MeOH (4 mL) was added K_2CO_3 (104 mg, 0.750 mmol) at r.t. After stirring for 12 h at r.t., the reaction mixture was diluted with H_2O (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by semi-preparative HPLC on a C18 column to afford **7a**; yield: 17 mg (47%); white solid; $[\alpha]_D^{25}$ –194.0 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 9.0 Hz, 1 H), 7.62 (d, *J* = 6.8 Hz, 1 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 5.98 (d, *J* = 14.8 Hz, 1 H), 5.74–5.54 (m, 2 H), 5.50 (d, *J* = 5.1 Hz, 1 H), 5.33 (d, *J* = 7.9 Hz, 1 H), 5.17–4.88 (m, 5 H), 4.82 (t, *J* = 6.6 Hz, 1 H), 4.74 (d, *J* = 14.1 Hz, 1 H), 4.65 (t, *J* = 8.7 Hz, 1 H), 4.53 (t, *J* = 7.2 Hz, 1 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.24 (s, 3 H), 3.11 (s, 3 H), 3.10 (s, 3 H), 2.71 (s, 3 H), 2.69 (s, 3 H), 2.55–1.95 (m, 8 H), 1.80–0.65 (m, 63 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 173.7, 173.6, 173.0, 172.0, 171.7, 171.4, 170.8, 170.6, 170.5, 170.1, 137.3, 133.4, 132.7, 114.5, 74.7, 58.7, 58.5, 58.0, 57.7, 55.6, 55.4, 54.5, 50.4, 48.9, 48.7, 48.4, 45.5, 40.6, 39.4, 38.9, 38.6, 37.2, 36.1, 35.9, 35.8, 34.0, 31.5, 31.3, 31.1, 29.9, 29.8, 29.5, 29.0, 25.4, 24.7, 24.6, 24.4, 23.8, 23.7, 23.6, 23.1, 22.9, 21.8, 21.0, 20.2, 19.8, 18.6, 18.3, 17.5, 16.7, 16.0, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{63}H_{111}DN_{11}O_{12}$ $[M + H]^+$: 1215.8553; found: 1215.8457.

(*E*)-(θ,θ-*d*,*d*)-ISA247 (7b)

To a stirred solution of *E*-acetyldiene **6b** (70 mg, 0.06 mmol) in MeOH (8 mL) was added K_2CO_3 (190 mg, 1.40 mmol) at r.t. After stirring for 12 h at r.t., the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by semi-preparative HPLC on a C18 column to afford **7b**; yield: 40 mg (59%); white solid; $[\alpha]_D^{25}$ –181.5 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 9.2 Hz, 1 H), 7.61 (d, *J* = 6.7 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 6.29 (d, *J* = 10.5 Hz, 1 H), 5.99 (dd, *J* = 15.2, 10.5 Hz, 1 H), 5.73–5.53 (m, 2 H), 5.50 (d, *J* = 5.2 Hz, 1 H), 5.32 (d, *J* = 8.9 Hz, 1 H), 5.16–4.90 (m, 3 H), 4.82 (t, *J* = 6.8 Hz, 1 H), 4.74 (d, *J* = 14.2 Hz, 1 H), 4.64 (t, *J* = 8.6 Hz, 1 H), 4.53 (t, *J* = 7.0 Hz, 1 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.25 (s, 3 H), 3.12 (s, 3 H), 3.10 (s, 3 H), 2.70 (s, 3 H), 2.69 (s, 3 H), 2.59–2.35 (m, 2 H), 2.20–1.92 (m, 6 H), 1.82–0.65 (m, 63 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 173.7, 173.6, 173.4, 171.6, 171.4, 171.2, 170.4 (2 C), 170.2, 170.1, 137.2, 133.5, 132.7, 114.5, 74.7, 58.7, 58.5, 58.1, 57.5, 55.6, 55.4, 55.3, 50.4, 48.9, 48.7, 48.4, 45.2, 40.6, 39.4, 38.9, 38.6, 37.3, 36.1, 35.9, 35.8, 34.0, 31.5, 31.3, 31.1, 29.9, 29.8, 29.5, 29.0, 25.4, 24.9, 24.8, 24.6, 23.8, 23.7, 23.6, 23.1, 22.9, 21.8, 21.0, 20.2, 19.8, 18.6, 18.3, 18.0, 16.8, 16.0, 9.8.

HRMS (ESI): *m*/*z* calcd for $C_{63}H_{110}D_2N_{11}O_{12}$ $[M + H]^+$: 1216.8615; found: 1216.8608.

(*E*)-(η,θ,θ-*d*,*d*,*d*)-ISA247 (7c)

To a stirred solution of *E*-acetyldiene **6c** (45 mg, 0.04 mmol) in MeOH (5 mL) was added K_2CO_3 (120 mg, 0.900 mmol) at r.t. After stirring for 12 h at r.t., the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by semi-preparative HPLC on a C18 column to afford **7c**; yield: 19 mg (43%); white solid; $[\alpha]_D^{25}$ –221.6 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 9.6 Hz, 1 H), 7.61 (d, *J* = 7.2 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.15 (d, *J* = 8.1 Hz, 1 H), 5.99 (d, *J* = 15.0 Hz, 1 H), 5.74–5.55 (m, 2 H), 5.50 (d, *J* = 5.9 Hz, 1 H), 5.30 (dd, *J* = 10.9, 3.2 Hz, 1 H), 5.16–4.90 (m, 3 H), 4.82 (t, *J* = 7.2 Hz, 1 H), 4.73 (d, *J* = 13.9 Hz, 1 H), 4.65 (t, *J* = 9.3 Hz, 1 H), 4.53 (t, *J* = 7.3 Hz, 1 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.25 (s, 3 H), 3.11 (s, 3 H), 3.10 (s, 3 H), 2.70 (s, 3 H), 2.69 (s, 3 H), 2.57–2.40 (m, 2 H), 2.20–1.94 (m, 6 H), 1.82–0.65 (m, 63 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8 (2 C), 173.6, 173.4, 171.5, 171.2, 171.1, 170.4, 170.3, 170.1, 170.0, 137.2, 133.4, 132.5, 114.5, 74.6, 58.7, 58.5, 57.9, 57.5, 55.6, 55.4, 55.3, 50.3, 48.7, 48.6, 48.2, 45.1, 40.6, 39.4, 38.9, 38.6, 37.3, 36.1, 35.9, 35.8, 34.0, 31.5, 31.3, 31.1, 29.7 (2 C), 29.5, 29.0, 25.4, 24.9 (2 C), 24.6, 23.8, 23.7, 23.6, 23.3, 22.9, 21.8, 21.1, 20.2, 19.8, 18.7, 18.3, 18.1, 16.8, 16.0, 9.9.

HRMS (ESI): *m*/*z* calcd for $C_{63}H_{109}D_3N_{11}O_{12}$ $[M + H]^+$: 1217.8677; found: 1217.8644.

***cyclo*-{[(2*S*,3*R*,4*R*,6*E*)-3-Acetoxy-4-methyl-2-(methylamino)-8-oxoct-6-enoyl]-L-2-aminobutyryl-*N*-methyl-glycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl} (8)**

A mixture of acetylcyclosporin A (**3**; 100 mg, 0.08 mmol), acrolein dimethyl acetal (0.018 mL, 0.16 mmol), Grubbs II catalyst (25 mg, 0.029 mmol), and CH_2Cl_2 (1 mL) was heated at 60 °C in a sealed tube for 12 h. After that time, additional Grubbs II catalyst (25 mg) and acrolein dimethyl acetal (0.018 mL) were added, and the mixture was stirred at the same temperature for an additional 12 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by semi-preparative HPLC to afford **8**; yield: 65 mg (64%); off-white solid; $[\alpha]_D^{25}$ –278.1 (*c* 0.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (d, *J* = 7.9 Hz, 1 H), 8.55 (d, *J* = 9.6 Hz, 1 H), 8.02 (d, *J* = 6.8 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.53 (d, *J* = 7.5 Hz, 1 H), 6.73 (ddd, *J* = 15.5, 10.0, 4.5 Hz, 1 H), 5.60 (dd, *J* = 15.5, 7.9 Hz, 1 H), 5.70–4.40 (m, 12 H), 3.46 (s, 3 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 3.21 (s, 3 H), 3.13 (s, 3 H), 2.68 (s, 3 H), 2.66 (s, 3 H), 2.50–1.50 (m, 10 H), 2.04 (s, 3 H), 1.40–0.75 (m, 58 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 173.2, 173.1, 173.0, 172.5, 172.1, 170.6 (2 C), 170.3, 169.8, 169.7, 169.5, 167.1, 156.0, 134.1, 72.0, 57.8, 56.7, 55.3, 54.9, 54.6, 53.5, 49.5, 48.1, 47.6, 47.3, 44.2, 40.3, 38.6 (2 C), 36.8, 35.3, 33.5, 32.1, 31.6, 31.0, 30.8 (2 C), 29.6, 29.3, 29.1, 28.9, 24.4, 24.2, 24.1, 24.0, 23.9, 23.5, 23.1, 22.9, 22.7, 21.6, 21.2, 20.7, 20.3, 20.0, 19.8, 19.0, 18.0, 17.4 (2 C), 16.9, 14.4, 9.2.

HRMS (ESI): *m*/*z* calcd for $C_{64}H_{112}N_{11}O_{14}$ $[M + H]^+$: 1258.8390; found: 1258.8439.

***cyclo*-{[(2*S*,3*R*,4*R*,6*E*,8*E*)-3-Acetoxy-4-methyl-2-(methylamino)-6,8,10-undecatrienoyl]-L-2-aminobutyryl-*N*-methyl-glycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl} (9)**

To a suspension of $Cp_2Zn(H)Cl$ (206 mg, 0.80 mmol) in CH_2Cl_2 (2 mL) at r.t. was added propargyltrimethylsilane (0.13 mL, 0.84 mmol). The mixture was stirred at r.t. for 10 min. A solution of aldehyde **8** (100 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was added, followed by $AgClO_4$ (3.0 mg, 0.016 mmol). The resulting mixture was stirred at r.t. for 12 h. The mixture was poured into sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by semi-preparative HPLC on a C18 column to afford **9**; yield: 30 mg (29%); white solid; $[\alpha]_D^{25}$ –297.8 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 9.6 Hz, 1 H), 8.05 (d, *J* = 6.7 Hz, 1 H), 7.70 (d, *J* = 9.1 Hz, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 6.36 (dt, *J* = 16.8, 9.8 Hz, 1 H), 6.17 (dd, *J* = 14.8, 9.9 Hz, 1 H), 6.08 (dd, *J* = 14.7, 9.7 Hz, 1 H), 5.92 (dd, *J* = 14.6, 9.7 Hz, 1 H), 5.69 (dd, *J* = 10.7, 3.6 Hz, 1 H), 5.53 (s, 2 H), 5.40–4.75 (m, 7 H), 4.65 (d, *J* = 14.2 Hz, 1 H), 4.44 (t, *J* = 7.3 Hz, 1 H), 3.45 (s, 3 H), 3.25 (s, 3 H), 3.21 (s, 3 H), 3.20 (s, 3 H), 3.11 (s, 3 H), 2.68 (s, 3 H), 2.67 (s, 3 H), 2.48–2.33 (m, 1 H), 2.25–2.10 (m, 4 H), 2.03 (s, 3 H), 1.75–0.70 (m, 66 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 173.4, 172.9, 172.8, 171.4, 171.2, 170.9, 170.8, 170.5, 170.3, 170.0, 168.0, 137.3, 133.6, 133.4, 132.2, 131.0, 116.0, 73.2, 58.3, 57.3, 56.2, 55.3, 54.8, 54.2, 50.0, 48.7, 48.2, 47.9, 44.7, 41.0, 39.3, 39.2, 37.1, 35.9, 34.5, 33.3, 32.3, 31.7, 31.4, 31.3, 30.1, 29.8, 29.7, 29.5, 25.0, 24.8, 24.7 (2 C), 24.5, 24.2, 23.7, 23.5 (2 C), 22.5, 21.8, 21.2, 21.1, 20.7, 20.4, 19.6, 18.6, 18.2, 18.1, 17.6, 15.0, 9.9.

HRMS (ESI): *m*/*z* calcd for $C_{67}H_{116}N_{11}O_{13}$ $[M + H]^+$: 1282.8754; found: 1282.8892.

***cyclo*-{[(2*S*,3*R*,4*R*,6*E*,8*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6,8,10-undecatrienoyl]-L-2-aminobutyryl-*N*-methyl-glycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl} (10)**

To a stirred solution of *E,E*-acetyltriene **9** (25 mg, 0.019 mmol) in MeOH (2 mL) was added K_2CO_3 (65 mg, 0.47 mmol) at r.t. After stirring for 12 h at r.t., the reaction mixture was diluted with H_2O (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by semi-preparative HPLC on a C18 column to afford **10**; yield: 18 mg (75%); white solid; $[\alpha]_D^{25}$ –201.1 (*c* 0.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.7 Hz, 1 H), 7.59 (d, *J* = 7.4 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 6.37 (dt, *J* = 16.8, 9.8 Hz, 1 H), 6.19–5.95 (m, 4 H), 5.72–5.60 (m, 2 H), 5.48 (d, *J* = 6.0 Hz, 1 H), 5.32 (dd, *J* = 11.4, 3.7 Hz, 1 H), 5.25–5.02 (m, 7 H), 4.93 (dd, *J* = 10.1, 5.8 Hz, 1 H), 4.82 (t, *J* = 7.2 Hz, 1 H), 4.78–4.62 (m, 3 H), 4.51 (t, *J* = 7.2 Hz, 1 H), 3.84 (t, *J* = 6.8 Hz, 1 H), 3.51 (s, 3 H), 3.39 (s, 3 H), 3.24 (s, 3 H), 3.11 (s, 3 H), 3.10 (s, 3 H), 2.70 (s, 3 H), 2.69 (s, 3 H), 2.52–2.35 (m, 1 H), 2.20–2.00 (m, 4 H), 1.75–0.70 (m, 60 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 173.7, 173.6, 173.4, 171.5, 171.2, 171.1, 170.4, 170.3, 170.1, 170.0, 137.3, 134.1, 133.7, 131.8, 130.9, 116.0, 74.4, 58.7, 57.9, 57.5, 55.5, 55.4, 55.3, 50.3, 48.7, 48.6, 48.2, 45.1, 40.6, 39.5, 38.9, 37.3, 36.1, 35.9, 35.8, 34.0, 31.5, 31.3, 31.1, 29.7 (2 C), 29.5, 29.0, 25.4, 24.9 (2 C), 24.6, 24.4, 23.8, 23.7, 23.6, 23.4, 23.3, 21.9, 21.8, 21.1, 20.2, 19.8, 18.7, 18.3, 18.1, 16.9, 16.0, 9.9.

HRMS (ESI): *m*/*z* calcd for $C_{65}H_{114}N_{11}O_{12}$ $[M + H]^+$: 1240.8648; found: 1240.8602.

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(5) The coupling constant $J_{\varepsilon,\zeta}$ of the corresponding *Z*-isomer is 11.0 Hz.

(6) Preparation of **1a** was conducted up to 10 g scale without reducing the *E*-selectivity.

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(9) The organozirconium chemistry also worked well in CH_2Cl_2. The desired product was the major portion of the crude product (typically 60–70%) by LC/MS or analytical HPLC analysis. However, the isolated yields were low in some cases after purification by semi-preparative HPLC. We usually got less than 70% recovery from semi-preparative HPLC purification.

(10) For pharmaceutical utilities of similar cyclosporin triene analogues, see the recent US Patent: Wu, F. X. H.; Or, Y. S. US Patent 2004/266669, **2004**.

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