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Biomimetic Total Synthesis of Cruentaren A via Aromatization of Diketodioxinones

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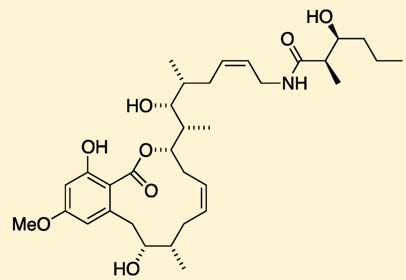
Supporting Information

ABSTRACT: The total synthesis of cruentaren A, a biologically active resorcylate natural product, is reported. The aromatic unit was constructed via late-stage cyclization and aromatization from a diketodioxinone intermediate and macrocyclization using Fürstner ring-closing alkyne metathesis.



Cruentaren A

INTRODUCTION

Cruentaren A (**1**) was isolated in 2006 by Höfle et al. from the myxobacterium *Byssovorax cruenta*. It is a member of the extensive resorcylic acid lactone family of natural products and contains a 12-membered lactone with a *Z*-double bond and an unsaturated amide side chain (Figure 1).[1] Cruentaren A (**1**) strongly inhibits the growth of yeast and filamentous fungi, shows high cytotoxicity against L929 mouse fibroblast cells with an IC_{50} value of 1.2 ng mL,[1] and selectively inhibits mitochondrial F-ATPase.[2] Structurally related resorcylate lactones include the estrone agonist zearalenone (**2**), the antimalarial and cyclin kinase dependent inhibitor aigialomycin D (**3**), and MEK inhibitor LL-783,277 (**4**).[3]

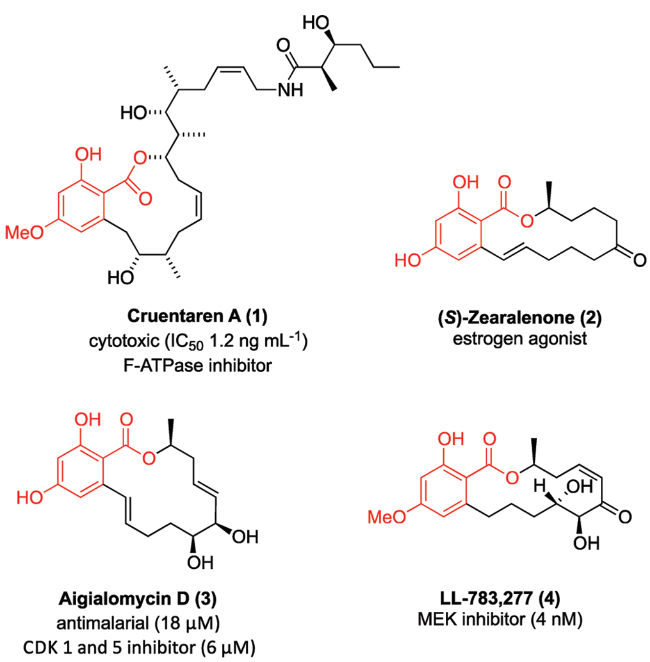


Figure 1. Cruentaren A and related natural products (resorcylate units are highlighted in red).

As a result of its interesting biological properties, two groups have already reported the total synthesis of cruentaren A (**1**) and analogues in 2007 and 2008.[4,5] The retrosynthetic strategies proposed by Maier[4] and Fürstner[5] have similar key disconnections. Both started with the derivatization of the aromatic unit (resorcylic and orsellinic acid respectively), and the macrolactone was elaborated using an esterification reaction followed by ring-closing alkyne metathesis and Lindlar hydrogenation to afford the unsaturated lactone desired (*Z*)-configuration. The esterification approach is commonly used for the synthesis of resorcylic acid lactones, despite being often low yielding because of the deactivation and steric hindrance of the carbonyl functionality due to the (protected) phenolic ring substituents. In addition to this, Fürstner and Maier faced another problem with the formation of the unwanted 6-membered lactone being observed under basic or acidic conditions.[4,5] Since many resorcylic acid lactones have highly promising diverse biologically activities and can be considered, in many cases, as medicinal chemistry hits (Figure 1),[3] we recently sought to develop a flexible biomimetic inspired strategy for the synthesis of this class of natural product.[6] The key features of our approach, which was inspired by the earlier work of Hyatt,[7] Harris,[8] and Boeckman,[9] are the trapping of the ketene intermediate **6**, obtained via retro-Diels–Alder reaction of diketo-dioxinone **5**[7] with an alcohol, providing triketoester **7**, which can subsequently undergo aromatization to produce

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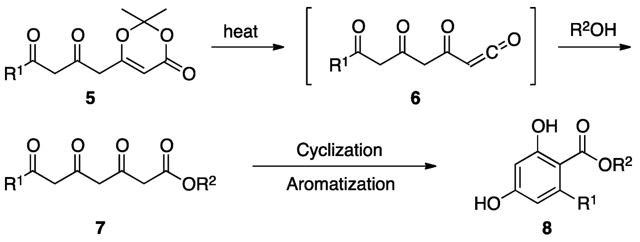
resorcylate **8** (Scheme 1). This flexible methodology has already been applied in total syntheses of (*S*)-zearalenone (**2**),[6a,c] aigialomycin D (**3**),[6b] LL-Z1640-2 (**4**)[6d] (Figure 1), and other natural products. Herein, we describe the application of this methodology to a more complex natural product, cruentaren A (**1**).

Scheme 1. Synthesis of Resorcylates 8 Using Diketo-dioxinones 5



■ RESULTS AND DISCUSSION

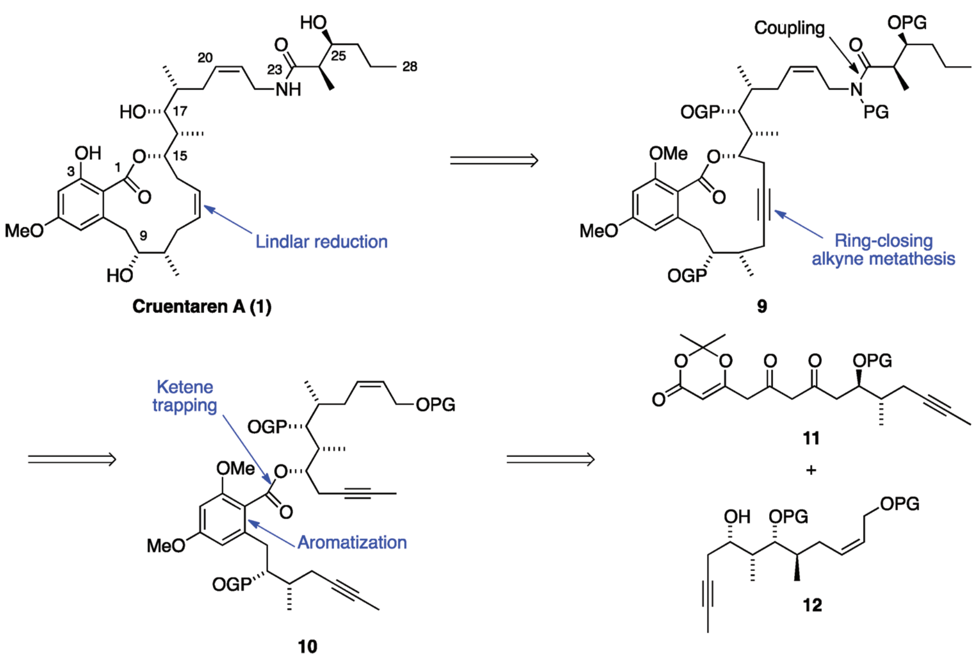
Our retrosynthetic analysis is illustrated in Scheme 2. The last step of the synthesis was projected to be a Lindlar reduction of the macrocyclic lactone alkyne functionality, which should afford cruentaren A (**1**) with a high *Z*/*E* selectivity.[4,5] Furthermore, the presence of the triple bond should prevent unwanted trans-lactonization involving the unprotected C-9 alcohol during earlier stages of the synthesis. Lactone **9** should be available using ring closing alkyne metathesis of the fully protected precursor **10**. The aromatic ring should be available from reaction of alcohol **12** with diketo-dioxinone **11** via ketene trapping and aromatization.

The initial target for synthesis was the carboxylic acid **19** (Scheme 3), which would later be converted to the key diketo-dioxinone **22** via *C*-acylation. Brown crotylation[10] of aldehyde **13** gave homoallylic alcohol **14** with the desired *anti*-configuration, which was subjected to sequential silyl ether protection and hydroboration[11] to give alcohol **15**. After oxidation to the corresponding aldehyde using IBX,[12] the acetylene moiety was introduced using a Seyferth–Gilbert reaction[13] by treatment with diazophosphonate **16**[14] to give acetylene **17** in 92% yield over two steps. Methylation of terminal alkyne **17** was carried out by deprotonation with *n*-butyllithium and alkylation with methyl iodide. Selective deprotection of the TBS group was achieved by allowing diether **18** to react with *p*-toluenesulfonic acid. Finally, TEMPO oxidation[15] of the resultant primary alcohol gave carboxylic acid **19**.

Diketo-dioxinone **22** was synthesized in two steps from acid **19** using a method developed in our group (Scheme 4).[16,17] Acid **19** was converted to the corresponding Weinreb amide **20**, which was allowed to react with the dianion derived from keto-dioxinone **21** in presence of diethylzinc. This straightforward variation of a crossed Claisen condensation reaction gave diketo-dioxinone **22** on gram scale in 12 steps.

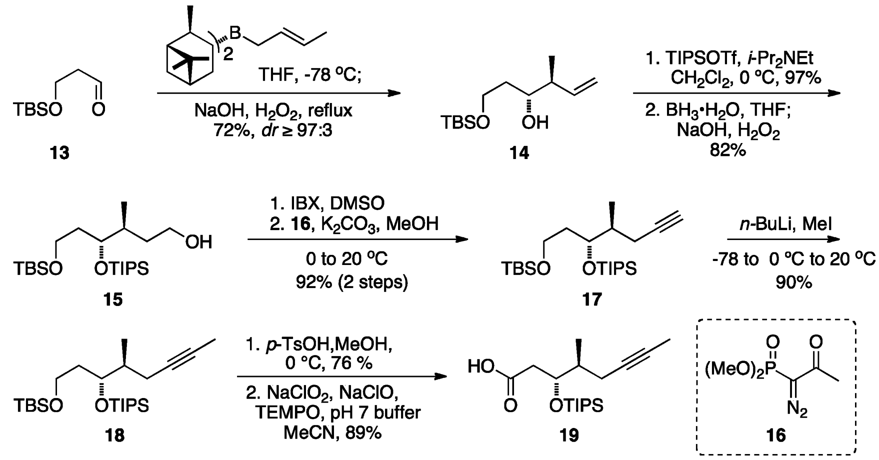
Alcohol **33** was synthesized from the chiral pool (*S*)-Roche ester **23** (Scheme 5). Following trityl protection, reduction with DIBAl-H gave the corresponding primary alcohol, which was 4-toluenesulfonylated. Subsequent nucleophilic substitution of tosylate **24** with the acetylide derived from propargyl 4-methoxybenzyl ether (**25**)[18] in DMSO and THF[19] gave the hexynediol derivative **26**. Interestingly, the use of HMPA as solvent resulted in elimination and not substitution. Deprotection of the trityl ether followed by Lindlar reduction gave (*Z*)-alkenol **27**. Swern oxidation of alkenol **27** followed by an Evans aldol reaction[20] gave the corresponding aldol **29** in good yield and high diastereoselectivity. Subsequent TBS protection followed by reductive cleavage of the chiral auxiliary using lithium borohydride gave alcohol **30**. The final steps in the elaboration of acetylene **33** were asymmetric propargylation and terminal acetylene methylation. After oxidation of **30** to the corresponding aldehyde, a Barbier type reaction, using indium and amino alcohol **31** as a chiral ligand,[21] gave the acetylenic alcohol **32** in good yield and with excellent diastereoselectivity. However, acetylene **32** was isolated admixed with the

Scheme 2. Retrosynthetic Analysis of Cruentaren A (1)

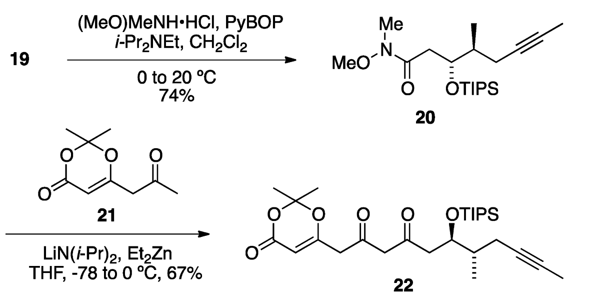


dx.doi.org/10.1021/jo300225z | J. Org. Chem. 2012, 77, 3060−3070

Scheme 3. Synthesis of Carboxylic Acid 19



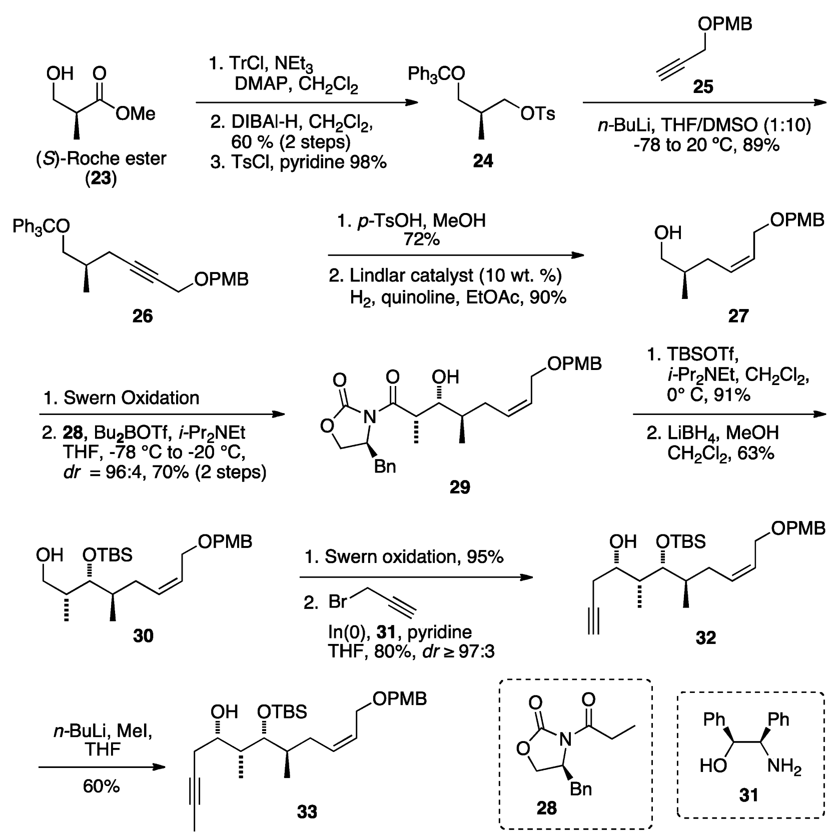
Scheme 4. Synthesis of Diketo-dioxinone 22 via C-Acylation



corresponding allene. The stereochemistry of acetylene **32** was confirmed by comparison of the ^{1}H NMR spectrum of the corresponding (*S*)- and (*R*)-Mosher esters.[22] Finally, direct methylation of the terminal alkyne gave the key alcohol **33**, and at this stage, the allene contaminant was easily removed by flash chromatography.

With alcohol **33** and diketo-dioxinone **22** in hand, we sought to examine the synthesis of the core resorcylate unit of cruentaren A (**1**) (Scheme 6). Thermolysis of diketo-dioxinone **22** in dichloromethane at 110 °C in a sealed tube presumably afforded the corresponding highly reactive ketene, which was trapped in situ with alcohol **33**. Direct treatment of the reaction mixture with cesium carbonate followed by acidification in methanol as solvent gave the resorcylate **34** (R = H) and its corresponding methyl ether **34** (R = Me) in a combined yield of 55% on a gram scale.[6] It is reasonable to suggest that the

Scheme 5. Synthesis of Alcohol 33



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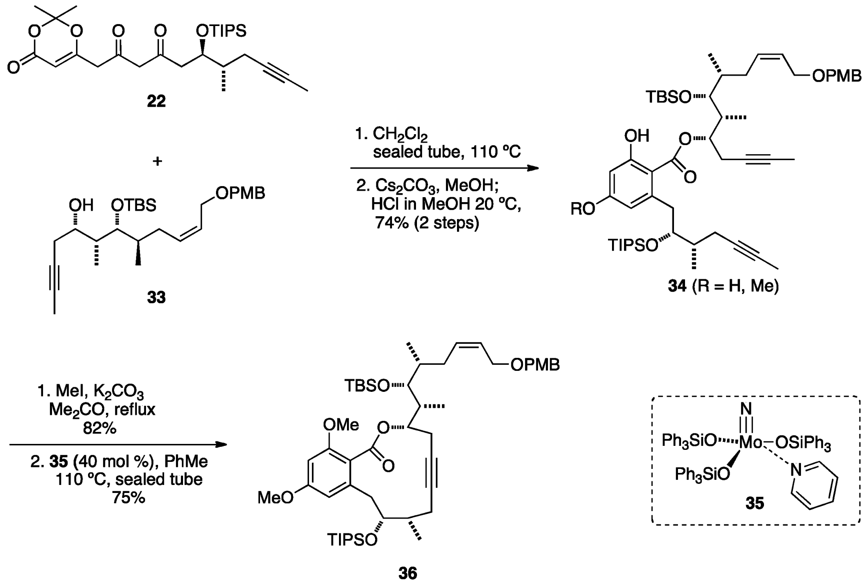
Scheme 6. Synthesis of 36, the Core Structure of Cruentaren A



methyl ether arose via formation of the cyclohexanedione ketal **37** and aromatization (Figure 2). The mixture of phenols **34**

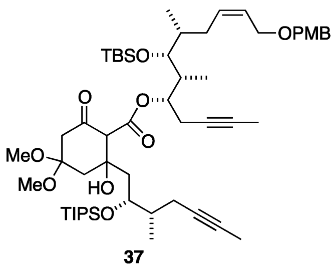


Figure 2. Presumed intermediate **37** leading to the resorcylate **34** (R = Me).

(R = H) and **34** (R = Me) was converted into the corresponding dimethyl ether by reaction with methyl iodide and potassium carbonate in acetone. It is worth noting that when the thermolysis of **33** with **22** was carried out under the usual conditions of toluene at reflux, degradation of diketo-dioxinone **22** was observed before complete reaction with alcohol **33**. Ring-closing alkyne metathesis using the excellent Fürstner molybdenum nitride precatalyst **35**[23] smoothly gave the macrolactone **36** in 75% yield. However, a high catalyst loading was required in order to shorten the reaction time and obtain an acceptable yield since degradation of diyne **34** was observed on extended heating.

Deprotection of the *p*-methoxybenzyl group in ether **36** using DDQ gave alcohol **38**, which was subsequently converted into the corresponding azide via a Mitsunobu reaction using zinc azide (Scheme 7).[24] Staudinger reduction gave access to the corresponding amine **39**, which was used immediately in the next step on account of its surprising and frustrating instability. Coupling between amine **39** and acid **40**[20,25] using HBTU and HOBt in DMF furnished the corresponding amide **41** in 67% yield. Regioselective monocleavage of the methyl ether group at the arene C-3 center was carried out using boron trichloride[26] while the silyl ether protecting groups were removed by treatment with hexafluorosilicic acid in acetonitrile at 40 °C to give resorcylate amide **42**. It was observed that the sterically hindered silyl group at C-17 underwent deprotection slowly, which necessitated the higher temperature for reaction (40 °C), however, no degradation was observed. Finally, Lindlar reduction of the remaining alkyne gave cruentaren A (**1**). The spectroscopic properties of the synthetic **1** were in full accordance with data reported for the natural product.[1,2]

■ CONCLUSION

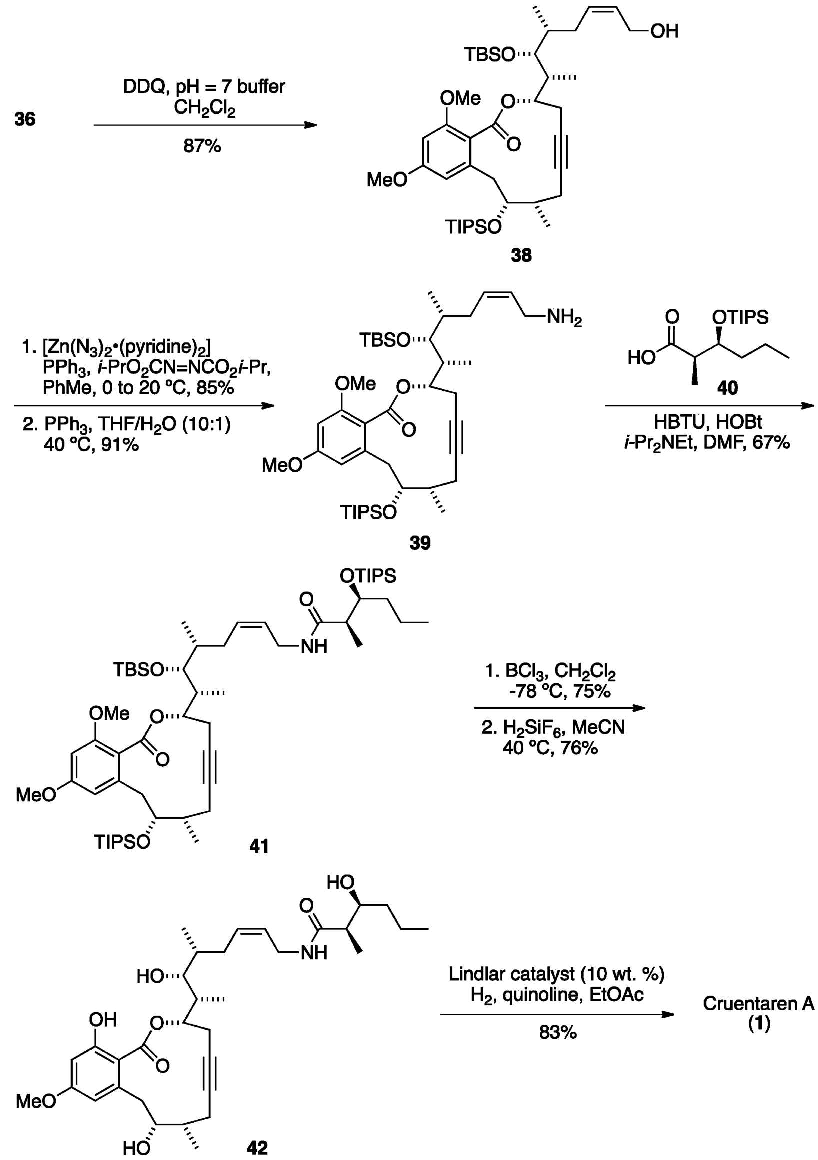
Cruentaren A (**1**) was successfully obtained using our resorcylate biomimetic synthetic strategy in 23 steps for the longest linear sequence. The synthesis of the core of cruentaren A (**1**) was achieved on gram scale from diketo-dioxinone **22** and alcohol **33**. The successful synthesis of **34** and the stability of delicate functionalities during the generation of the resorcylate unit by late stage aromatization proved that this biomimetic strategy is a powerful method for the synthesis of complex polyfunctional macrocyclic resorcylate natural products and appropriate for the convergent parallel synthesis of analogues.

■ EXPERIMENTAL SECTION

General Methods. All reactions were carried out in oven-dried glassware under N_2, using commercially supplied solvents and reagents unless otherwise stated. THF, CH_2Cl_2, Et_3N, and MeOH were redistilled from Na−Ph_2CO, CaH_2, CaH_2, and Mg turnings−I_2, respectively. Hexanes refers to the petroleum fraction with bp 40−60 °C. Column chromatography was carried out on silica gel using flash techniques (eluants are given in parentheses). Analytical thin-layer chromatography was performed on precoated silica gel F_{254} aluminum plates with visualization under UV light or by staining using either acidic vanillin, anisaldehyde, or ninhydrin spray reagents. Melting points were obtained using a melting point apparatus and are uncorrected. Infrared data were carried out neat unless otherwise stated with adsorptions reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 400 or 500 MHz with chemical shifts (δ) quoted in parts per million (ppm) and coupling constants (J) recorded in hertz (Hz). ^{13}C NMR spectra were recorded at 100 or 125 MHz with chemical shifts (δ) quoted in ppm.

Synthesis of Acid 19. *(3R,4S)-1-[(tert-Butyldimethylsilyl)oxy]-4-methylhex-5-en-3-ol (14).* *n*-BuLi (2.5 M in hexanes, 53 mL) was added with stirring to *t*-BuOK in THF (1 M; 146 mL) and *trans*-2-butene (30 mL) at −78 °C. After complete addition, the

Scheme 7. Total Synthesis of Cruentaren A (1)



mixture was stirred at −45 °C for 10 min, recooled to −78 °C, and (−)-(Ipc)$_2$BOMe in THF (1 M; 175 mL) added dropwise. After a further 30 min, $BF_3 \cdot Et_2O$ (24 mL, 196 mmol) and aldehyde **13**[27] (27.5 g, 146 mmol) were added sequentially dropwise at −78 °C. After 4 h at −78 °C, aqueous NaOH (3 M; 150 mL) and H_2O_2 in H_2O (50 wt %; 40 mL) were added, and the mixture was heated at reflux for 1 h. The organic layer was separated, washed with H_2O and brine, dried ($MgSO_4$), filtered, and rotary evaporated and the residue chromatographed (Et_2O/hexanes 1:19) to afford the alcohol **14** (19.0 g, 74%) as a colorless oil: R_f 0.20 (Et_2O/hexanes 1:9); $[\alpha]_D$ −9.2 (*c* 2, $CHCl_3$); NMR analysis of the crude material showed the presence of one diastereoisomer (dr ≥ 97: 3); IR ν_{max} 3417, 1465, 1386, 1254, 1086, 832, 775, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.82 (m, 1H), 5.12−5.07 (m, 2H), 3.95−3.90 (m, 1H), 3.86−3.81 (m, 1H), 3.74−3.70 (m, 1H), 2.28−2.20 (m, 1H) 1.66−1.61 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 115.1, 75.1, 62.8, 43.9, 35.5, 25.9, 18.1, 15.8, −5.5; MS (CI) *m*/*z* 245 [M + H]$^+$; HRMS (CI) *m*/*z* calcd for $C_{13}H_{29}O_2Si$ [M + H]$^+$ 245.1937, found 245.1934. The ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ were in full agreement with a sample prepared by a published route.[28]

(3S,4R)-6-[(tert-Butyldimethylsilyl)oxy]-3-methyl-4-{[tris(propan-2-yl)silyl]oxy}hexan-1-ol (**15**). **1.** 2,6-Lutidine (19 mL, 195 mmol) and *i*-Pr_3SiOTf (31 mL, 94 mmol) were added sequentially with stirring to alcohol **14** (19 g, 78 mmol) in CH_2Cl_2 (500 mL) at 0 °C. After 4 h, saturated aqueous NH_4Cl was added and the aqueous layer extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated, and the residue was chromatographed (Et_2O/hexanes 1:9) to afford the corresponding silyl ether (30 g, 97%) as a colorless oil: R_f 0.85 (EtOAc/hexanes 1:9); $[\alpha]_D$ +4.9 (*c* 2.1, CH_2Cl_2); IR ν_{max} 1464, 1391, 1253, 1097, 883, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.76 (m, 1H), 5.03−4.98 (m, 2H), 3.98 (td, *J* = 6.1, 3.1 Hz, 1H), 3.66 (t, *J* = 5.7 Hz, 2H), 2.43−2.35 (m, 1H) 1.62 (dd, *J* = 12.9, 6.5 Hz, 2H), 1.08 (s, 21H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H); 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 114.4, 72.7, 60.2, 43.2, 36.5, 25.9, 18.2, 14.5, 12.9, −5.5; MS (ESI) *m*/*z* 401 [M + H]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{49}O_2Si_2$ [M + H]$^+$ 401.3271, found 401.3260. Anal. Calcd for $C_{22}H_{48}O_2Si_2$: C, 65.93; H, 12.07. Found: C, 66.02; H, 12.03.

2. BH_3 in THF (1 M; 135 mL) was slowly added with stirring to the previously prepared silyl ether (18.0 g, 45 mmol) in THF (150 mL) at 0 °C and the mixture allowed to warm to room temperature. After 18 h, it was cooled to 0 °C and slowly added via cannula to aqueous NaOH (2.5 M; 300 mL) at 0 °C, aqueous H_2O_2 (30 wt %, 150 mL) was added, and stirring was continued stirred for 1 h at room temperature. The mixture was diluted with Et_2O, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and rotary evaporated. The crude material was chromatographed (Et_2O/hexanes 1:4) to afford disilyl ether **15** (15.4 g, 82%) as a colorless oil: R_f 0.30 (Et_2O/hexanes 1:9); $[\alpha]_D$ +9.1 (*c* 2.2, CH_2Cl_2); IR ν_{max} 3330, 1464, 1384, 1253, 1092, 1052, 1005, 940, 832, 774, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (td, *J* = 6.1, 3.1 Hz, 1H), 3.75−3.57 (m, 4H), 1.86−1.50 (m, 5H), 1.08 (s, 21H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.2, 60.5, 60.2, 36.1, 35.0, 25.9, 18.2, 15.0, 12.9, −5.4; MS (ESI) *m/z* 419 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{51}O_3Si_2$ $[M + H]^+$ 419.3377, found 419.3366. Anal. Calcd for $C_{22}H_{50}O_3Si_2$: C, 63.09; H, 12.03. Found: C, 63.15; H, 12.05.

(7R)-2,2,3,3,10-Pentamethyl-7-[(2S)-pent-4-yn-2-yl]-9,9-bis-(propan-2-yl)-4,8-dioxa-3,9-disilaundecane (17). **1.** Iodoxybenzoic acid (9.0 g, 30 mmol) and, after 10 min, alcohol **15** (6.5 g, 15.5 mmol) in DMSO (10 mL) were added with stirring to DMSO (50 mL). After 4 h, the mixture was filtered, and the filtrate diluted with Et_2O and washed with H_2O. The organic layer was dried ($MgSO_4$), filtered, and rotary evaporated. The residue was filtered through silica (Et_2O/hexanes 1:19) to provide the corresponding aldehyde (4.8 g, 74%) as a colorless oil: R_f 0.90 (Et_2O/hexanes 1:9); IR ν_{max} 2712, 1727, 1464, 1252, 1093, 1049, 832, 774, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 3.94 (dt, *J* = 6.1, 2.8 Hz, 1H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.51−2.44 (m, 1H), 2.32−2.23 (m, 2H), 1.77−1.48 (m, 3H), 1.07 (s, 21H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H); 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 73.1, 59.8, 46.3, 36.8, 32.9, 25.9, 18.2, 16.3, 12.9, −5.4; MS (ESI) *m/z* 417 $[M - H]^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{49}O_3Si_2$ $[M + H]^+$ 417.3220, found 417.3213.

2. Freshly prepared diazophosphonate (**16**)[29] (5.7 g, 22.6 mmol) was added with stirring to the foregoing aldehyde (4.7 g, 11.3 mmol) and anhydrous K_2CO_3 (5.7 g, 33.9 mmol) in MeOH (200 mL) at room temperature and the mixture rapidly turned milky green. After 3 h, the mixture was diluted with Et_2O, and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1:19) to afford acetylene **17** (4.3 g, 92%) as a colorless oil: R_f 0.90 (Et_2O/hexanes 1:19); $[\alpha]_D$ +5.4 (*c* 2.6, CH_2Cl_2); IR ν_{max} 3318, 1467, 1390, 1256, 1092, 1011, 939, 882, 834, 777, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (td, *J* = 6.2, 3.8 Hz, 1H), 3.74−3.65 (m, 2H), 2.20 (ddd, *J* = 16.8, 6.3, 2.6 Hz, 1H), 2.08 (ddd, *J* = 16.8, 8.2, 2.6 Hz, 1H), 1.94 (t, *J* = 2.8 Hz, 1H), 1.92 − 1.89 (m, 1H), 1.67−1.51 (m, 2H), 1.07 (s, 21H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H); 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.8, 72.1, 69.0, 60.0, 38.0, 35.9, 25.9, 21.3, 18.3, 15.1, 12.9, −5.4; MS (ESI) *m/z* 413 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{23}H_{49}O_2Si_2$ $[M + H]^+$ 413.3271, found 413.3271. Anal. Calcd for $C_{23}H_{48}O_2Si_2$: C, 66.92; H, 11.72. Found: C, 66.94; H, 12.00.

(7R)-7-[(2S)-Hex-4-yn-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis-(propan-2-yl)-4,8-dioxa-3,9-disilaundecane (18). *n*-BuLi in hexanes (2.5 M; 6.2 mL) was added slowly with stirring to acetylene **17** (4.3 g, 10.4 mmol) in THF (60 mL) at −78 °C. After 45 min, MeI (1.3 mL, 20.8 mmol) was added and the mixture stirred at room temperature for 3 h. Saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:19) to afford acetylene **18** (4.0 g, 90%) as a colorless oil: R_f 0.95 (Et_2O/hexanes 1: 19); $[\alpha]_D$ +8.1 (*c* 1.8, CH_2Cl_2); IR ν_{max} 3317, 1465, 1391, 1363, 1253, 1097, 834, 376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (td, *J* = 5.8, 3.7 Hz, 1H), 3.75−3.66 (m, 2H), 2.12−1.98 (m, 2H), 1.89−1.82 (m, 1H), 1.76 (t, *J* = 2.4 Hz, 3H), 1.62−1.58 (m, 2H), 1.07 (s, 21H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.2, 76.2, 71.9, 60.2, 38.7, 35.5, 25.9, 22.0, 18.2, 14.8, 12.9, 3.5, −5.3; MS (ESI) *m/z* 427 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{24}H_{51}O_2Si_2$ $[M + H]^+$ 427.3428, found 427.3415.

(3R,4S)-4-Methyl-3-{[tris(propan-2-yl)silyl]oxy}oct-6-ynoic Acid (19). **1.** *p*-TsOH (0.9 g, 4.7 mmol) was added with stirring to silyl ether **18** (4.0 g, 9.4 mmol) in MeOH (100 mL) at 0 °C and the mixture allowed to warm to room temperature. After 2 h, $NaHCO_3$ (1.5 g) was added, and the mixture was stirred for 10 min, filtered, and rotary evaporated. The residue was diluted with Et_2O, washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:9) to afford the corresponding unprotected alcohol (2.7 g, 92%) as a colorless oil: R_f 0.2 (Et_2O/hexanes 1:9); $[\alpha]_D$ +8.1 (*c* 1.8, CH_2Cl_2); IR ν_{max} 3347, 1463, 1384, 1092, 1060, 1034, 882, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (td, *J* = 5.7, 4.4 Hz, 1H), 3.79 (t, *J* = 6.3 Hz, 2H), 2.09−2.05 (m, 2H), 1.95−1.89 (m, 1H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.71−1.67 (m, 2H), 1.09 (s, 21H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.7, 77.2, 73.5, 60.7, 38.6, 34.0, 22.6, 18.2, 14.4, 13.0, 3.4; MS (ESI) *m/z* 313 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{37}O_2Si$ $[M + H]^+$ 313.2563, found 313.2547.

2. Phosphate buffer (H_3PO_4/NaH_2PO_4; 0.5 M, pH = 7; 60 mL), $NaClO_2$ (1.8 g, 20.0 mmol), TEMPO (0.1 g, 0.64 mmol), and aqueous NaClO (0.05 mL) were added with stirring to the previously prepared alcohol (2.5 g, 8 mmol) in MeCN (60 mL) at 0 °C. After 20 min, saturated aqueous $Na_2S_2O_3$ (10 mL) was added, the aqueous layer was extracted with EtOAc (2×), and the combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (EtOAc/hexanes 1:4) to afford acid **19** (2.0 g, 79%) as a colorless oil: R_f 0.25 (EtOAc/hexanes 1:9); $[\alpha]_D$ +3.5 (*c* 0.8, $CHCl_3$); IR ν_{max} 1712, 1467, 1300, 1090, 1068, 1002, 948, 882, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47−4.43 (m, 1H), 2.54 (ddq, *J* = 15.6, 5.2, 2.4 Hz 1H), 2.47 (ddq, *J* = 15.6, 6.4, 2.4 Hz, 1H), 2.11−2.08 (m, 2H), 2.00−1.94 (m, 1H), 1.78 (t, *J* = 2.4 Hz, 3H), 1.08 (s, 21H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 77.2, 77.1, 71.8, 39.1, 37.6, 22.4, 18.1, 14.4, 12.7, 3.4; MS (ESI) *m/z* 325 $[M - H]^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{33}O_3Si$ $[M - H]^+$ 325.2199, found 325.2200. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.26; H, 10.39.

Synthesis of Diketodioxinone 22. *(3R,4S)-N-Methoxy-N,4-dimethyl-3-{[tris(propan-2-yl)silyl]oxy}oct-6-ynamide (20).* *i*-Pr_2NEt (4.0 mL, 23 mmol) was added with stirring to carboxylic acid **19** (2.5 g, 7.7 mmol), *N*-methoxy-*N*-methylamine (1.0 g, 10 mmol), and PyBOP (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) (4.0 g, 8 mmol) in CH_2Cl_2 (20 mL) at 0 °C and allowed to warm to room temperature. After 30 min, the mixture was poured into Et_2O, and the organic layer was washed with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes 1:4) to afford amide **20** (2.1 g, 74%) as a colorless oil: R_f 0.20 (CH_2Cl_2); $[\alpha]_D$ +16.3 (*c* 0.3, $CHCl_3$); IR ν_{max} 1664, 1383, 1181, 1093, 1064, 1013, 940, 882, 741, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (ddd, *J* = 7.5, 4.8, 3.3 Hz, 1H), 3.69 (s, 3H), 3.17 (s, 3H), 2.64 (dd, *J* = 15.2, 7.5 Hz, 1H), 2.42 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.17−2.10 (m, 1H), 2.05−1.89 (m, 2H), 1.77 (t, *J* = 2.44 Hz, 3H), 1.06 (s, 21H), 1.03 (d, *J* = 6.70 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8, 76.6, 71.5, 61.2, 39.3, 35.2, 32.1, 22.0, 18.1, 14.6, 12.7, 3.5; MS (ESI) *m/z* 370 $[M - H]^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{40}NO_3Si$ $[M + H]^+$ 370.2777, found 370.2771. Anal. Calcd for $C_{20}H_{39}NO_3Si$: C, 64.99; H, 10.64, N 3.79. Found: C, 65.12; H, 10.71, N 3.82.

(6R,7S)-1-(2,2-Dimethyl-6-oxo-2,6-dihydro-1,3-dioxin-4-yl)-7-methyl-6-{[tris(propan-2-yl)silyl]oxy}undec-9-yne-2,4-dione (22). Keto-dioxinone **21**[6b] (2.4 g, 12.8 mmol) was added dropwise with stirring to freshly prepared LiN(*i*-Pr)$_2$ (27.8 mmol) in THF (25 mL) at −78 °C. After 30 min at −40 °C, the mixture was recooled to −78 °C, and Et_2Zn in THF (1 M; 25.7 mL) was added. After another 30 min at −40 °C, amide **20** (1.6 g, 4.28 mmol) was added, and after a further 4 h at −5 °C, the reaction was quenched with aqueous HCl (1 M) and the mixture extracted with EtOAc (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:9 to 1:4) to give dioxinone **22** (1.4 g, 67%) as a light yellow oil: R_f 0.55 (EtOAc/hexanes 1:4); $[\alpha]_D$ +9.5 (*c* 0.6, $CHCl_3$); IR ν_{max} 1731, 1604, 1378, 1271, 1014, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 15.1 (br s, 1H),

5.63 (s, 1H), 5.40 (s, 1H), 4.47−4.43 (m, 1H), 3.20 (s, 2H), 2.42 (dd, *J* = 14.2, 4.7 Hz, 1H), 2.34 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.07−2.05 (m, 2H), 1.97−1.87 (m, 1H), 1.77 (t, *J* = 2.46 Hz, 3H), 1.7 (s, 6H), 1.04 (s, 21H), 0.98 (d, *J* = 6.83 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 188.3, 164.9, 160.6, 107.1, 101.4, 96.4, 77.2, 76.7, 72.1, 43.5, 41.1, 39.1, 25.0, 22.2, 18.1, 14.4, 12.8, 3.4; MS (ESI) *m*/*z* 493 [M + H]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{45}O_6Si$ [M + H]$^+$ 493.2985, found 493.3003. Anal. Calcd for $C_{27}H_{44}O_6Si$: C, 65.82; H, 9.00. Found: C, 65.75; H, 8.99.

Synthesis of Alcohol 33. *(2S)-2-Methyl-3-(triphenylmethoxy)-propyl 4-Methylbenzenesulfonate (**24**).* **1.** Et_3N (52 mL, 372 mmol), DMAP (4.1 g, 33.9 mmol) and methyl (2*S*)-3-hydroxy-2-methyl-propanoate (**23**) (20 g, 169 mmol) were added with stirring to Ph_3CCl (95 g, 339 mmol) in CH_2Cl_2 (600 mL). After 12 h at room temperature, H_2O was added, and the mixture extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated to leave the crude ester, which was used without further purification.

2. DIBAl-H in CH_2Cl_2 (1.0 M; 400 mL) was added dropwise with stirring to the preceding ester in CH_2Cl_2 (500 mL) at −40 °C. After 4 h, the mixture was allowed to warm to room temperature, when H_2O followed by aqueous NaOH (10 wt %) were added with stirring. After 1 h, the aqueous layer was extracted with CH_2Cl_2 (2 ×), and the combined organic layers were washed with brine, dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 3:7) to give the corresponding alcohol (34 g, 60%) as white needles: mp 72−74 °C (EtOAc/hexane); R_f 0.20 (EtOAc/hexanes 1: 4); $[\alpha]_D$ +25 (*c* 2.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.41 (m, 6H), 7.33−7.22 (m, 9H), 3.63−3.55 (m, 2H), 3.23 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.03 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.33 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 128.6, 127.8, 127.0, 86.9, 67.8, 67.5, 36.0, 13.8. These data are in agreement with literature values.[30]

3. The preceding ester (20 g, 60 mmol) in pyridine (50 mL) was added with stirring to TsCl (17 g, 90 mmol) in pyridine (50 mL) at 0 °C. After 5 h at 0 °C, reaction was quenched with H_2O and stirring continued for 10 min to hydrolyze the excess TsCl. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was triturated in hexanes to afford sulfonate **24** as a white solid (28 g, 98%): mp 90−92 °C (CH_2Cl_2/hexane); R_f 0.70 (EtOAc/hexanes 1:4); $[\alpha]_D$: +10.0 (*c* 1.8, CH_2Cl_2); IR ν_{max} 1492, 1448, 1360, 1174, 976, 809, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.74 (m, 2H), 7.34−7.22 (m, 17H), 4.13 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.00 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.03 (dd, *J* = 10.9, 5.0 Hz, 1H), 2.93 (dd, *J* = 10.9, 6.5 Hz, 1H), 2.43 (s, 3H), 2.08−2.00 (m, 1H), 0.89 (d, *J* = 7.06 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144 6, 143.9, 133.0, 129.8, 128.6, 127.9, 127.7, 127.0, 86.4, 72.5, 64.2, 34.0, 21.7, 13.9; MS (ESI) *m*/*z* 509 [M + Na]$^+$, 525 [M + K]$^+$, 243 [CPh_3]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{30}O_4SNa$ [M + Na]$^+$ 509.1763, found 509.1743.

*1-Methoxy-4-({[(5R)-5-methyl-6-(triphenylmethoxy)hexyl]oxy}-methyl)benzene (**26**).* *n*-BuLi in hexanes (2.5 M; 40.6 mL) was added dropwise with stirring to propargylic ether **25**[18] (17.9 g, 101 mmol) in THF (20 mL) at −78 °C. After 30 min at 0 °C, sulfonate **24** (26.0 g, 53 mmol) in DMSO (180 mL) was added, and, after a further 2 h, reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (2×), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1:19) to give acetylene **26** (22.0 g, 89%) as a colorless oil: R_f 0.25 (EtOAc/hexanes 1:4); $[\alpha]_D$ +4.3 (*c* 1, $CHCl_3$); IR ν_{max} 1611, 1586, 1512, 1490, 1461, 1356, 1247, 1173, 1067, 1033, 986, 819, 763, 697 cm^{-1}; ^{1}H NMR δ 7.46−7.44 (m, 6H), 7.31−7.20 (m, 11H), 6.90−6.86 (m, 2H), 4.46 (s, 2H), 4.08 (t, *J* = 2.1 Hz, 2H), 3.81 (s, 3H), 3.05 (dd, *J* = 8.9, 5.5 Hz, 1H), 3.01 (dd, *J* = 8.9, 6.9 Hz, 1H), 2.47 (dt, *J* = 16.6, 5.6, 2.0 Hz, 1H), 2.28 (dt, *J* = 16.6, 7.2, 2.0 Hz, 1H), 2.06−1.95 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.3, 129.7, 128.7, 127.7, 126.8, 113.8, 86.2, 85.4, 70.9, 67.0, 57.3, 55.3, 33.6, 23.2, 16.8; MS (ESI) *m*/*z* 513 [M + Na]$^+$, 529 [M + K]$^+$, 243 [CPh_3]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{34}O_3Na$ [M + Na]$^+$ 513.2406; found 513.2414. Anal. Calcd for $C_{34}H_{34}O_3$: C, 83.23; H, 6.98. Found: C, 83.17; H, 6.86.

*(2R,4Z)-6-[(4-Methoxyphenyl)methoxy]-2-methylhex-4-en-1-ol (**27**).* **1.** *p*-TsOH (13.7 g, 720 mmol) was added with stirring to acetylene **26** (23.5 g, 480 mmol) in MeOH (250 mL) at 0 °C and the mixture allowed to warm to room temperature. After 2 h, saturated aqueous $NaHCO_3$ was added, and after 15 min, the mixture was filtered and rotary evaporated. The residual oil was dissolved in Et_2O and washed with brine, and the organic layer was dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 3:17 to 1:4) to give the corresponding alcohol (8.5 g, 72%) as a colorless oil: R_f 0.20 (EtOAc/hexanes 1:4); $[\alpha]_D$ +6.0 (*c* 1, CH_2Cl_2); IR ν_{max} 1614, 1588, 1516, 1461, 1356, 1356, 1246, 1175, 1034, 989, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* 8.7 Hz, 2H), 4.52 (s, 2H), 4.13 (t, *J* = 2.2 Hz, 2H), 3.81 (s, 3H), 3.58 (d, *J* = 6.1 Hz, 2H), 2.34 (ddt, *J* = 16.8, 6.2, 2.2 Hz, 1H), 2.27 (ddt, *J* = 16.8, 6.4, 2.2 Hz, 1H), 1.96−1.84 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 129.7, 113.8, 85.0, 71.0, 67.1, 57.3, 55.3, 33.1, 22.7, 16.3 (one quaternary C missing); MS (CI) *m*/*z* 266 [M + NH_4]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}NO_3$ [M + NH_4]$^+$ 266.1756, found 266.1686. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 7.96.

2. Quinoline (11 mL, 6.6 mmol) and Lindlar catalyst (5 wt % Pd on $CaCO_3$, poisoned with lead, 130 mg, 10 wt %) were added to the preceding alcohol (13.5 g, 54 mmol) in EtOAc (150 mL). The mixture was placed under H_2, stirred for 2 h, and filtered through Celite, and the filtrate was washed with aqueous HCl (1 M). The organic layer was rotary evaporated and chromatographed (short pad, EtOAc/hexanes 1:4) to give alkenol **27** (12.2 g, 90%, *Z*/*E* > 95:5 by ^{1}H NMR) as a colorless oil: R_f 0.15 (EtOAc/hexanes 1:4); $[\alpha]_D$ −2.0 (*c* 1.1, CH_2Cl_2); IR ν_{max} 3423, 1614, 1590, 1515, 1464, 1356, 1303, 1248, 1178, 1080, 1034, 986, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.74−5.62 (m, 2H), 4.47 (s, 2H), 4.09−4.00 (m, 2H), 3.81 (s, 3H), 3.48−3.40 (m, 2H), 2.21−2.15 (m, 1H), 2.04−1.97 (m, 1H), 1.77−1.69 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.5, 130.1, 129.5, 127.0, 113.8, 72.1, 67.0, 65.1, 55.3, 35.8, 31.0, 16.5; MS (ESI) *m*/*z* 251 [M + H]$^+$, HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_3$ [M + H]$^+$ 251.1647; found 251.1643. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.89; H, 8.73.

*(4S)-4-Benzyl-3-[(2S,3R,4R,6Z)-3-hydroxy-8-[(4-methoxyphenyl)-methoxy]-2,4-dimethyloct-6-enoyl]-1,3-oxazolidin-2-one (**29**).* **1.** DMSO (11.2 mL, 157 mmol) and after 20 and a further 45 min, respectively, alcohol **27** (11.2 g, 44.8 mmol) in CH_2Cl_2 (40 mL) and Et_3N (30.0 mL, 179 mmol) were added dropwise with stirring to oxalyl chloride (7.6 mL, 89.6 mmol) in CH_2Cl_2 (200 mL) at −78 °C. The mixture was slowly allowed to warm to 0 °C and the reaction quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with saturated aqueous $CuSO_4$, brine, and H_2O, dried ($MgSO_4$), filtered, and rotary evaporated to afford the crude aldehyde (11.0 g, 100%) which was used immediately without any further purification.

2. Bu_2BOTf (40 mL, 1 M) followed by *i*-Pr_2NEt (7 mL, 40.3 mmol) were added slowly with stirring to oxazolidinone **28** (11.5 g, 49.2 mmol) in CH_2Cl_2 (100 mL) at −78 °C, and the mixture was allowed to warm to room temperature. After 1 h, the mixture was recooled to −78 °C, and the preceding aldehyde (11.0 g, 44.8 mmol) in CH_2Cl_2 (10 mL) was added slowly with stirring. After 3 h at −78 °C, the mixture was allowed to warm to −20 °C and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (EtOAc/hexane 1:4 to 2:3) to give the aldol adduct **29** (15.7 g, 73% yield over two steps, dr = 96: 4 by ^{1}H NMR of the crude material) as a colorless oil: R_f 0.20 (EtOAc/hexanes 1:9); $[\alpha]_D$ +27.5 (*c* 2.3, CH_2Cl_2); IR ν_{max} 3529, 1776, 1693, 1612, 1585, 1512, 1454, 1384, 1351, 1241, 1208, 1075, 1032, 983, 819, 750, 701 cm^{-1}; ^{1}H NMR δ 7.36−7.19 (m, 7H), 6.87 (d, J = 8.6 Hz, 2H), 5.72−5.61 (m, 2H), 4.69−4.63 (m, 1H), 4.44 (s, 2H), 4.19−4.17 (m, 2H), 4.12−4.02 (m, 2H), 3.93 (qd, J = 6.9, 2.1 Hz, 1H), 3.79 (s, 3H), 3.63 (dd, J = 8.8, 3.0 Hz, 1H), 3.26 (dd, J = 13.4, 3.3 Hz, 1H), 2.79 (dd, J = 13.4, 9.5 Hz, 1H), 2.39 (dt, J = 15.4, 5.3 Hz, 1H), 2.14 (dt, J = 15.6, 6.0 Hz 1H), 1.76−1.66 (m, 1H), 1.23 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 159.1, 152.8, 135.0, 131.5, 130.4, 129.4, 128.9, 127.7, 127.4, 113.7, 74.3, 71.9, 66.1, 65.5, 55.2, 55.1, 39.4, 37.7, 35.8, 30.7, 15.3, 9.5; MS (ESI) m/z 482 $[M + H]^+$, 504 $[M + Na]^+$, 520 $[M + K]^+$; HRMS (ESI) m/z calcd for $C_{28}H_{36}NO_6$ $[M + H]^+$ 482.2543, found 482.2535. Anal. Calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33. Found: C, 69.98; H, 7.50.

(2R,3R,4R,6Z)-3-[(tert-Butyldimethylsilyl)oxy]-8-[(4-methoxyphenyl)methoxy]-2,4-dimethyloct-6-en-1-ol (**30**). *i*-Pr_2NEt (16.4 mL, 94 mmol) followed by *t*-$BuMe_2SiOTf$ (11 mL, 47 mmol) were added with stirring to the aldol adduct **29** (11.3 g, 23.5 mmol) in CH_2Cl_2 (150 mL) at 0 °C. After 3 h, the mixture was added to saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAC/hexanes 1:9) to afford the corresponding silyl ether (12.7 g, 91%) as a colorless oil: R_f 0.60 (EtOAc/hexanes: 7); $[\alpha]_D$ +52.1 (0.6, CH_2Cl_2); IR ν_{max} 1781, 1696, 1612, 1513, 1463, 1381, 1351, 1249, 1210, 1085, 1036, 971, 836, 774, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (m, 7H), 6.86 (d, J = 8.6 Hz, 2H), 5.65−5.52 (m, 2H), 4.61−4.55 (m, 1H), 4.41 (s, 2H), 4.15−3.96 (m, 6H), 3.79 (s, 3H), 3.25 (dd, J = 13.3, 3.2 Hz, 1H), 2.75 (dd, J = 13.3, 9.6 Hz, 1H), 2.23−2.17 (m, 1H), 1.84−1.76 (m, 1H), 1.64−1.58 (m, 1H), 1.23 (d, J = 6.5 Hz), 0.94−0.92 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 159.1, 152.9, 135.3, 132.3, 130.5, 129.4, 129.3, 128.9, 127.4, 113.8, 76.4, 71.8, 66.0, 65.6, 55.6, 55.2, 41.4, 39.2, 37.6, 30.0, 26.1, 18.4, 16.3, 13.9, −3.7, −4.1 (CTBS); MS (ESI) m/z 596 $[M + H]^+$, 618 $[M + Na]^+$, 634 $[M + K]^+$; HRMS (ESI) m/z calcd for $C_{34}H_{50}NO_6Si$ $[M + H]^+$ 596.3407; found 596.3417. Anal. Calcd for $C_{34}H_{49}NO_6Si$: C, 68.54; H, 8.29, N, 2.35. Found: C, 68.58; H, 8.18, N 2.29.

2. $LiBH_4$ (0.7 g, 30 mmol) was added with stirring to the preceding oxazolidinone (9.0 g, 15.1 mmol) in CH_2Cl_2 and MeOH (10: 1; 100 mL) at 0 °C. After 15 min at 0 °C and 2 h at room temperature, saturated aqueous NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes 1:4) to afford the alcohol **30** (3.8 g, 63%) as a colorless oil: R_f 0.20 (EtOAc/hexanes 1:4); $[\alpha]_D$ −5.2 (*c* 0.6, CH_2Cl_2); IR ν_{max} 1613, 1513, 1463, 1381, 1302, 1249, 1172, 1092, 1037, 836, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.68−5.55 (m, 2H), 4.45 (s, 2H), 4.10−3.96 (m, 2H), 3.81 (s, 3H), 3.69 (dd, J = 5.2, 2.2 Hz, 1H), 3.50−3.37 (m, 2H), 2.28−2.21 (m, 1H), 1.88−1.69 (m, 3H), 0.90−0.83 (m, 15H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.9, 130.3, 129.5, 126.7, 113.8, 75.4, 72.1, 66.3, 65.5, 55.2, 38.2, 38.1, 31.3, 26.0, 18.3, 16.5, 11.7, −4.0, −4.3; MS (ESI) m/z 423 $[M + H]^+$, 445 $[M + Na]^+$, 461 $[M + K]^+$; HRMS (ESI) m/z calcd for $C_{24}H_{43}O_4Si$ $[M + H]^+$ 423.2931, found 423.2936. Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.20; H, 9.88.

(4S,5R,6R,7R,9Z)-6-[(tert-Butyldimethylsilyl)oxy]-11-[(4-methoxyphenyl)methoxy]-5,7-dimethylundec-9-en-1-yn-4-ol (**32**). **1.** DMSO (2.2 mL, 32 mmol) and after 20 min and a further 45 min, respectively, alcohol **30** (3.8 g, 9 mmol) in CH_2Cl_2 (5 mL) and Et_3N (750 μL, 4.4 mmol) were added dropwise with stirring to oxalyl chloride (1.5 mL, 18 mmol) in CH_2Cl_2 (60 mL) at −78 °C. The mixture was allowed to warm to 0 °C, and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with saturated aqueous $CuSO_4$, brine, and H_2O, dried ($MgSO_4$), filtered, and rotary evaporated to afford the crude aldehyde (3.6 g, 95%), which was used without any further purification: R_f 0.80 (EtOAc/hexanes 1:9).

2. Amino alcohol **31** (2.8 mg, 13 mmol), pyridine (1.0 mL, 13 mmol), and propargyl bromide (80 wt % in PhMe, 1.4 mL, 13 mmol) were added with stirring to indium powder (1.5 g, 3.07 mmol) in THF (25 mL) at −20 °C. After 45 min, the preceding aldehyde (1.8 g, 4.3 mmol) was added with stirring, and, after 16 h, the mixture was allowed to warm to room temperature. Aqueous HCl (1 M) was added, the aqueous layer was extracted with EtOAc and hexanes (1: 1; 2×), and the combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (EtOAc/hexanes 1:9) to afford a mixture of acetylene **32** and the corresponding allene (10: 1, 1.5 g, 75%) as a colorless oil. The ^{1}H NMR spectrum and Mosher ester analysis showed the presence of one diastereoisomer in the acetylene component (dr ≥ 97: 3): R_f 0.50 (EtOAc/hexanes 1:4); $[\alpha]_D$ −8.5 (*c* 0.8, CH_2Cl_2); IR ν_{max} 1686, 1613, 1513, 1463, 1302, 1249, 1173, 1086, 1034, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.68−5.54 (m, 2H), 4.44 (s, 2H), 4.03 (d, J = 6.0 Hz, 2H), 3.80−3.77 (s, 4H), 3.66 (dd, J = 4.6, 2.6 Hz, 1H), 2.38 (dd, J = 6.5, 2.6 Hz, 2H), 2.19−2.13 (m, 1H), 2.01 (t, J = 2.62 Hz, 1H), 1.89−1.83 (m, 2H), 1.78−1.72 (m, 1H), 0.94−0.89 (m, 15H), 0.08 (s, 3H), 0.07 (s, 3H), (allene 10%, characteristic peaks δ 5.20−5.18 (m, 1H), 4.86 (dt, J = 6.5, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.3, 130.4, 129.4, 127.2, 113.8, 81.2, 77.9, 72.9, 71.9, 70.5, 65.6, 55.3, 38.9, 38.8, 31.0, 26.1, 25.0, 18.3, 16.0, 8.81, −3.5, −4.2; MS (ESI) m/z 461 $[M + H]^+$, 483 $[M + Na]^+$, 499 $[M + K]^+$; HRMS (ESI) m/z calcd for $C_{27}H_{45}O_4S_i$ $[M + H]^+$ 461.3087, found 461.3085. Anal. Calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63. Found: C, 72.46; H, 9.57.

Preparation of the (S)- and (R)-Mosher Esters of Alcohol **32**. EDC (3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine) (65 mg, 0.34 mmol), (*S*)-PhC(OMe)(CF_3)CO_2H (80 mg, 0.34 mmol), and DMAP (42 mg, 0.34 mmol) were added with stirring to alcohol **32** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL). After 48 h, H_2O was added, the aqueous layer was extracted with Et_2O (2×), and the combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1:19) to give the (*S*)-Mosher ester of **32** (30 mg, 40%) as a white gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.53 (m, 2H), 7.42−7.40 (m, 3H), 7.26 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.68−5.61 (m, 1H), 5.59−5.53 (m, 1H), 5.16 (dd, J = 5.8 Hz, 1H), 4.43 (s, 2H), 4.04 (d, J = 6.2 Hz, 1H), 3.80 (s, 3H), 3.50 (s, 3H), 3.40 (t, J = 4.7 Hz, 1H), 2.65−2.54 (m, 2H), 2.23−2.14 (m, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.88−1.82 (m, 1H), 1.74−1.67 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

In an entirely analogous fashion, the (*R*)-Mosher-ester of **32** was prepared using (*R*)-PhC(OMe)(CF_3)CO_2H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.42−7.40 (m, 3H), 7.28 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 5.69−5.63 (m, 1H), 5.59−5.52 (m, 1H), 5.19−5.15 (m, 1H), 4.45 (s, 2H), 4.05 (d, J = 6.2 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.35 (t, J = 4.7 Hz, 1H), 2.70 (ddd, J = 7.5, 2.5, 2.5 Hz, 1H), 2.62 (ddd, J = 7.5, 2.7, 2.7 Hz, 1H), 2.20−2.13 (m, 2H), 2.02 (t, J = 2.4 Hz, 1H), 1.84−1.78 (m, 1H), 1.68−1.65 (m, 1H), 0.90 (s, 9H), 0.82 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

(5S,6R,7R,8R,10Z)-7-[(tert-Butyldimethylsilyl)oxy]-12-[(4-methoxyphenyl)methoxy]-6,8-dimethyldodec-10-en-2-yn-5-ol (**33**). *n*-BuLi in hexanes (2.5 M; 3.0 mL) followed by MeI (1.2 mL, 18.5 mmol) were added with stirring to acetylene **32** (1.7 g, 3.7 mmol) in THF (3 mL) at −78 °C. After 2 h, the mixture was added to saturated aqueous NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:9) to afford acetylene **33** (1.0 g, 60%) as a colorless oil: R_f 0.45 (EtOAc/hexanes 1:4); $[\alpha]_D$ −9.5 (0.4, $CHCl_3$); IR ν_{max} 3450, 1613, 1513, 1463, 1302, 1249, 1173, 1086, 1034, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.68 5.55 (m, 2H), 4.44 (s, 2H), 4.04 (d, J = 5.8 Hz, 2H), 3.81 (s, 3H), 3.73−3.68(m, 1H), 3.63 (dd, J = 4.6, 3.4 Hz, 1H), 2.34−2.31 (m, 2H), 2.20−2.14 (m, 1H), 1.91−1.81 (m, 2H), 1.79−1.70 (m, 4H), 0.94−0.88 (m, 15H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.4, 130.4, 129.4, 127.2, 113.8, 78.1, 77.8, 75.6, 72.9, 71.9, 65.6, 55.3, 39.3, 38.7, 30.9, 26.1, 25.5, 18.3, 16.1, 9.1, 3.5, −3.5, −4.1; MS (ESI) m/z 475 $[M + H]^+$, 497 $[M + Na]^+$, 513 $[M + K]^+$; HRMS (ESI) m/z calcd for $C_{28}H_{47}O_4Si$ $[M + H]^+$ 475.3244,

found 475.3245. Anal. Calcd for $C_{28}H_{46}O_4Si$: C, 70.84; H, 9.77. Found: C, 70.96; H, 9.69.

Synthesis of Acid 40. *(2R,3S)-2-Methyl-3-{[tris(propan-2-yl)silyl]oxy}hexanoic Acid (**40**).* **1.** *i*-Pr_3SiOTf (1.2 mL, 4.7 mmol) was added with stirring to (4*R*)-4-benzyl-3-[(2*R*,3*S*)-3-hydroxy-2-methylhexanoyl]-1,3-oxazolodin-2-one[4,5] (1.1 g, 3.6 mmol) and 2,6-lutidine (1 mL, 9 mmol) in CH_2Cl_2 (75 mL) at 0 °C. After 4 h, H_2O was added, the aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were washed with brine, dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (EtOAc/hexanes 1:9) to afford the corresponding silyl ether (1.3 g, 78%) as a white gum: R_f 0.60 (EtOAc/hexanes 1:9) $[\alpha]_D$ −60.1 (*c* 1.5, $CHCl_3$); IR ν_{max} 3526, 1719, 1693, 1385, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H), 4.58, (ddd, *J* = 9.8, 7.3, 2.6 Hz, 1H), 4.24 (dt, *J* = 8.1 Hz, 4.3 Hz, 1H), 4.20−4.08 (m, 2H), 3.85 (dq, *J* = 6.9, 4.0 Hz, 1H), 3.32 (dd, *J* = 13.4, 2.1 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.4 Hz, 1H), 1.65−1.53 (m, 2 H), 1.40−1.30 (m, 2 H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 21 H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 153.1, 135.4, 129.4, 128.9, 127.3, 73.0, 66.0, 55.9, 42.5, 38.0, 37.0, 18.2, 17.7, 14.4, 13.1, 10.3; MS (ESI) *m/z* 462 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{44}NO_4Si$ $[M + H]^+$ 462.3040, found 462.3035.

2. Aqueous H_2O_2 (30 wt %; 2 mL) and LiOH (0.4 g, 10 mmol) in H_2O (10 mL) were added with stirring to the preceding oxazolidinone (1.9 g, 4.1 mmol) in THF (40 mL). After 4 h, aqueous Na_2SO_3 (1.3 M) was added with stirring and, after a further 30 min, the aqueous layer was first extracted with CH_2Cl_2 and acidified to pH 3 with aqueous HCl (1 M) and finally re-extracted with CH_2Cl_2 (3X). The combined organic layers (of the second extraction) were dried ($MgSO_4$), filtered and rotary evaporated to afford carboxylic acid **40** (0.9 g, 70%) as a colorless oil: R_f 0.50 (EtOAc/hexanes 1:9) $[\alpha]_D$ −9.8 (*c* 2.1, $CHCl_3$); IR ν_{max} 1706, 1462, 1385, 1234, 1137, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (td, *J* = 10.0, 5.5 Hz, 1H), 2.72−2.66 (qd, *J* = 7.1, 5.5 Hz, 1H), 1.61−1.50 (m, 2H), 1.43−1.31 (m, 2H), 1.14 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 21H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.3, 44.0, 36.1, 18.6, 18.0, 17.7, 14.3, 12.6, 11.25; MS (ESI) *m/z* 301 $[M-H]^-$; HRMS (ESI) *m/z* calcd for $C_{16}H_{33}O_3Si$ $[M - H]^-$ 301.2199, found 301.2192.

Synthesis of Cruentaren A (1). *(5S,6R,7R,8R,10Z)-7-[(tert-Butyldimethylsilyl)oxy]-12-[4-methoxyphenyl)methoxy]6,8-dimethyldodec-10-en-2-yn-5-yl 2,4-Dihydroxy-6-[(2R,3S)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]benzoate (**34**, R = H) and (5S,6R,7R,8R,10Z)-7-[(tert-Butyldimethylsilyl)oxy]-12-[4-methoxyphenyl)methoxy]6,8-dimethyldodec-10-en-2-yn-5-yl 2-dihydroxy-4-methoxy-6-[(2R,3S)-3-methyl-2-{[tris(propan-2-yl)silyl]-oxy}hept-5-yn-1-yl]-4-methoxybenzoate (**34**, R = Me).* Diketo-dioxinone **22** (1.26 g, 2.55 mmol) and alcohol **33** (1.15 g, 2.42 mmol) in CH_2Cl_2 (20 mL) were heated to 110 °C in a sealed tube. After 2 h, the solvent was rotary evaporated, the residue was dissolved in MeOH (20 mL), and Cs_2CO_3 (2.4 g, 7.0 mmol) was added. After 20 min, HCl in MeOH (1.25 M; 30 mL) was added and the mixture stirred for 30 min and extracted with EtOAc (3×). The combined organic extracts were washed with aqueous HCl (1 M) and brine, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1: 19) to afford resorcylates **34** (R = H) (0.68 g) and **34** (R = Me) (0.52 mg) with a combined yield of 55%. Resorcylate **34** (R = H): R_f 0.55 (EtOAc/hexanes 3:7) $[\alpha]_D$ +12.0 (0.4, $CHCl_3$); IR ν_{max} 3372, 1614, 1515, 1466, 1248, 1086, 1035, 834, 772, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 5.68−5.52 (m, 2H), 5.30−5.26 (m, 1H), 5.10 (s, 1H), 4.45 (s, 2H), 4.22 (dt, *J* = 8.2, 4.0 Hz), 4.07−4.05 (m, 2H), 3.80 (s, 3H), 3.50 (dd, *J* = 5.7, 2.8 Hz, 1H), 3.30 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.90 (dd, *J* = 14.1, 8.2 Hz, 1H), 2.70−2.56 (m, 2H), 2.32 − 2.31 (m, 3H), 2.08−2.01 (m, 1H), 1.93−1.70 (m, 9H), 1.06−0.86 (m, 39H), 0.08 (m, 3H), 0.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 164.6, 160.0, 159.6, 145.5, 132.1, 130.5, 129.4, 127.5, 113.8, 112.2, 106.5, 101.7, 78.3, 77.7, 75.9, 75.7, 75.6, 74.2, 71.9, 65.7, 55.3, 39.4, 38.5, 38.2, 37.6, 30.1, 26.1, 22.7, 22.0, 18.2, 18.1, 16.1, 14.7, 13.0, 10.8, 3.5 (2 C), −3.7; MS (ESI) *m/z* 891 $[M + H]^+$, 913 $[M + Na]^+$; HRMS (ESI) *m/z* calcd for $C_{52}H_{83}O_8Si_2$ $[M + H]^+$ 891.5681, found 891.5654. Resorcylate **34** (R = Me): R_f 0.65 (EtOAc/hexanes 3:7) $[\alpha]_D$ +14.0 (*c* 0.4, $CHCl_3$); IR ν_{max} 3475, 1618, 1462, 1248, 1086, 1039, 834, 773, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 5.68−5.52 (m, 2H), 5.30−5.27 (m, 1H), 4.44 (s, 2H), 4.25−4.22 (m, 1H), 4.06 (d, *J* = 6.1 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.51 (dd, *J* = 5.7, 2.8 Hz, 1H), 3.30 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.95 (dd, *J* = 14.1, 8.6 Hz, 1H), 2.70−2.56 (m, 2H), 2.33−2.20 (m, 3H), 2.09−2.01 (m, 1H), 1.93−1.68 (m, 9H), 1.06−0.86 (m, 39H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 164.7, 163.5, 159.2, 144.6, 132.1, 130.5, 129.4, 127.5, 113.8, 111.9, 106.1, 99.3, 78.8, 78.3, 75.9, 75.8, 75.5, 74.2 (2 C), 71.9, 65.7, 55.3 (2 C), 39.4, 38.5, 38.4, 37.7, 30.9, 26.1, 22.7, 22.0, 18.2, 18.1, 16.1, 14.8, 13.0, 10.8, 3.5 (2 C), −3.7; MS (ESI) *m/z* 905 $[M + H]^+$, 927 $[M + Na]^+$; HRMS (ESI) *m/z* calcd for $C_{53}H_{85}O_8Si_2$ $[M + H]^+$ 905.5783, found 905.5786.

*(3S,8S,9R)-3-[(2R,3R,4R,6Z)-3-[(tert-Butyldimethylsilyl)oxy]-8-[4-methoxyphenyl)methoxy]-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-1-one (**36**).* **1.** K_2CO_3 (1.5 mg, 21.1 mmol) followed by MeI (1.3 mL, 21.1 mmol) were added with stirring to resorcylate **34** (R = H, Me) (0.9 g, 1.06 mmol) in Me_2CO (40 mL), and the mixture was heated at 60 °C for 2 h. Saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:19) to afford the corresponding protected resorcylate (0.80 mg, 82%) as a colorless oil: R_f 0.60 (EtOAc/hexanes 1:4) $[\alpha]_D$ +14.0 (*c* 0.6, $CHCl_3$); IR ν_{max} 1721, 1605, 1513, 1463, 1249, 1159, 1087, 1044, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 2.6 Hz, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 5.67−5.56 (m, 2H), 5.11−5.04 (m, 1H), 4.44 (s, 2H), 4.31−4.27 (m, 1H), 4.07 (d, *J* = 6.1 Hz, 2H), 3.79 (s, 6H), 3.75 (s, 3H), 3.58−3.55 (m, 1H), 2.75−2.58 (m, 4H), 2.29−1.74 (m, 7H), 1.77 (t, *J* = 2.3 Hz, 3H), 1.76 (t, *J* = 2.3 Hz, 3H), 1.00−0.88 (m, 39H), 0.07(s, 3H), 0.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 160.7, 159.1, 157.8, 139.1, 132.6, 130.5, 129.4, 127.2, 117.8, 113.8, 107.0, 96.7, 78.1, 78.0, 76.3, 75.2, 74.6, 71.8, 65.7, 55.6, 55.2 (2 C), 38.8, 37.9, 37.8, 36.1, 30.1, 26.1, 22.7, 22.0, 18.2, 18.1, 16.7, 14.6, 13.0, 10.4, 3.6, 3.5, −3.7, (2 quaternary C of low intensity); MS (ESI) *m/z* 919 $[M + H]^+$, 941 $[M + Na]^+$; HRMS (ESI) *m/z* calcd for $C_{54}H_{87}O_8Si_2$ $[M + H]^+$ 919.5940, found 919.5960.

2. Catalyst **35** (130 mg, 40 mol %) was added to the preceding resorcylate (300 mg, 0.33 mmol) in PhMe (20 mL) at 110 °C under a closed Ar atmosphere. After 8 h, the mixture was filtered through a short pad of silica, and the resulting filtrate was rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1:9) to afford macrocycle **36** (215 mg 75%) as a colorless oil: R_f 0.60 (EtOAc/hexanes 1:4) $[\alpha]_D$ −14,4 (*c* 0.6, $CHCl_3$); IR ν_{max} 1739, 1604, 1514, 1466, 1258, 1157, 1087, 1055, 837, 772, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 5.65−5.53 (m, 2H), 5.47 (br s, 1H), 4.43 (s, 2H), 4.06−4.00 (m, 3H), 3.80−3.72 (m, 10H), 3.49 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.51−2.39 (m, 4H), 2.19−2.13 (m, 2H), 1.99−1.94 (m, 1H) 1.88−1.77 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.97−0.91 (m, 33H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 160.3, 159.2, 157.3, 139.5, 132.4, 130.5, 129.3, 127.2, 118.2, 113.8, 108.3, 96.7, 81.4, 79.7, 77.3, 76.5, 74.8, 71.9, 65.7, 55.8, 55.3 (2 C), 40.9, 38.7, 37.7, 37.6, 30.12, 26.1, 23.8, 23.3, 18.5, 18.1, 17.9, 17.0, 13.0, 11.4, −3.6, −3.5; MS (ESI) *m/z* 865 $[M + H]^+$, 882 $[M + H_2O]^+$, 887 $[M + Na]^+$, 903 $[M + K]^+$; HRMS (ESI) *m/z* calcd for $C_{50}H_{80}O_8Si_2$ $[M + H]^+$ 865.5470, found 865.5468.

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*(3S,8S,9R)-3-[(2R,3R,4R,6Z)-3-[(tert-Butyldimethylsilyl)oxy]-8-hydroxy-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-1-one (**38**).* DDQ (100 mg, 0.3 mmol) was added with vigorous stirring to ether **36** (200 mg, 0.23 mmol) in CH_2Cl_2 and H_2O (1: 1; 2 mL). After 20 min, the solution was added to saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2×) The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes 1:19 to 1:4) to give alcohol **38** (150 mg, 87%) as a colorless oil: R_f 0.30 (EtOAc/hexanes 1:4) $[\alpha]_D$ −16.0 (*c* 0.9, $CHCl_3$); IR ν_{max} 3427, 1732, 1603, 1461, 1265, 1158, 1083, 1051, 832, 769, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J* = 2.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 5.68−5.62 (m, 1H), 5.57 − 5.48 (m, 2H), 5.48 (s, 1H), 4.25 − 4.12 (m, 2H), 4.01 (d, *J* = 8.8 Hz, 1H), 3.80−3.73 (m, 7H), 3.50 (dd, *J* = 4.4, 4.4 Hz, 1H), 2.55−2.39 (m, 4H), 2.27−2.14 (m, 2H), 1.99−1.92 (m, 1H), 1.90−1.77 (m, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.98−0.91 (m, 36H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.3, 157.3, 139.5, 131.8, 129.5, 118.1, 108.4, 96.7, 81.3, 79.6, 77.2, 74.8, 58.6, 55.8, 55.2, 41.0, 38.6, 37.6, 37.4, 29.8, 26.1, 23.9, 23.3, 18.4, 18.1, 17.9, 17.3, 13.0, 11.6, −3.7, (1 C missing, underneath $CDCl_3$ peak); MS (ESI) *m*/*z* 745 $[M + H]^+$, 767 $[M + Na]^+$, 783 $[M + K]^+$; HRMS (ESI) *m*/*z* calcd for $C_{42}H_{73}O_7Si_2$ $[M + H]^+$ 745.4895, found 745.4921.

*(3S,8S,9R)-3-[(2R,3R,4R,6Z)-8-Amino-3-[(tert-butyldimethylsilyl)-oxy]-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-1-one (**39**).* **1.** $Zn(N_3)_2\cdot(pyridine)_2$ (213 mg, 0.7 mmol) and PPh_3 (190 mg, 0.7 mmol) were added with stirring to alcohol **38** (130 mg, mmol) in PhMe (20 mL), and the mixture was cooled to 0 °C, when *i*-$PrO_2CN{=}NCO_2$-*i*-Pr (140 μL, 0.7 mmol) was added. After 4 h at room temperature, the mixture was filtered and the filtrate rotary evaporated. The residue was chromatographed (Et_2O/hexanes 1:9) to give the corresponding azide (115 mg, 85%) as an amorphous solid: R_f 0.70 (EtOAc/hexanes 1:4) $[\alpha]_D$ −24.1 (*c* 0.8, CH_2Cl_2); IR ν_{max} 2099, 1739, 1608, 1461, 1263, 1161, 1091, 1057, 833, 774 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 6.41 (d, *J* = 2.2 Hz, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 5.76−5.69 (m, 1H), 5.58−5.51 (m, 1H), 5.46−5.37 (m, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.79−3.68 (m, 9H), 3.50 (dd, *J* = 4.6, 4.6 Hz, 1H), 2.49−2.36 (m, 4H), 2.24−2.12 (m, 2H), 1.96−1.74 (m, 4H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.96−0.89 (m, 36 H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 167.8, 161.0, 157.8, 140.0, 135.6, 123.7, 118.7, 109.1, 97.1, 81.7, 80.2, 77.9, 77.0, 75.1, 56.3, 55.8 (2 C), 47.3, 41.5, 39.1, 38.2, 38.1, 30.4, 26.5, 24.3, 23.8, 18.9, 18.5, 18.2, 17.5, 13.6, 11.7, −3.3, −3.4; MS (ESI) *m*/*z* 770 $[M + H]^+$, 792 $[M + Na]^+$, 808 $[M + K]^+$; HRMS (ESI) *m*/*z* calcd for $C_{42}H_{73}O_7Si_2$ $[M + H]^+$ 770.4960, found 770.4966.

2. PPh_3 (360 mg, 13.7 mmol) was added with stirring to the preceding azide (105 mg, 0.14 mmol) in THF and H_2O (10:1; 1.5 mL). The reaction mixture was stirred at 50 °C for 4 h and rotary evaporated and the residue chromatographed (CH_2Cl_2/MeOH/$NH_3\cdot H_2O$ 9:1:0.1) to afford amine **39** (90 mg, 91%) as an amorphous solid: R_f 0.40 (CH_2Cl_2/MeOH/$NH_3\cdot H_2O$ 9:1:0.1). Due to its high instability, amine **39** was not characterized but directly used without delay whatsoever.

*(2R,3S)-N-[(2Z,5R,6R,7R)-6-[(tert-Butyldimethylsilyl)oxy]-7-[(3S,8S,9R)-12,14-dimethoxy-8-methyl-1-oxo-9-{[tris(propan-2-yl)-silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododeca-3-yl]-5-methyloct-2-en-1-yl]-2-methyl-3-{[tris(propan-2-yl)silyl]oxy}-hexanamide (**41**).* HBTU (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (80 mg, 0.33 mmol), HOBt (30 mg, 0.33 mmol), and *i*-Pr_2NEt (0.1 mL, 0.62 mmol) were added with stirring to acid **40** (100 mg, 0.33 mmol) in DMF (5 mL). After 30 min, amine **39** (75 mg, 0.1 mmol) was added, and after an additional 30 min, the reaction was quenched with by addition of H_2O. The aqueous layer was extracted with Et_2O (2×), and the combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (EtOAc/hexanes 1:4) to afford **41** (85 mg, 67%) as a white gum: R_f 0.60 (EtOAc/hexanes 1:4) $[\alpha]_D$ −17.5 (*c* 0.4, CH_2Cl_2); IR ν_{max} 3347, 1735, 1660, 1611, 1464, 1260, 1224, 1163, 1091, 1062, 883, 838, 779 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 6.44 (t, *J* = 5.3 Hz), 6.43 (d, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 5.54−5.49 (m, 1H), 5.46−5.41 (m, 2H), 4.00−3.95 (m, 2H), 3.90−3.78 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.51 (dd, *J* = 4.6, 4.6 Hz, 1H), 2.54−2.38 (m, 5H), 2.23−2.14 (m, 2H), 1.97−1.76 (m, 4H), 1.53−1.27 (m, 4H), 1.10−0.88 (m, 66H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 174.0, 167.8, 160.9, 157.8, 140.0, 132.3, 127.3, 118.7, 109.0, 97.0, 81.6, 80.2, 77.9, 77.0, 75.8, 75.2, 56.3, 55.8, 46.0, 41.4, 39.1, 38.2 (2 C), 38.1, 36.9, 36., 30.3, 26.5, 24.3, 23.8, 19.8, 18.9, 18.6, 18.5, 18.4, 18.2, 17.4, 14.7, 13.6, 13.3, 12.9, 11.6, −3.3, −3.4; MS (ESI) *m*/*z* 1028 $[M + H]^+$, 1050 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{58}H_{106}NO_8Si_3$ $[M + H]^+$ 1028.7226, found 1028.7225.

*(2R,3S)-N-[(2Z,5R,6R,7S)-7-[(3S,8S,9R)-9,14-Dihydroxy-12-methoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-3-yl]-6-hydroxy-5-methyloct-2-en-1-yl]-3-hydroxy-2-methylhexanamide (**42**).* BCl_3 in CH_2Cl_2 (1 M; 75 μL) was added with stirring to amide **41** (35 mg, 0.034 mmol) in CH_2Cl_2 at −78 °C. After 1 h, reaction was quenched by the addition of MeOH and the resulting solution rotary evaporated. The residue was dissolved again in MeOH and the solution rotary evaporated. The crude oil was chromatographed (MeOH/CH_2Cl_2 1:19) to afford the corresponding macrocycle (26 mg, 75%) as an amorphous solid: R_f 0.65 (EtOAc/hexanes 1:4) $[\alpha]_D$ −17.5 (*c* 0.4, CH_2Cl_2); IR ν_{max} 3347, 1649, 1620, 1469, 1276, 1260, 1163, 1100, 1041, 765, 750 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 11.09 (s, 1H), 6.48 (t, *J* = 5.4 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 5.49−5.41 (m, 2H), 5.22 (br s, 1H), 4.24−4.22 (m, 2H), 3.98 (ddd, *J* = 5.7, 5.6, 3.6 Hz, 1H), 3.89 (ddd, *J* = 14.6, 5.9, 5.5 Hz, 1H), 3.81 (ddd, *J* = 14.6, 5.9, 5.5 Hz, 1H), 3.79 (s, 3H), 3.53 (dd, *J* = 5.8, 2.1 Hz, 1H), 2.89−2.86 (m, 1H), 2.63−2.60 (m, 1H), 2.52 (dq, *J* = 7.3, 3.6 Hz, 1H), 2.47 (d, *J* = 7.0 Hz, 1H), 2.31−2.26 (m, 1H), 2.23−2.18 (m, 2H), 2.08−2.05 (m, 1H), 1.92−1.85 (m, 2H), 1.72−1.67 (m, 1H), 1.54−1.27 (m, 4H), 1.10−076 (m, 66H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 174.1, 171.6, 164.9, 164.0, 144.3, 132.0, 127.6, 107.4 (2 C), 99.4, 76.6 (2 C), 76.2, 75.8, 55.8, 46.1, 39.5, 39.4 (2 C), 38.2, 37.1, 36.5, 31.3, 26.4, 22.4 (2 C), 19.8, 18.9, 18.6, 18.5, 16.2, 14.7, 13.7, 13.4, 12.9, 11.6, −3.3, −3.4 (2 quaternary C missing); MS (ESI) *m*/*z* 1014 $[M + H]^+$, 1036 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{57}H_{104}NO_8Si_3$ $[M + H]^+$ 1014.7070, found 1014.7049.

2. H_2SiF_6 in H_2O (25 wt %; 0.5 mL) was added with stirring to the preceding macrocycle (20 mg, 0.02 mmol) in MeCN (0.5 mL) at room temperature. The mixture was stirred at 40 °C for 8 h, cooled to 0 °C, diluted with CH_2Cl_2, and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was chromatographed (MeOH/CH_2Cl_2 1:19) to afford macrocycle **42** (9 mg, 76%) as an amorphous solid: R_f 0.40 (MeOH/CH_2Cl_2 1:19); $[\alpha]_D$ +1.5 (*c* 0.2, CH_2Cl_2); IR ν_{max} 3355, 1712, 1616, 1460, 1260, 1162, 1097, 1019, 803 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 10.93 (s, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.25 (s, 1H), 5.65−5.59 (m, 1H), 5.445.39 (m, 1H), 5.36 (ddd, *J* = 8.2, 4.1, 4.1 Hz, 1H), 4.00 (dddd, *J* = 14.9, 7.6, 6.5, 1.2 Hz, 1H), 3.94 (ddd, *J* = 10.3, 3.0, 3.0 Hz, 1H), 3.81 (s, 3H), 3.80−3.70 (m, 3H), 3.46−3.40 (m, 2H), 3.05 (br s, 1H), 2.80−2.76 (m, 2H), 2.63−2.58 (m, 1H), 2.42−2.36 (m, 1H), 2.31−2.22 (m, 3H), 2.18−2.12 (m, 2H), 2.05−2.00 (m, 1H), 1.75−1.67 (m, 2H), 1.47−1.38 (m, 2H), 1.34−1.26 (m, 2H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.93−0.87 (m, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 176.5, 170.7, 164.0, 163.4, 143.4, 130.0, 127.0, 111.3, 107.0, 99.3, 82.7, 79.4, 77.6, 74.9, 73.6, 71.8, 55.4, 44.9, 38.1, 37.3, 36.8, 36.6, 36.5, 35.8, 30.6, 22.6, 21.3, 19.2, 15.8, 15.1, 13.9, 11.0, 8.2; MS (ESI) *m*/*z* 588 $[M + H]^+$, 610 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{50}NO_8$ $[M + H]^+$ 588.3536, found 588.3522.

*(2R,3S)-N-[(2Z,5R,6R,7S)-7-[(3S,8S,9R)-9,14-Dihydroxy-12-methoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecin-3-yl]-6-hydroxy-5-methyloct-2-en-1-yl]-3-hydroxy-2-methylhexanamide (**1**).* Quinoline (2.5 μL, mmol) followed by Lindlar's catalyst (5 wt % Pd on $CaCO_3$, poisoned with lead, 6 mg, 100 wt %) were added with stirring to macrocycle **42** (6 mg, 0.015 mmol) in EtOAc (2 mL). The mixture was stirred under a H_2 atmosphere for

20 min, filtered through Celite, and rotary evaporated. The residue was chromatographed (MeOH/CH_2Cl_2 1:19) to afford cruentaren A (**1**) (7.5 mg, 83%) as a colorless oil (in total, 15 mg of **1** were prepared in two batches): R_f 0.45 (MeOH/CH_2Cl_2 1:19); $[\alpha]_D$ −3.0 (*c* 0.4, CH_2Cl_2); IR ν_{max} 3345, 1643, 1616, 1580, 1542, 1460, 1444, 1380, 1317, 1253, 1224, 1204, 1141, 1104, 1055, 1041, 1017, 990, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.48 (s, 1H), 6.37 (d, *J* = 2.7 Hz, 1H), 6.31 (d, *J* = 2.7 Hz, 1H), 6.14 (t, *J* = 5.7 Hz, 1H), 5.64−5.60 (m, 1H), 5.48 (ddd, *J* = 11.0, 2.9, 1.0 Hz, 1H), 5.44 (ddd, *J* = 11.0, 4.5, 1.9 Hz, 1H), 5.42−5.39 (m, 1H), 5.30 (ddd, *J* = 11.6, 5.6, 1.8 Hz, 1H), 3.92 (dddd, *J* = 14.9, 7.5, 5.7, 1.2 Hz, 1H), 3.87−3.82 (m, 2H), 3.80 (s, 3H), 3.76 (dd, *J* = 12.8, 1.4 Hz, 1H), 3.65 (ddd, *J* = 10.8, 2.3, 1.4 Hz, 1H), 3.46 (d, *J* = 8.9 Hz, 1H), 3.15 (br s, 1H), 2.83 (dt, *J* = 14.3, 11.6 Hz, 1H), 2.76 (br s, 1H), 2.33 (dt, *J* = 14.3, 11.8 Hz, 1H), 2.28 (qd, *J* = 7.2, 2.8 Hz, 1H), 2.30−2.20 (m, 4H), 2.05−1.95 (m, 3H), 1.70 (qddd, *J* = 6.8, 6.8, 2.3, 2.0 Hz, 1H), 1.52−1.42 (m, 2H), 1.38 (br s, 1H), 1.29−1.36 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 171.5, 165.7, 163.5, 143.7, 132.1, 130.9, 126.7, 125.8, 112.3, 104.9, 99.7, 78.0, 74.7, 73.1, 71.8, 55.4, 44.8, 39.2, 38.2, 36.8, 36.6, 36.5, 35.8, 31.6, 30.7, 29.8, 19.2, 16.1, 14.2, 14.0, 11.2, 8.6; MS (ESI) *m*/*z* 590 $[M + H]^+$, 497 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{52}NO_8$ $[M + H]^+$ 590.3693, found 590.3701. The ^1H and ^{13}C NMR spectra, $[\alpha]_D$, and IR spectrum were in full agreement with the isolated natural product[1] and samples prepared by published routes.[2]

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra corresponding to all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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