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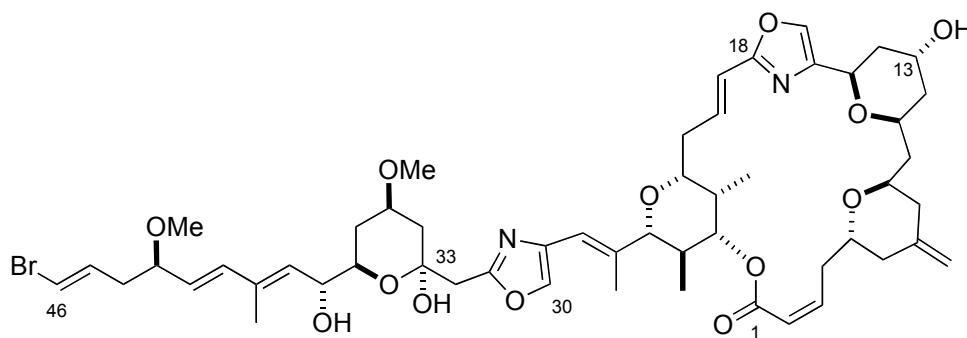
SYNTHESIS OF A 16-TRIAZOLE PHORBOXAZOLE A ANALOG VIA INTRAMOLECULAR TRIAZOLE FORMATION

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Abstract – The intramolecular formation of a triazole using a Cu(I)-catalyzed Huisgen [3+2]-cycloaddition between an organic azide and terminal alkyne enabled the preparation of a C16-C18 triazole analog of phorboxazole A.

Phorboxazole A (**1**, **Figure 1**) and its C13 epimer are natural products isolated from Indian Ocean marine sponges *Phorbas sp* and *Raspailia sp*.¹ With a mean GI₅₀ < 1.6 nM against the NCI panel of 60 tumor cell lines,² phorboxazoles are among the most potent cytostatic agents discovered. Due to their unique structures, remarkable antitumor activities and very limited availability from natural sources, the phorboxazoles have instigated substantial activity within the synthetic organic chemistry community.³



1: phorboxazole A

Figure 1. Structure of Phorboxazole A

To evaluate the potential of phorboxazole structural variants as chemical biology probes and leads for pharmaceutical development, we developed the first total synthesis of phorboxazole A.^{3a} The original tri-component coupling strategy has since been applied to the preparation of designed analogs for structure-activity relationship (SAR) studies⁴ and of probes for mechanism and mode of action studies.⁵ Preliminary SAR studies indicated that the C33-hemiketal and C45-C46 vinyl bromide in **1** could be

replaced with a mixed methyl ketal (**2**, **Figure 2**) and an alkyne (**3**), respectively, without substantially diminishing the anticancer activity of **1**.⁴ Hence, 33-*O*-methyl-45,46-dehydrobromophorboxazole A (MDHBPA, **4**) was identified as a lead analog. Significant effort has since been devoted towards the optimization of the preparative chemistry towards **4**, while further structural simplifications have also been pursued.

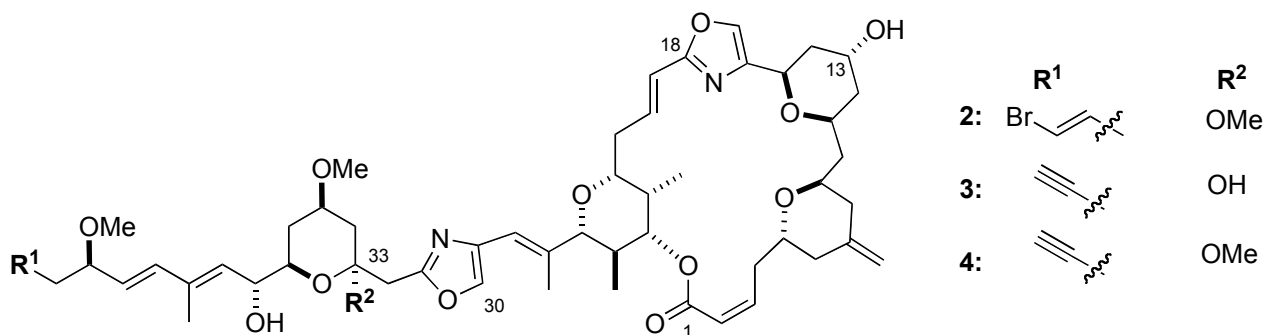
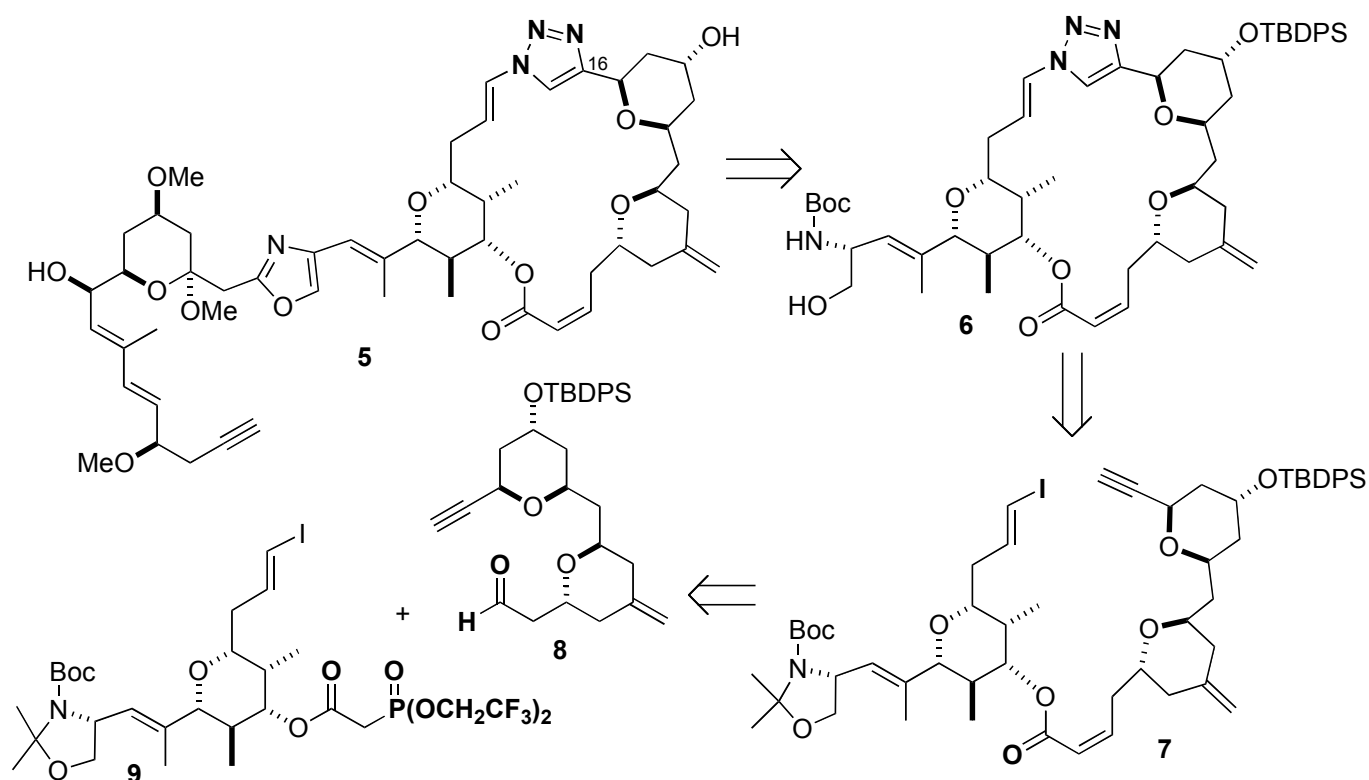


Figure 2. Structures of active phorboxazole A analogs

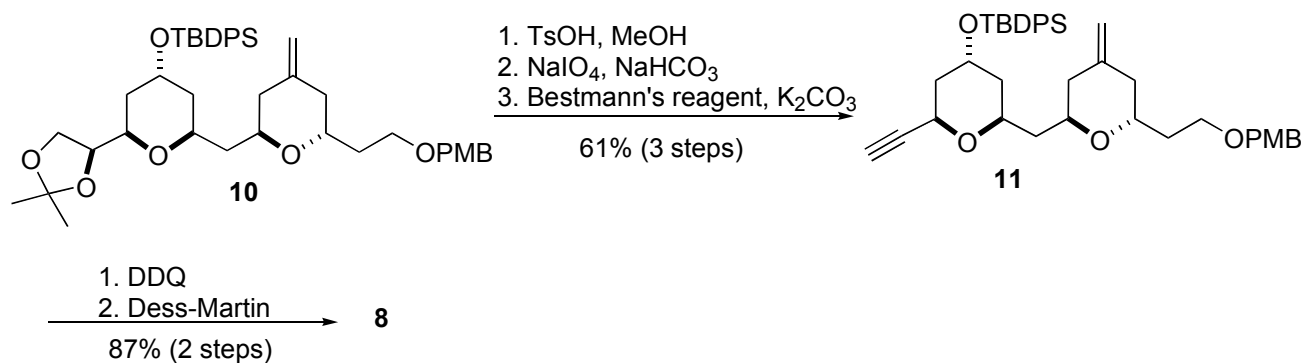
Our installation of the oxazoles imbedded within **1-4** employed a modification of Crimmin's oxidation / cyclodehydration protocol.⁶ Although this *de novo* oxazole formation method has proven to be efficient and reliable, it involves a series of protecting group manipulations to afford the main building blocks via several subsequent linear steps. Utilization of a modified synthetic sequence involving replacement of the macrolide's oxazole with an isosteric moiety was envisioned to potentially shorten the synthetic routes to viable phorboxazole analogs.

In this context, we recognized the potential application of a Cu(I)-catalyzed Huisgen [3+2]-cycloaddition between a vinyl azide and a terminal alkyne⁷ to provide an option to replace the C16-C18 oxazole with a triazole moiety. Moreover, the established *in situ* generation of a vinyl azide could potentially facilitate the one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles to furnish the desired alkenyl triazole subunit.⁸ 16-Triazole MDHBPA (**5**, **Scheme 1**) was thus identified as our primary synthetic target. Retrosynthetically, **5** could be readily derived from the triazole macrolide **6**, which, in turn, could be obtained via an intramolecular triazole formation process. Accordingly, the triazole macrolide **6** could be prepared from **7**, which would in turn be accessed from coupling of aldehyde **8** and phosphoryl acetate **9**. Both **8** and **9** were expected to be quickly generated from our established phorboxazole A advanced synthetic intermediates.



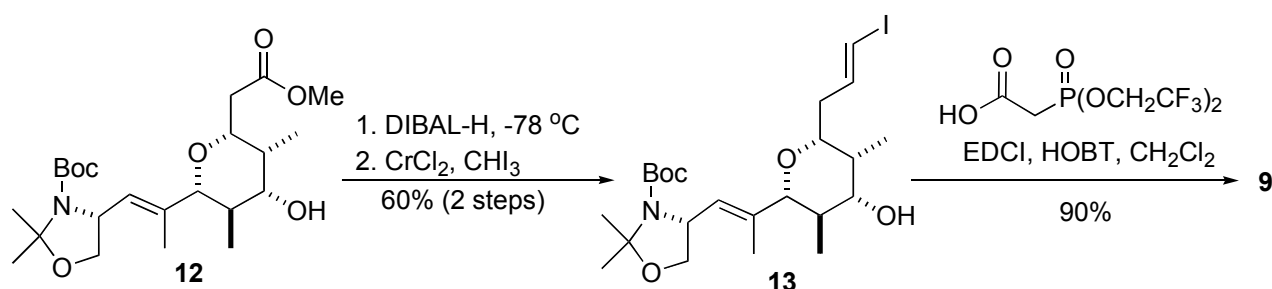
Scheme 1. Retrosynthesis of the 16-triazole MDHBPA analog

Synthesis of the C3-C18 building block **8** commenced with acetonide **10** (Scheme 2), an advanced precursor toward the original synthesis of the C3-C17 domain of phorboxazole A.⁹ Removal of the acetonide protecting group under acidic conditions, followed by oxidative cleavage of the resulting diol with NaIO_4 afforded the C17 aldehyde. The aldehyde was converted into alkyne **11** by treatment with the Bestmann reagent.¹⁰ The PMB group was then removed by subjecting **11** to DDQ and the resulting primary alcohol (**8a**) was oxidized with the Dess-Martin periodinane reagent to provide aldehyde **8**.



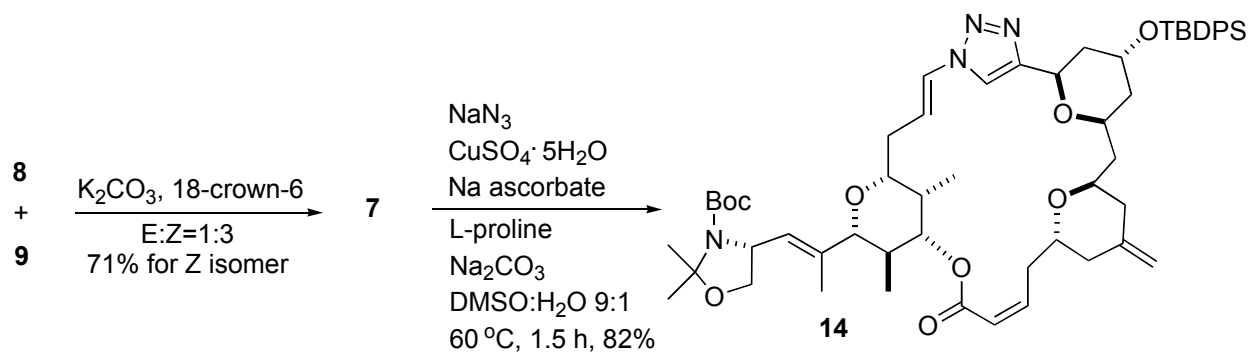
Scheme 2. Synthesis of bis-pyran intermediate **8**

Preparation of the complementary fragment **9** was similarly straightforward (**Scheme 3**). Treatment of ester **12**, an advanced precursor towards the synthesis of the C18-C30 domain of phorboxazole A,¹¹ with DIBAL followed by Takai olefination¹² afforded vinyl iodide **13** with an E/Z ratio of 8:1 and 70% yield over 2 steps. EDCI / HOBT mediated esterification with bis-(2,2,2-trifluoroethoxy)phosphoryl acetic acid^{3a} then provided the desired bis-(2,2,2-trifluoroethoxy)phosphoryl acetate **9**.



Scheme 3. Synthesis of macrolide intermediate **9**

Fragments **8** and **9** were subjected to an intermolecular Still-Gennari olefination¹³ to provide the (Z)-acrylate **7** in 71% yield (**Scheme 4**). The key step of intramolecular triazole formation was then executed to close the macrolide and afforded the desired triazole product **14** in 82% yield. Notably, this intramolecular triazole formation proceeded to completion in 1.5 h instead of the 12 h reported for intermolecular couplings.⁸ This indicates that the conformation of the vinyl azide *in situ* generated from **7** and intramolecularity of the process greatly expedited the triazole formation process.

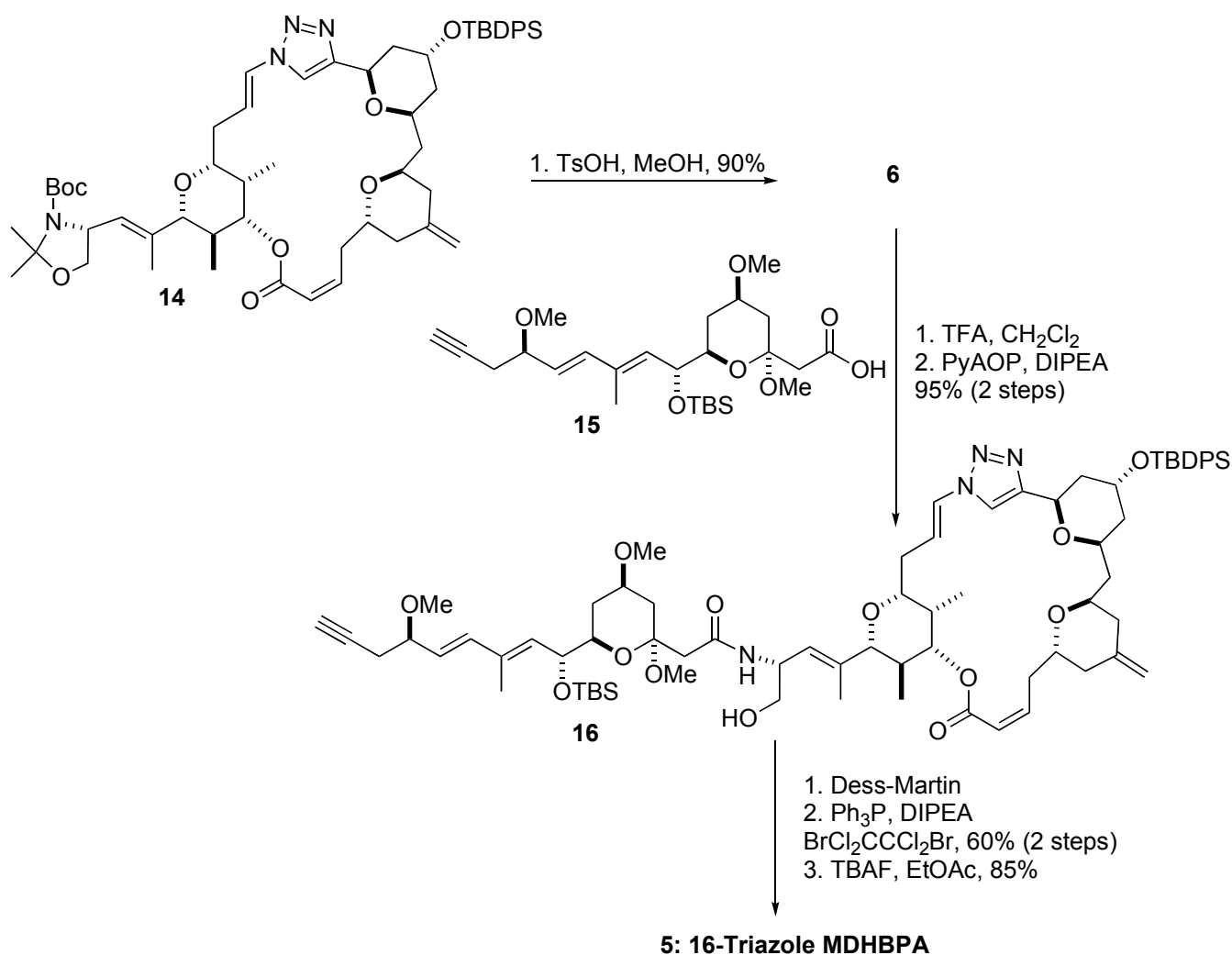


Scheme 4. Synthesis of triazole-containing macrolide **14**

With macrolide **14** in hand, attention was turned to the synthesis of 16-triazole MDHBPA (**5**). After removal of the acetonide and Boc protecting groups under acidic conditions to give the C29 ammonium salt **6a**, the macrolide domain was subsequently coupled with the tail domain carboxylic acid **15**^{1b} via PyAOP mediated amidation^{3a} to afford amide-alcohol **16** in excellent yield (**Scheme 5**). The central

oxazole was then installed using our optimized oxidation / cyclodehydration protocol^{11b} to give the bis-silylated pentultimate intermediate **16b**. Subsequent global desilylation using TBAF provided the desired **5** without complication.

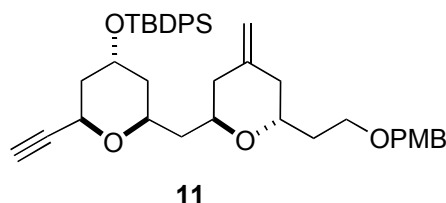
In summary, an intramolecular triazole formation strategy was successfully applied to the synthesis of the novel phorboxazole A analog 16-triazole MDHBPA (**5**). The desired macrolide domain was prepared in 2 linear steps from the specifically functionalized building blocks derived from our original tri-component coupling strategy. This work demonstrates the applicability of an intramolecular Cu(I)-catalyzed Huisgen [3+2]-cycloaddition between a vinyl azide and a terminal alkyne for macrolide triazole formation. Subsequent biological assays will elucidate whether substitution of the C16 oxazole of phorboxazole A with the corresponding triazole allows maintenance of the profound anticancer activities of the parent compound.



Scheme 5. Synthesis of 16-triazole MDHBPA

EXPERIMENTAL

General Methods. All air and moisture sensitive reactions were carried out under argon or nitrogen in oven-dried glassware using standard syringe, cannula, and septa techniques. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from Na/benzophenone ketyl under nitrogen. CH₂Cl₂, CH₃CN, triethylamine (Et₃N), *N,N*-diiso-propyl-ethylamine (*i*-Pr₂NEt), *N,N*-diiso-propylamine (*i*-Pr₂NH), benzene, toluene and borontrifluoride diethyletherate (BF₃·OEt₂) were distilled from CaH₂ under nitrogen. DMSO was distilled from CaH₂ under vacuum. DMF was distilled over CaH₂ and stored over activated 3 Å molecular sieves. CuI was dried under high vacuum for 48 h at ambient temperature. PdCl₂(PPh₃)₂ and chromium (II) chloride of 99.9% purity were used as received from Aldrich Chemical Co. Flash column chromatography was performed using Baker Flash silica gel 60 (40 µm) and the solvent system indicated. Analytical and preparative TLC was performed with 0.25 mm or 0.5 mm Merck Kiesegel (EM science) silica gel 60 F₂₅₄ plates, respectively, and visualized by fluorescence upon 254 nm irradiation and/or staining with anisaldehyde reagent (450 mL of 95% ethanol (EtOH), 25 mL of H₂SO₄, 15 mL of acetic acid (AcOH), and 25 mL of *p*-anisaldehyde). NMR spectra obtained in CDCl₃ are referenced to residual CHCl₃ at 7.26 ppm (¹H) and 77.0 ppm (¹³C) at ambient temperature unless otherwise noted. NMR spectra obtained in C₆D₆ are referenced to residual C₆H₆ at 7.16 ppm (¹H) and 128.0 ppm (¹³C). NMR spectra were obtained using 200, 300 or 500 MHz Varian instruments. Optical rotations were obtained using a 2.5 i.d. x 50 mm cylindrical glass cell and were reported as follows: [α]_D²³, concentration (*c* in g/100 mL) and solvent (all rotation were measured at 23 °C). Infrared (IR) spectra were obtained using MIDAC Prospect FT-IR spectrophotometer calibrated relative to polystyrene using 5 mm NaCl plates. High resolution mass spectral analyses were performed using a Bruker BioTOF with ESI.

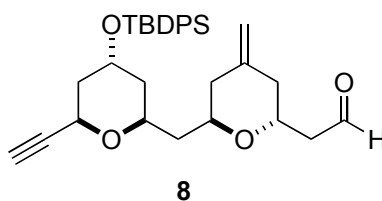


Alkyne (11). To a stirred solution of acetone **10** (95 mg, 0.13 mmol) in MeOH (14 mL) was added *p*-toluenesulfonic acid (28.5 mg, 0.15 mmol). The reaction mixture was stirred at rt for 3 h before it was quenched with saturated aqueous NaHCO₃ (2 mL). The resulting mixture was dried with Na₂SO₄, filtered and concentrated under vacuum by rotary evaporation. The crude diol was submitted directly to the next

step without further purification.

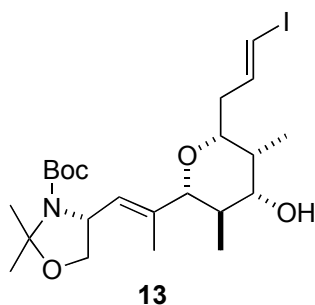
To a stirred solution of the crude diol in CH_2Cl_2 (7 mL) was added saturated aqueous NaHCO_3 (0.7 mL) and sodium periodate (300 mg, 1.4 mmol) sequentially. The resulting mixture was stirred at rt for 12 h before saturated aqueous NaHCO_3 (15 mL) was added. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were dried with Na_2SO_4 , filtered with silica gel and concentrated under vacuum by rotary evaporation. The crude aldehyde was submitted directly to the next step without further purification.

To a stirred solution of the crude aldehyde in methanol (MeOH, 1.5 mL) at 0 °C was sequentially added dimethyl 1-diazo-2-oxopropylphosphonate (40 mg, 0.21 mmol) and K_2CO_3 (30 mg, 0.22 mmol). The resulted mixture was stirred at rt for 12 h before ethyl acetate (EtOAc, 10 mL) and saturated aqueous NH_4Cl (10 mL) were added. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 8:1, v/v) of the residue gave alkyne **11** (52 mg, 61%) as a colorless oil: R_f 0.50 (hexanes-EtOAc, 4:1, v/v); ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, $J = 2, 6$ Hz, 4H), 7.40 (m, 6H), 7.25 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 7.5$ Hz, 2H), 4.76 (m, 3H), 4.42 (d, $J = 10.5$, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.21 (s, 1H), 4.05 (m, 2H), 3.93 (m, 1H), 3.80 (s, 3H), 3.54 (m, 2H), 2.44 (d, $J = 2$ Hz, 1H), 2.42 (dd, $J = 5, 13.5$ Hz, 1H), 2.32 (dd, $J = 3, 12.5$ Hz, 1H), 2.01 (m, 2H), 1.88 (dq, $J = 5.5, 13.5$ Hz, 1H), 1.81 (dd, $J = 1.5, 13.5$ Hz, 1H), 1.73 (m, 2H), 1.60 (m, 1H), 1.45 (m, 1H), 1.32 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.1, 142.1, 135.8, 135.7, 133.8, 133.7, 130.7, 129.8, 129.2, 127.7, 113.8, 110.3, 83.6, 72.7, 69.6, 68.9, 66.9, 65.5, 62.7, 55.3, 40.1, 39.7, 39.2, 39.0, 38.2, 34.3, 27.1, 19.3; HR-MS (ESI) calcd for $[\text{C}_{40}\text{H}_{50}\text{O}_5\text{Si} + \text{Na}]^+$ 661.3320, found 661.3337; $[\alpha]_D^{23}$ -9.0 (0.91, CHCl_3).



Aldehyde (8). To a stirred solution of alkyne **11** (10 mg, 0.016 mmol) in CH_2Cl_2 (3 mL) was sequentially added pH=7 phosphate buffer (0.3 mL), *t*-BuOH (0.3 mL, 3.4 mmol) and DDQ (25 mg, 0.11 mmol) at 0 °C. The reaction mixture was kept stirring at 0 °C for 35 min before saturated aqueous NaHCO_3 (10 mL) was added. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 6:1, v/v) of the residue gave the primary alcohol **8a** as a colorless oil. To a stirred solution of **8a** in CH_2Cl_2 (1.2 mL) was sequentially added NaHCO_3 (25 mg, 0.3 mmol),

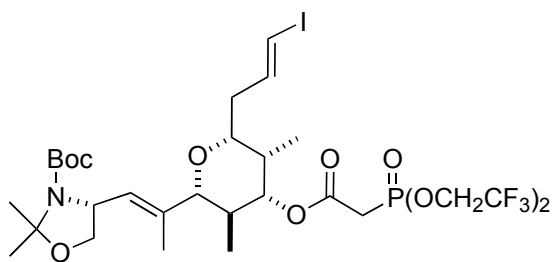
t-BuOH (30 μ L, 0.33 mmol) and 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane, 20 mg, 0.047 mmol). The reaction mixture was stirred at rt for 45 min before saturated aqueous NaS₂O₃ (2 mL) was added. The resulting mixture was stirred vigorously for 2 h and the aqueous phase was extracted with Et₂O (3 $\times$ 5 mL). The combined organic phases were dried with Na₂SO₄, filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 4:1, v/v) of the residue gave aldehyde **8** (7 mg, 87%) as a colorless oil: *R*_f 0.50 (hexanes-EtOAc, 2:1, v/v); IR (neat, cm⁻¹) 3473, 3074, 3036, 2975, 2933, 2888, 1641, 1496, 1458, 1379, 1166, 1104, 1044, 1021, 915, 736, 694; ¹HNMR (300 MHz, CDCl₃) δ 9.76 (s, 1H), 7.64 (d, *J* = 6.3 Hz, 4H), 7.44 (m, 6H), 4.80 (d, *J* = 6.9 Hz, 2H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.35 (m, 1H), 4.20 (s, 1H), 4.01 (m, 2H), 2.62 (dd, *J* = 2.4, 7.2 Hz, 1H), 2.52 (m, 1H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.40 (m, 1H), 2.30 (m, 2H), 2.03 (m, 2H), 1.74 (m, 2H), 1.53 (d, *J* = 13.2 Hz, 1H), 1.41 (dt, *J* = 6.3, 14.1 Hz, 1H), 1.27 (d, *J* = 11.1 Hz, 1H), 1.08 (s, 9H); ¹³CNMR (75 MHz, CDCl₃, partial spectrum) δ 201.0, 140.7, 135.6, 129.7, 127.6, 127.5, 111.2, 83.3, 72.4, 69.5, 69.4, 66.9, 65.2, 62.5, 47.6, 39.4, 39.3, 38.8, 38.5, 37.8, 26.7, 19.1; HR-MS (ESI) calcd for [C₃₂H₄₀O₄Si + MeOH + Na]⁺ 571.2845, found 571.2847; [α]_D²³ -25.0 (0.50, MeOH).



Alcohol (13). To a stirred solution of ester **12** (24mg, 0.058 mmol) in CH₂Cl₂ (3 mL) was slowly added di-*iso*-butylaluminum hydride (0.12 mL, 1 M solution in toluene) at -78 °C. The resulting solution was stirred at -78 °C for 45 min before methanol (2 mL) and saturated aqueous Na/K tartrate (5 mL) were added. The mixture was stirred at rt for 2 h before it was diluted with EtOAc (5 mL). The aqueous phase was extracted with EtOAc (3 $\times$ 5 mL) and the combined organic phases were washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 3:1, v/v) of the residue gave the desired aldehyde (20 mg, 85%) as a colorless oil.

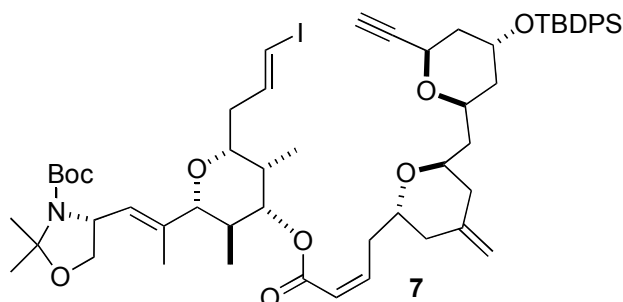
To a stirred suspension of CrCl₂ (100 mg, 0.82 mmol) in THF (0.5 mL) was slowly added a solution of the aldehyde (20 mg, 0.049 mmol) and iodoform (200 mg, 0.51 mmol) in dioxane (3 mL). The resulting brownish mixture was stirred at rt for 2 h before saturated aqueous NaHCO₃ (20 mL) was added. The separated aqueous phase was extracted with Et₂O (3 $\times$ 5 mL) and the combined organic phases were

washed with brine (10 mL), dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 6:1, v/v) of the residue gave alcohol **13** (18 mg, 70%) as a light yellow oil: R_f 0.45 (hexanes-EtOAc, 2:1, v/v); IR (neat, cm^{-1}) 3446, 2975, 2930, 2865, 2363, 2336, 1257, 1090, 1052, 1021, 949, 846, 804, 736, 664; ^1H NMR (500 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers) δ 6.48 (ddd, J = 6, 8, 15 Hz, 1H), 6.10 (d, J = 14.5 Hz, 1H), 5.36 (br, 1H), 4.61 (br, 1H), 4.06 (s, 1H), 3.77 (d, J = 8.5 Hz, 1H), 3.43 (t, J = 5.5 Hz, 2H), 3.29 (d, J = 5 Hz, 1H), 2.33 (m, 1H), 2.16 (m, 1H), 1.87 (t, J = 6.5 Hz, 1H), 1.67 (m, 10H), 1.43 (m, 9H), 0.92 (d, J =7 Hz, 3H), 0.87 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers) δ 151.9, 142.4, 137.8, 129.5, 93.9, 88.9, 88.3, 80.5, 79.7, 68.9, 68.1, 54.6, 39.1, 37.7, 33.8, 28.5, 28.3, 26.9, 25.2, 23.5, 13.6, 13.0, 12.8, 5.4; HR-MS (ESI) calcd for $[\text{C}_{23}\text{H}_{38}\text{INO}_5+\text{Na}]^+$ 558.1692, found 558.1672; $[\alpha]_D^{23}$ 6.0 (0.60, CH_2Cl_2).

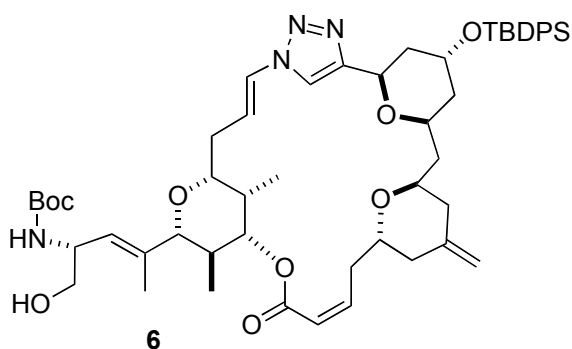


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Ester (9). To a stirred solution of alcohol **13** (7.5 mg, 0.014 mmol) in CH_2Cl_2 (3.8 mL) was sequentially added bis(2,2,2-trifluoroethoxy)phosphorylacetic acid (54 mg, 0.18 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (34 mg, 0.16 mmol) and *N*-hydroxybenzotriazole (1 mg, 7.4 μmol). The resulting mixture was stirred at rt for 12 h before saturated aqueous NH_4Cl (5 mL) was added. The aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 3:1, v/v) of the residue gave ester **9** (10.3 mg, 90%) as a colorless oil: R_f 0.35 (hexanes-EtOAc, 2:1, v/v); IR (neat, cm^{-1}) 2977, 2933, 1734, 1703, 1457, 1419, 1390, 1369, 1173, 1073, 964, 809; ^1H NMR (500 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers) δ 6.46 (ddd, J = 6, 8, 14.5 Hz, 1H), 6.10 (d, J = 14.5 Hz, 1H), 5.38 (br, 1H), 4.74 (dd, J = 5, 10.5 Hz, 1H), 4.60 (br, 1H), 4.45 (m, 4H), 4.06 (s, 1H), 3.77 (d, J = 8.5 Hz, 1H), 3.49 (t, J = 6 Hz, 1H), 3.37 (d, J = 10 Hz, 1H), 3.21 (s, 1H), 3.17 (s, 1H), 2.34 (m, 1H), 2.12 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.68 (m, 9H), 1.43 (m, 9H), 0.92 (d, J = 7 Hz, 3H), 0.75 (br, 3H); ^{13}C NMR (75 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers) δ 163.9, 156.1, 151.6, 141.7, 124.0, 120.4, 120.2, 88.6, 88.0, 80.9, 79.5, 76.1, 68.7, 67.8, 62.6, 62.1, 54.4, 53.2, 38.8, 34.9, 33.0, 31.2, 28.3, 28.1, 27.4, 26.7, 24.8, 23.4, 13.2, 12.5, 5.74; HR-MS (ESI) calcd for $[\text{C}_{29}\text{H}_{43}\text{F}_6\text{INO}_9\text{P}+\text{Na}]^+$ 844.1522, found 844.1531; $[\alpha]_D^{23}$ 9.22 (0.90, CHCl_3).

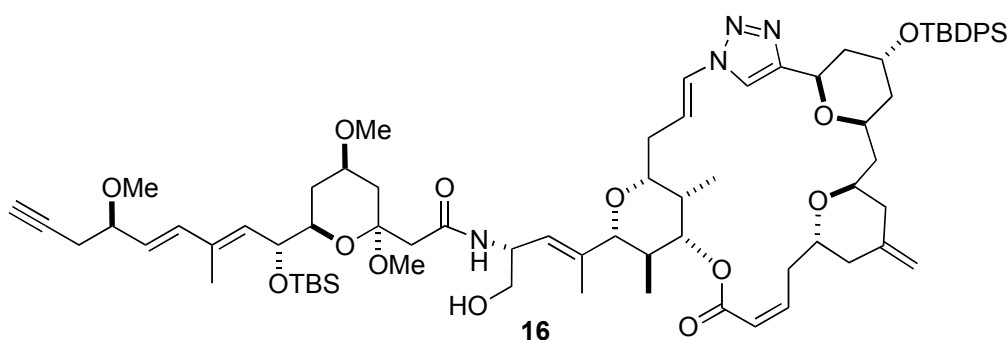


Z-Alkene (7). To a stirred suspension of K_2CO_3 (18.5 mg, 0.13 mmol) in toluene (11 mL) was added 1,4,7,10,13,16-hexaoxacyclooctadecane (140 mg, 0.53 mmol). The resulting mixture was stirred vigorously at rt for 3 h before a solution of ester **9** (17.5 mg, 0.021 mmol) and aldehyde **8** (12.5 mg, 0.024 mmol) in toluene (11 mL) was added slowly. The reaction mixture was stirred rt for another 2 h before it was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Careful silica gel column chromatography (hexanes-EtOAc, 8:1, v/v) of the residue gave *Z*-alkene **7** (16 mg, 71%) as a colorless oil: R_f 0.72 (hexanes-EtOAc, 2:1, v/v); IR (neat, cm^{-1}) 3428, 2363, 2337, 1075, 804; ^1H NMR (500 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers) δ 7.64 (d, $J = 7.5$ Hz, 4H), 7.41 (m, 7H), 6.71 (ddd, $J = 6, 8, 15$ Hz, 1H), 6.41 (br, 1H), 1.09 (d, $J = 16$ Hz, 1H), 5.79 (d, $J = 11.5$ Hz, 1H), 5.39 (br, 1H), 4.79 (s, 1H), 4.76 (m, 2H), 4.70 (dd, $J = 5, 11.5$ Hz, 1H), 4.62 (br, 1H), 4.21 (s, 1H), 4.06 (m, 3H), 3.89 (m, 1H), 3.74 (dd, $J = 2, 8$ Hz, 1H), 3.5 (t, $J = 7$ Hz, 1H), 3.39 (d, $J = 10.5$ Hz, 1H), 2.96 (m, 1H), 2.81 (m, 1H), 2.44 (dd, $J = 2, 12.5$ Hz, 2H), 2.33 (dd, $J = 4, 8.5$ Hz, 2H), 2.13 (m, 1H), 2.04 (m, 3H), 1.90 (br, 1H), 1.78 (m, 2H), 1.70 (m, 2H), 1.60 (br 2H), 1.56 (m, 4H), 1.43 (s, 9H), 1.38 (m, 2H), 1.29 (m, 2H), 1.09 (s, 9H), 0.92 (d, $J = 7$ Hz, 3H), 0.72 (br, 3H); ^{13}C NMR (125 MHz, CDCl_3 , 1:1 mixture of carbamate rotamers, partial spectrum) δ 152.7, 142.1, 141.6, 135.7, 133.6, 129.8, 127.6, 127.7, 111.7, 110.7, 94.2, 83.5, 79.7, 78.0, 76.8, 73.5, 72.5, 70.9, 69.7, 69.2, 65.4, 62.6, 54.7, 47.0, 39.9, 39.6, 39.2, 39.1, 38.8, 38.1, 35.2, 33.8, 28.5, 28.3, 27.0, 23.5, 21.9, 19.3, 6.2; HR-MS (ESI) calcd for $[\text{C}_{57}\text{H}_{78}\text{INO}_9\text{Si} + \text{Na}]^+$ 1098.4383, found 1098.4375; $[\alpha]_D^{23}$ -7.0 (0.60, CHCl_3).



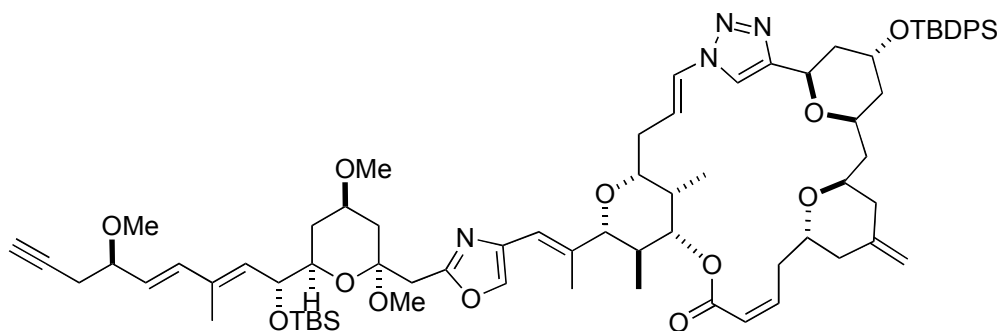
Macrolide (6). To a vial containing **7** (12.6 mg, 0.012 mmol) was added L-proline (115 mg, 1 mmol), Na_2CO_3 (106.5 mg, 1 mmol), NaN_3 (390 mg, 6 mmol), sodium ascorbate (200 mg, 1 mmol), a co-solvent of DMSO / H_2O (20 mL, 9:1) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (125.5 mg, 0.5 mmol). The reaction mixture was stirred vigorously at 60 °C for 90 min before it was poured into ice-cold saturated aqueous NH_4OH (100 mL). The resulting mixture was extracted with Et_2O (3×20 mL) and the combined organic phases were washed with brine (3×10 mL), dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 4:1, v/v) of the residue gave acetone **14** (9.5 mg, 82%) as a light yellow oil.

To a stirred solution of acetone **14** (11.1 mg, 0.011 mmol) in methanol (7.5 mL) was added *p*-toluenesulfonic acid (14 mg, 0.074 mg). The reaction mixture was stirred at rt for 12 h before saturated aqueous NaHCO_3 (0.2 mL) was added. The resulting mixture was dried with MgSO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 3:1, v/v) of the residue gave macrolide **6** (9.4 mg, 90%) as an amorphous solid: R_f 0.30 (hexanes-EtOAc, 2:1, v/v); IR (neat, cm^{-1}) 3398, 2963, 2934, 2854, 1262, 1071, 1033, 793, 668; ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, J = 8 Hz, 4H), 7.43 (m, 6H), 7.30 (s, 1H), 6.03 (m, 1H), 5.94 (d, J = 8 Hz, 1H), 5.77 (ddd, J = 5.5, 8.5, 15.5 Hz, 1H), 5.32 (d, J = 8.5 Hz, 1H), 5.18 (d, J = 11 Hz, 1H), 4.83 (s, 1H), 4.74 (br, 1H), 4.67 (s, 1H), 4.52 (dd, J = 4.5, 11.5 Hz, 1H), 4.46 (br 1H), 4.37 (s, 1H), 4.18 (m, 2H), 4.00 (m, 1H), .71 (dd, J = 4, 12 Hz, 1H), 3.65 (dd, J = 6.5, 10.5 Hz, 1H), 3.58 (q, J = 5 Hz, 1H), 3.46 (d, J = 10 Hz, 1H), 3.42 (m, 1H), 2.59 (m, 2H), 2.50 (t, J = 12 Hz, 3H), 2.38 (m, 1H), 2.31 (t, J = 5.5 Hz, 1H), 2.12 (d, J = 13.5 Hz, 1H), 2.00 (m 2H), 1.84 (dd, J = 5, 8.5 Hz, 1H), 1.80 (s, 3H), 1.75 (d, J = 13.5 Hz, 1H), 1.53 (d, 12.5 Hz, 1H), 1.45 (s, 9H), 1.41 (m, 1H), 1.36 (t, J = 6 Hz, 2H), 1.11 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3 , partial spectrum) δ 165.9, 155.9, 149.9, 145.0, 142.9, 135.8, 135.7, 134.2, 133.6, 129.9, 129.8, 127.8, 127.7, 127.0, 120.9, 118.4, 118.1, 112.3, 109.3, 88.9, 79.4, 77.4, 77.2, 73.3, 69.1, 68.9, 68.1, 65.6, 41.1, 39.5, 37.2, 36.8, 32.7, 31.2, 31.0, 30.8, 28.3, 27.1, 19.3, 13.2, 12.0, 5.5; HR-MS (ESI) calcd for $[\text{C}_{54}\text{H}_{74}\text{N}_4\text{O}_9\text{Si}+\text{Na}]^+$ 973.5117, found 973.5134; $[\alpha]_{\text{D}}^{23}$ 52.0 (0.10, CHCl_3).



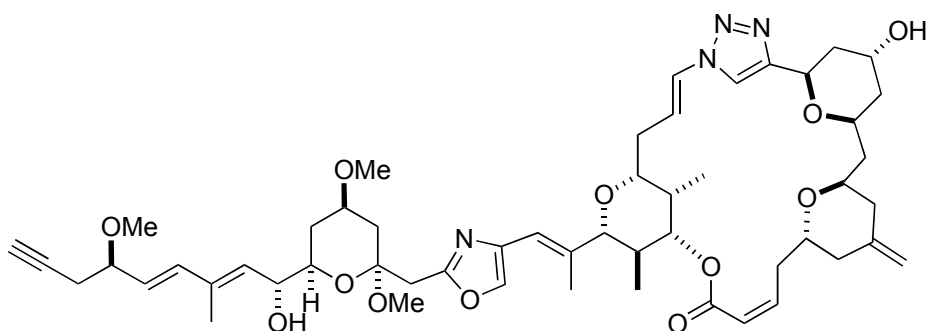
Alcohol (16). To a stirred solution of (*Z*)-macrolide **6** (3 mg, 3.2 μ mol) in CH_2Cl_2 (0.68 mL) was added trifluoroacetic acid (0.068 mL). The reaction mixture was stirred at rt for 45 min before the volatile components were removed under a stream of N_2 . The residue was dried under vacuum for 1 h before the aqueous phosphate buffer (pH= 5.7, 3 mL) was added. The resulting mixture was stirred vigorously at rt for 1 h before it was diluted with EtOAc (2 mL). The aqueous phase was separated and extracted with EtOAc (5×2 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation to give the crude ammonium salt **6a**.

To a stirred solution of carboxylic acid **15** (1.7 mg, 3.4 μ mol) in CH_2Cl_2 (1 mL) was added (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (2 mg, 4 μ mol) and *i*- Pr_2NEt (17 μ L, 0.1 mmol). The resulting mixture was stirred at rt for 1 min before it was added to a solution of **6a** in CH_2Cl_2 (1 mL). After stirring at rt for 45 min, saturated aqueous NaHCO_3 (2 mL) was added. The separated aqueous layer was extracted with EtOAc (5×2 mL) and the combined organic phase was dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 1:2, v/v) of the residue gave alcohol **16** (4.3 mg, 95%) as an amorphous solid: R_f 0.40 (EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, J = 8 Hz, 4H), 7.51 (s, 1H), 7.43 (m, 6H), 7.29 (d, J = 15 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 6.27 (dd, J = 8, 16 Hz, 2H), 6.03 (m, 1H), 5.94 (d, J = 11 Hz, 1H), 5.77 (m, 1H), 5.63 (dd, J = 7, 15.5 Hz, 1H), 5.44 (d, J = 9 Hz, 1H), 5.39 (m, 1H), 5.17 (d, J = 11 Hz, 1H), 4.83 (m, 2H), 4.80 (m, 2H), 4.67 (s, 1H), 4.52 (m, 2H), 4.37 (s, 1H), 4.21 (m, 1H), 4.19 (br, 1H), 4.00 (m, 1H), 3.93 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H), 3.67 (m, 2H), 3.60 (m, 1H), 3.53 (m, 1H), 3.50 (s, 3H), 3.46 (m, 2H), 3.30 (s, 3H), 3.23 (m, 1H), 3.20 (s, 3H), 2.76 (d, J = 16 Hz, 2H), 2.66 (m, 1H), 2.59 (m, 1H), 2.51 (m, 4H), 2.43 (m, 2H), 2.38 (m, 2H), 2.32 (m, 2H), 2.22 (m, 2H), 2.12 (d, J = 12.5 Hz, 1H), 2.05 (s, 3H), 1.99 (m, 2H), 1.90 (m, 2H), 1.87 (m, 1H), 1.81 (d, J = 4 Hz, 1H), 1.53 (d, J = 12.5 Hz, 1H), 1.44 (m, 1H), 1.36 (m, 1H), 1.22 (m, 1H), 1.11 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.75 (d, J = 6 Hz, 3H); HR-MS (ESI) calcd for $[\text{C}_{75}\text{H}_{108}\text{N}_4\text{O}_{13}\text{Si}_2+2\text{Na}]^{2+}$ 1374.7236, found 1374.7338.



Oxazole (16b). NaHCO₃ (60 mg, 0.72 mmol), Dess-Martin periodinane (50 mg, 0.12 mmol) and *t*-BuOH (20 μ L, 0.22 mmol) were mixed in 1 mL of CH₂Cl₂ and the mixture was stirred at rt for 5 min before being cooled to 0 °C. To the resulting mixture was added a solution of alcohol **16** (1 mg, 0.9 μ mol) in CH₂Cl₂ (0.5 mL). The resulting mixture was stirred for 45 min. One-half of the CH₂Cl₂ was evaporated with a stream of N₂ before Et₂O (1 mL) was added. The resulting mixture was submitted to flash column chromatography (Et₂O) to remove the Dess-Martin periodinane by-products. The eluant was evaporated with a stream of N₂ and the resulting aldehyde residue was placed under a high vacuum for 1 h.

To a stirred solution of the aldehyde in CH₂Cl₂ (1 mL) was sequentially added triphenylphosphine (35 mg, 43 μ mol), *i*-Pr₂NEt (35 μ L, 0.21 mmol) and 1,2-dibromotetrachloroethane (40 mg, 0.12 mmol). The resulting mixture was stirred at rt for 1 h before additional *i*-Pr₂NEt (35 μ L) was added. After another 2 h, the reaction solution was diluted with Et₂O (1 mL) and washed with saturated aqueous NH₄Cl (2 mL). The aqueous phase was extracted with Et₂O (3 $\times$ 2 mL) and the combined organic phases were dried with Na₂SO₄, filtered and concentrated under vacuum by rotary evaporation. Silica gel column chromatography (hexanes-EtOAc, 3:1, v/v) of the residue gave the oxazole **16b** (0.6 mg, 60%) as a colorless oil: *R*_f 0.50 (hexanes-EtOAc, 1:1, v/v); ¹HNMR (500 MHz, C₆D₆) δ 7.81 (m, 2H), 7.77 (m, 2H), 7.54 (s, 1H), 7.24 (m, 6H), 7.16 (s, 1H), 6.90 (d, *J* = 15 Hz, 1H), 6.39 (s, 1H), 6.26 (d, *J* = 15.5 Hz, 1H), 5.82 (d, *J* = 15.5 Hz, 1H), 5.62 (dd, *J* = 8, 15.5 Hz, 1H), 5.54 (dd, *J* = 4, 15.5 Hz, 1H), 5.49 (d, *J* = 12.5 Hz, 1H), 5.37 (m, 1H), 5.74 (s, 1H), 4.64 (s, 1H), 4.63 (m, 1H), 4.53 (dd, *J* = 7, 9 Hz, 1H), 4.34 (t, *J* = 10.5 Hz, 1H), 4.26 (s, 1H), 4.06 (m, 1H), 3.75 (m, 1H), 3.65 (m, 2H), 3.60 (q, *J* = 6.5 Hz, 1H), 3.45 (d, *J* = 11 Hz, 1H), 3.40 (s, 3H), 3.35 (m, 1H), 3.31 (m, 1H), 3.06 (s, 3H), 3.05 (s, 3H), 2.98 (d, *J* = 15 Hz, 1H), 2.77 (d, *J* = 13 Hz, 1H), 2.69 (m, 1H), 2.60 (m, 2H), 2.40 (m, 2H), 2.35 (m, 1H), 2.32 (m, 1H), 2.27 (m, 1H), 2.23 (m, 1H), 2.13 (m, 1H), 2.10 (s, 3H), 2.06 (m, 1H), 2.03 (m, 1H), 1.95 (m, 3H), 1.78 (d, *J* = 13.5 Hz, 1H), 1.72 (d, *J* = 13 Hz, 1H), 1.67 (s, 3H), 1.59 (m, 1H), 1.54 (d, *J* = 13.5 Hz, 1H), 1.33 (m, 2H), 1.24 (m, 1H), 1.21 (s, 9H), 1.15 (m, 1H), 1.04 (s, 9H), 0.87 (d, *J* = 7 Hz, 3H), 0.79 (d, *J* = 7 Hz, 3H), 0.20 (s, 3H), 0.14 (s, 3H); HR-MS (ESI) calcd for [C₇₅H₁₀₄N₄O₁₂Si₂+2Na]²⁺ 1354.6974, found 1354.7044.



16-triazole MDHBPA (5)

16-Triazole MDHBPA (5). To a stirred solution of the oxazole **16b** (1.1 mg, 0.86 μ mol) in EtOAc (0.88 mL) was added TBAF (0.35 mL of 1.0 M solution in THF). The resulting reaction mixture was stirred at rt for 7 h before saturated aqueous NH_4Cl (2 mL) was added. The aqueous phase was extracted with EtOAc (6×2 mL) and the combined organic phases were dried with Na_2SO_4 , filtered and concentrated under vacuum by rotary evaporation. The residue was purified with preparative TLC (EtOAc) to give 16-triazole MDHBPA **5** (0.7 mg, 85%) as a colorless oil: R_f 0.35 (EtOAc-MeOH, 20:1, v/v); ^1H NMR (500 MHz, C_6D_6) δ 7.55 (s, 1H), 7.09 (s, 1H), 6.89 (d, J = 13.5 Hz, 1H), 6.34 (s, 1H), 6.31 (d, J = 15.5 Hz, 1H), 5.82 (d, J = 12 Hz, 1H), 5.62 (q, J = 7.5 Hz, 2H), 5.54 (m, 1H), 5.35 (dt, J = 7.5, 15.5 Hz, 1H), 5.13 (d, J = 11 Hz, 1H), 4.69 (s, 1H), 4.64 (m, 1H), 4.62 (m, 2H), 4.35 (dd, J = 5.5, 7.5 Hz, 1H), 4.19 (br, 1H), 4.04 (br, 2H), 3.78 (s, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 3.59 (m, 1H), 3.47 (ddd, J = 2, 7, 11.5 Hz, 1H), 3.44 (d, J = 9.5 Hz, 1H), 3.31 (dd, J = 6, 9.5 Hz, 1H), 3.17 (s, 3H), 3.12 (d, J = 11 Hz, 1H), 3.08 (s, 3H), 3.03 (s, 3H), 2.91 (d, J = 15 Hz, 1H), 2.70 (dd, J = 3.5, 16.5 Hz, 1H), 2.50 (dd, J = 4, 13.5 Hz, 1H), 2.43 (m, 2H), 2.40 (m, 2H), 2.35 (dd, J = 2, 6 Hz, 1H), 2.31 (m, 1H), 2.22 (m, 2H), 2.10 (m, 2H), 2.07 (s, 3H), 1.98 (m, 2H), 1.92 (m, 1H), 1.85 (m, 2H), 1.78 (m, 1H), 1.65 (s, 3H), 1.60 (d, J = 11 Hz, 2H), 1.54 (d, J = 7.5 Hz, 2H), 1.22 (m, 1H), 0.85 (d, J = 7 Hz, 3H), 0.77 (d, J = 3H); HR-MS (ESI) calcd for $[\text{C}_{53}\text{H}_{72}\text{N}_4\text{O}_{12}+\text{Na}]^+$ 979.5039, found 979.5050.

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REFERENCES

1. P. A Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126. (b) R. J. Capon, C. Skene, H. E. Liu, E. Lacey, J. H. Gill, K. Heiland, and T. Friedel, *Nat. Prod. Res.*, 2004, **18**, 305.
2. T. F. Molinski, *Tetrahedron Lett.*, 1996, **37**, 7879.
3. (a) C. J. Forsyth, F. Ahmed, R. D. Cink, and C. S. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 5597. (b) D. A. Evans, D. M. Fitch, T. E. Smith, and V. J. Cee, *J. Am. Chem. Soc.*, 2000, **122**, 10033. (c) A. B. Smith III, T. M. Razler, J. P. Ciavarri, T. Hirose, and T. Ishikawa, *Org. Lett.*, 2005, **7**, 4399. (d) M. A. Gonzalez and G. Pattenden, *Angew. Chem.*, 2003, **115**, 1293; *Angew. Chem. Int. Ed.*, 2003, **42**, 1255. (e) D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner, and J. T. Reeves, *Angew. Chem.*, 2003, **115**, 1296; *Angew. Chem. Int. Ed.*, 2003, **42**, 1258. (f) D.-R. Li, D.-H. Zhang, C.-Y. Sun, J. W. Zhang, L. Yang, J. Chen, B. Liu, C. Su, W.-S. Zhou, and G.-Q. Lin, *Chem. Eur. J.*, 2006, **12**, 1185. (g) B. S. Lucas, V. Gopalsamuthiram, and S. D. Burke, *Angew. Chem. Int. Ed.*, 2007, **46**, 769. (h) J. D. White, T. H. Lee, and P. Kuntiyong, *Org. Lett.*, 2006, **8**, 6043.

4. (a) F. M. Uckun and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1181. (b) F. M. Uckun, R. M. Narla, C. J. Forsyth, C. S. Lee, F. Ahmed, and R. D. Cink, U.S. Patent 6797721, 2004; WO 01/36394, 2001; Priority: US 99-165452 19991115.
5. (a) T. M. Hansen, M. M. Engler, and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2127. (b) J. Chen, L. Ying, T. M. Hansen, M. M. Engler, C. S. Lee, J. J. La Clair, and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 901. (c) C. J. Forsyth, L. Ying, J. Chen, and J. J. La Clair, *J. Am. Chem. Soc.*, 2006, **128**, 3858.
6. (a) M. J. Crimmin, P. J. O'Hanlon, N. H. Rogers, F. M. Sime, and G. Walker, *J. Chem. Soc., Perkin Trans. I*, 1989, 2059. (b) P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604. (c) P. Wipf and S. Lim, *J. Am. Chem. Soc.*, 1995, **117**, 558.
7. (a) R. Huisgen, *Pure Appl. Chem.*, 1989, **61**, 613. (b) R. Huisgen, G. Szeimies, and L. Moebius, *Chem. Ber.*, 1967, **100**, 2494. (c) V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2596. (d) C. W. Tornøe, C. Christensen, and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
8. A. K. Feldman, B. Colasson, and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.
9. (a) R. D. Cink and C. J. Forsyth, *J. Org. Chem.*, 1997, **62**, 5672. (b) J. Chen, Ph.D. Dissertation, University of Minnesota, Minneapolis, 2004.
10. (a) S. Müller, B. Liepold, G. J. Roth, and H. J. Bestmann, *Synlett.*, 1996, 521. (b) G. J. Roth, B. Liepold, S. Müller, and H. J. Bestmann, *Synthesis*, 2004, 59.
11. (a) C. S. Lee and C. J. Forsyth, *Tetrahedron Lett.*, 1996, **37**, 6449. (b) Hansen, T. M. Ph.D. Dissertation, University of Minnesota, Minneapolis, 2002.
12. (a) K. Takai, K. Nitta, and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408. (b) D. A. Evans, and W. C. Black, *J. Am. Chem. Soc.*, 1993, **115**, 4497.
13. W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.