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Studies on the synthesis of reidispongiolide A: stereoselective synthesis of the C(22)–C(36) fragment

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ABSTRACT

A highly stereoselective synthesis of the C(22)–C(36) fragment **2** of reidispongiolide A is described. This synthesis features the highly stereoselective mismatched double asymmetric crotylboration reaction of the aldehyde derived from **5** and the new chiral reagent (*S*)-(*E*)-**7** that provides **12** with >15:1 dr. Subsequent coupling of the derived vinyl iodide **3** with aldehyde **16** provided allylic alcohol **17**, that was elaborated by three steps into the targeted reidispongiolide fragment **2**.

1. Introduction

The reidispongiolides and sphinxolides are structurally related, biologically active families of marine natural products isolated from the New Caledonian sponges *Reidispongia coerulea* and *Neosiphonia superstes*.[1–4] According to previous research, these compounds inhibit actin filament assembly assembling and induce F-actin depolymerization.[5] These compounds also have the ability to circumvent multi-drug resistance mediated by P-glycoprotein in cell-based assays.[5] Reidispongiolide A, the most active member of reidispongiolide family, exhibits potent cytotoxicity against various human cancer cell lines (IC_{50} 0.01–0.16 μg/mL).[3]

The relative configuration of the C(7), C(10–15), C(24–28), and C(32–33) subunits of sphinxolide B were first assigned by J-based NMR methods.[6] The relative and absolute stereochemistry of the C(17–22)[7], C(22–35),[8] and C(5–16)[9] subunits of reidispongiolide A were assigned via asymmetric synthesis. The absolute configuration of this family of natural products was determined from the actin-bound X-ray crystal structure of reidispongiolide A (Fig. 1).[10]

The structure complexity and biological properties of reidispongiolide A have stimulated interest in its synthesis. The total synthesis of reidispongiolide A was reported by Paterson and co-workers in 2007.[11,9,12] More recently, Suenaga and co-workers reported the synthesis of the C(11–22) and C(23–35) fragments of **1**.[13] Because recent research suggests that the C(24)–C(36) side chain plays a very important role in the binding of the reisipongiolides to the actin target,[14,15] we have focused our current efforts on this segment of the natural product.

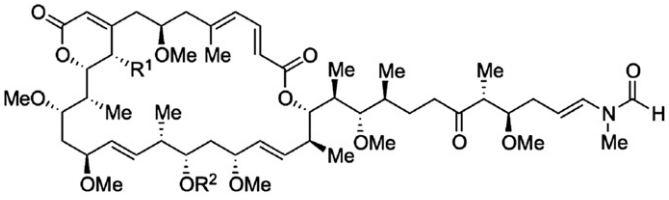

Fig. 1. Structures of selected members of the reidispongiolide–sphinxolide natural products.

We report here a highly stereoselective synthesis of the reidispongiolide A C(22)–C(36) subunit **2** that proceeds along the general outline of the retrosynthetic analysis that is presented in Scheme 1. The synthetic target **2** possesses seven stereocenters, including the C(26)–C(28) anti–anti stereotriad that represents a historically difficult challenge for synthesis via asymmetric aldol or crotylmetalation reactions,[16] as this bond construction is stereochemically

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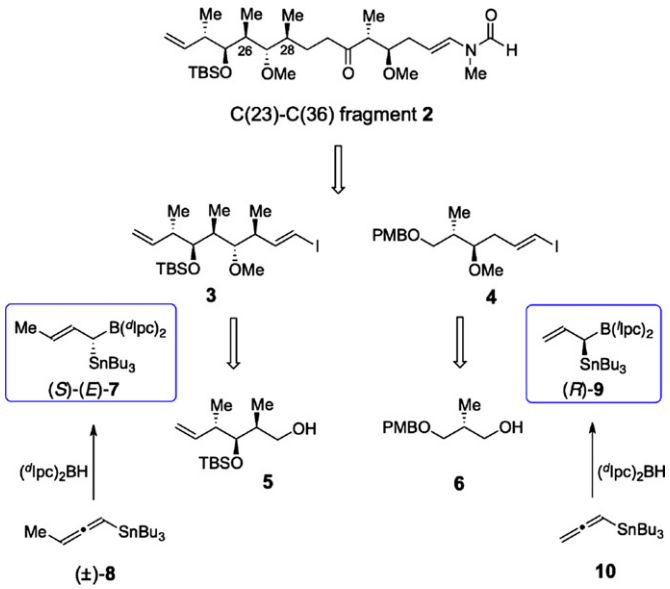
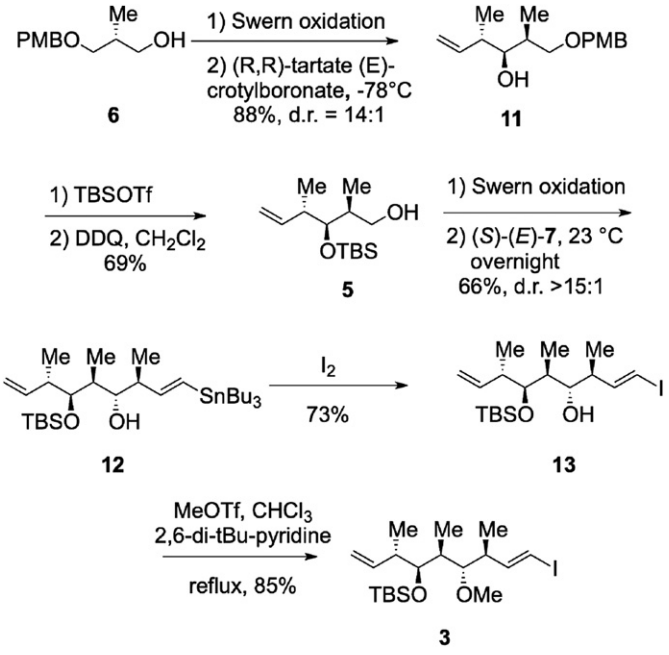
mismatched. However, synthesis of the anti, anti stereotriad with exceptional stereochemical control is now possible by virtue of the remarkable enantioselectivity of the new α-stannyl crotylborane **7**, that is, accessible via enantioselective hydroboration of racemic allene **8** with diisopinocampheylborane [$(Ipc)_2BH$].[17,18] Thus, by application of this new crotylboration technology we anticipated that vinyl iodide intermediate **3** could be assembled via α-stannylcrotylboration of the aldehyde deriving from **5** with the chiral reagent (*S*)-(*E*)-**7**. Similarly, we anticipated that vinyl iodide fragment **4** would be accessible via α-stannylallylboration of the aldehyde deriving from **6** with the α-stannylallylborane (*R*)-**9**, that is, readily accessible via the hydroboration of allenylstannane **10** with [$(^{l}Ipc)_2BH$].[19]



Scheme 1. Retrosynthetic analysis of **2**.

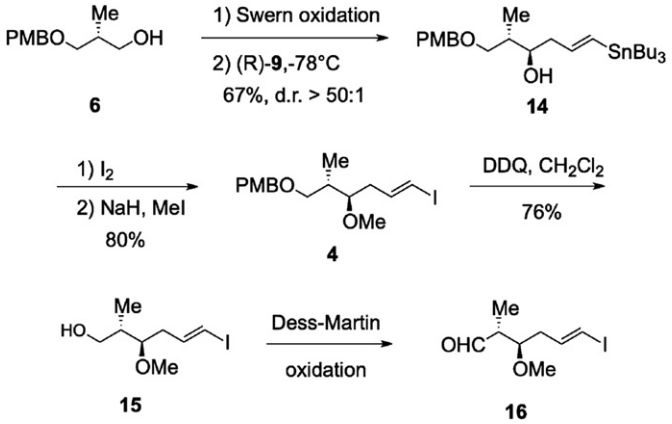
2. Results and discussion

The synthesis of fragment **3** (Scheme 2) starts from the primary alcohol **6**, which is prepared in two steps from commercially available precursors.[20] Alcohol **6** was oxidized to the corresponding aldehyde using a Swern procedure[21] and then the aldehyde was treated with the diisopropyl (*R*,*R*)-tartrate (*E*)-crotylboronate reagent[22] to give the known homoallylic alcohol **11** in 88% yield with 14:1 diastereoselectivity.[23] Protection of the hydroxyl group of **11** as a TBS ether followed by PMB ether deprotection with DDQ[24] provided primary alcohol **5** in 69% yield over the two steps. Alcohol **5** was then oxidized to the corresponding aldehyde and then added to a solution of α-stannylcrotylborane (*S*)-(*E*)-**7** that was generated, as previously described, via the hydroboration of racemic allene **8** with $(^{d}Ipc)_2BH$.[17] This reaction proceeded overnight at ambient temperature and provided the vinylstannane product **12**, with the requisite anti–anti stereochemistry at C(26–28), in 66% yield with >15:1 dr. The stereochemistry of **12** was assigned by analogy to related mismatched double asymmetric reactions described elsewhere.[18] Treatment of **12** with I_2 in Et_2O effected tin–iodine exchange and afforded vinyl iodide **13** in 73% yield. O-Methylation of the hindered hydroxyl group of **13** proved challenging. Attempted use of NaH and MeI for this step caused partial migration of the TBS unit between two hydroxyl groups, while use of Me_3OBF_4 and Proton Sponge® led to partial deprotection of TBS ether. Fortunately, use of MeOTf and 2,6-di-*tert*-butylpyridine resulted in a very clean reaction that provided **3** in 85% yield.[25]



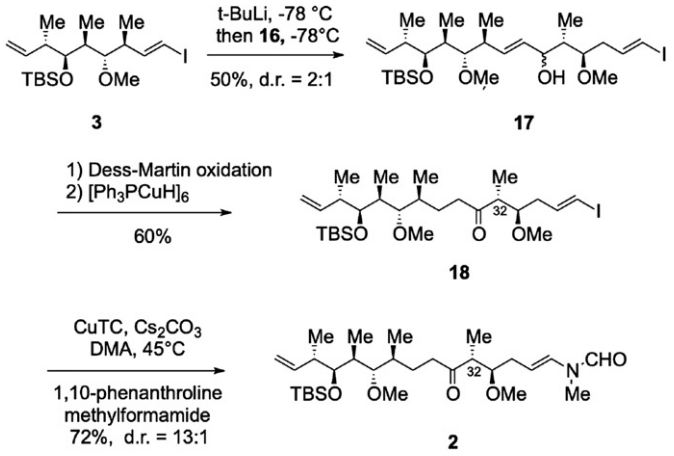
Scheme 2. Synthesis of vinyl iodide **3**.

Alcohol **6** also served as the starting material for synthesis of vinyl iodide fragment **4** (Scheme 4). The aldehyde generated by Swern oxidation of **6** was added to a −78 °C solution the α-stannylallylborane reagent (*R*)-**9**, generated by the hydroboration of allenylstannane **10** with $(^{l}Ipc)_2BH$ as previously described,[19] to give **14** in 67% yield and with >50:1 dr. The (*R*)-stereochemistry of the hydroxyl group of **14** was assigned by using the Mosher ester method. Treatment of **14** with I_2 followed by alcohol O-methylation gave vinyl iodide **4** in 80% yield. Deprotection of PMB ether of **4** gave the primary alcohol **15** in 76% yield, which was then oxidized under Dess–Martin oxidation[26] conditions to give aldehyde **16**. Aldehyde **16** is not stable for long-term storage and was usually freshly prepared before immediately before use in subsequent chemistry (Scheme 3).



Scheme 3. Synthesis of vinyl iodide **4** and elaboration to aldehyde **16**.

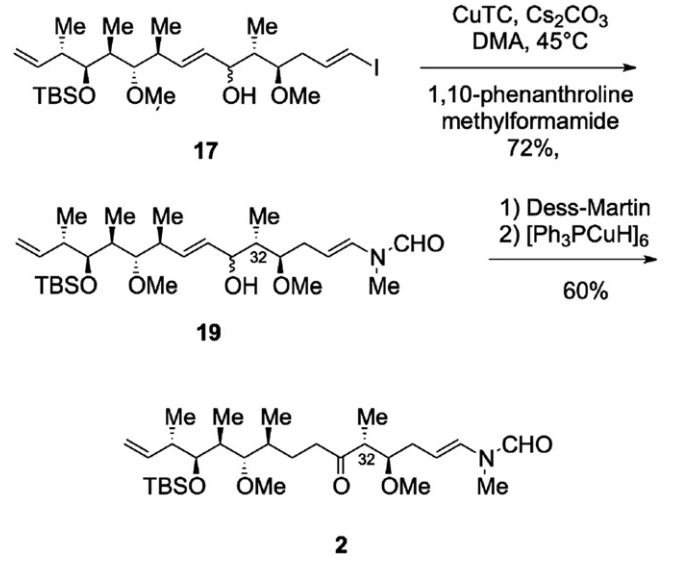
Treatment of vinyl iodide **3** with *t*-BuLi at −78 °C generated the corresponding the vinyllithium intermediate which was then treated with aldehyde **16**, also at −78 °C. This reaction gave alcohol **17** in 50% yield as a ca. 2:1 mixture of diastereomers (Scheme 4). This mixture was of no consequence, as both alcohols smoothly were oxidized in the next step upon treatment with the Dess–Martin periodinane reagent. The resulting enone was then



Scheme 4. Initial studies on the coupling of vinyl iodide **3** and aldehyde **16**.

treated with Stryker's copper hydride reagent[27] to give ketone **18** in 60% yield from **17**. It was anticipated that **18** would be a suitable substrate for introduction of the *N*-methylformamide unit, by application of Porco's procedure.[28–31] While this proved to be the case, a small amount of epimerization occurred at C(32) in the conversion of **18** to **2** owing to the basicity of these reaction conditions. Unfortunately, the epimerization at C(32) could not be avoided, and the best result that we obtained was a 13:1 mixture of **2** and its (C32)-epimer.

Fortunately, this epimerization process could be avoided by introducing the *N*-methyl formamide unit prior to oxidation of the C(31)-alcohols (Scheme 5). Thus, the *N*-methyl formamide was introduced at the stage of alcohol **17** to give **19** in 72% yield.[30,31] Subsequent oxidation of **19** with the Dess–Martin periodinane reagent, followed by reduction of the enone using Stryker's copper hydride reagent afforded **2** in 50% over the final two steps. The ^{1}H NMR spectrum of **2** showed no evidence of epimerization of the C32 stereocenter.



Scheme 5. Completion of the synthesis of **2**.

3. Conclusion

In summary, we have developed a highly stereoselective synthesis of C(22)–C(36) fragment **2** of reidispongiolide A that features the highly stereoselective mismatched double asymmetric crotylboration reaction of the aldehyde derived from **5** and the new chiral reagent (*S*)-(*E*)-**7** that provides **12** with >15:1 dr. Subsequent coupling of the derived vinyl iodide **3** with aldehyde **16** provided allylic alcohol **17**, that was elaborated by three steps into the targeted reidispongiolide fragment **2**. This work sets the stage for further studies on the chemistry and biology of reidispongiolide A, that will be reported in due course.

4. Experimental

4.1. General experimental details

All reaction solvents were purified before use. Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were purified by passing through a solvent column composed of activated A-1 alumina. Unless indicated otherwise, all reactions were conducted under an atmosphere of argon using flame-dried or oven-dried (170 °C) glassware. 4 Å molecular sieves were activated under high vacuum with at 180 °C for 12 h and re-activated through flame-drying immediately prior to use.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on commercial instruments at 400 or 500 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. The proton signal for residual non-deuterated solvent (δ 7.26 for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CHCl_3$. Coupling constants are reported in Hz. Infrared (IR) spectra were recorded as films on an FTIR instrument. Mass spectra were recorded on a commercial spectrometer. Optical rotations were measured at 25 °C on a polarimeter using a 10-cm, 1-mL quartz cell.

4.2. Experimental procedures

*4.2.1. (2S,3S,4S)-1-((4-Methoxybenzyl)oxy)-2,4-dimethylhex-5-en-3-ol (**11**).* A solution of the oxalyl chloride (1 mL, 11.4 mmol) in dry CH_2Cl_2 (20 mL) was added DMSO (1.86 mL, 26 mmol) dropwise at −78 °C. This mixture was stirred for 15 min, then a solution of alcohol **6** (2.10 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min. Diisopropylethylamine (9.2 mL, 52.8 mmol) was then added and the mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (100 mL). The organic phase was separated and washed with 1 N HCl, sat aqueous $NaHCO_3$ solution and brine, and then dried over $MgSO_4$. Filtration and concentration of this solution under reduced pressure provided the aldehyde as colorless oil, which was used immediately in the next step without further purification.

A 1.0 M solution of diisopropyl (*R*,*R*)-tartrate (*E*)-crotylboronate in toluene (20 mL, 20 mmol) was added to a slurry of powdered 4 Å molecular sieves (0.4 g) in toluene (10 mL) at ambient temperature. The mixture was stirred for 20 min, then was cooled to −78 °C and a solution of the aldehyde in toluene (10 mL) was added dropwise. After being stirred for 8 h at −78 °C, the reaction mixture was quenched by 1 M NaOH (40 mL). The resulting two-phase mixture was stirred vigorously for 30 min, and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (4:1 hexanes/EtOAc) provided the known alcohol **11** (2.32 g, 88% for two steps) as colorless oil.[23]

*4.2.2. (2S,3S,4S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-1-ol (**5**).* A solution of the alcohol **11** (1.79 g, 6.8 mmol) and 2,6-lutidine (1.6 mL, 13.6 mmol) in CH_2Cl_2 (60 mL) at −78 °C was treated with TBSOTf (1.85 mL, 10.2 mmol). The reaction mixture was stirred for 1 h and warmed to 0 °C over 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (30 mL).

The resulting mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (9:1 hexanes/EtOAc) provided the known TBS ether (2.29 g, 89%) as a colorless oil.[23]

To a 0 °C stirred CH_2Cl_2 solution (40 mL) of the above TBS ether (2.29 g, 6.06 mmol) was added a small amount of pH 7 buffer (5% relative to CH_2Cl_2) followed by DDQ (1.66 g, 7.3 mmol). The resulting mixture was stirred at 0 °C for 30 min, then was allowed to warm to room temperature and stirred for another 30 min. The mixture was then diluted with saturated aqueous $NaHCO_3$ (50 mL) and was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were treated with $NaBH_4$ (500 mg, 12.5 mmol) and then washed with saturated aqueous $NaHCO_3$, and brine. The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (4:1 hexanes/EtOAc) provided the known alcohol **5** (1.23 g, 78%) as a colorless oil.[32]

*4.2.3. (3S,4S,5S,6S,7S,E)-6-((tert-Butyldimethylsilyl)oxy)-3,5,7-trimethyl-1-(tributylstannyl)nona-1,8-dien-4-ol (**12**).* To a solution of oxalyl chloride (0.19 mL, 2.32 mmol) in dry CH_2Cl_2 (10 mL) was added DMSO (0.36 mL, 5.1 mmol) dropwise at −78 °C. This mixture was stirred for 15 min, then a solution of alcohol **5** (500 mg, 1.93 mmol) in CH_2Cl_2 (3 mL) was added dropwise and the reaction left at −78 °C for 30 min. Diisopropylethylamine (1.77 mL, 10.2 mmol) was then added and the mixture was allowed to warm to room temperature. Et_2O (50 mL) was added to dilute the mixture. The organic layer was separated and washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$. After being filtered, this solution was concentrated under vacuum to give the aldehyde as colorless oil, which was used immediately in the next step without further purification.

Generation of α-stannylcrotylborane (*S*)-(*E*)-**7** was performed as follows.[17] Finely powdered (^{d}Ipc)$_2$BH (1.05, 3.86 mmol) was weighed into a round bottom flask containing a stir bar in a glove box. Et_2O (10 mL) was added to the flask and the mixture was cooled to 0 °C. Racemic allenylstannane **8** (1.33 g, 3.86 mmol) was added dropwise. This mixture was stirred for 5 h at 0 °C, during which time the solid (^{d}Ipc)$_2$BH dissolved to leave a colorless solution of the reagent, (*S*)-(*E*)-**7**.

A solution of the aldehyde (theoretically 1.93 mmol) in 3 mL of Et_2O was added at 0 °C dropwise to the freshly prepared solution of (*S*)-(*E*)-**7**. The mixture was allowed to warm to room temperature and stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C, then saturated aqueous $NaHCO_3$ (6 mL) was added followed by slow addition of 30% H_2O_2 (3 mL). This mixture was stirred vigorously for 4 h at room temperature. After separation, the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$ filtered and concentrated. Purification of the crude product by column chromatography (silica gel neutralized with 1% Et_3N in hexanes; 50:1 hexanes/Et_2O) providing alcohol **8** (766 mg, 66% yield over two steps) as a colorless oil: $[\alpha]_D$ −5.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06–5.97 (m, 2H), 5.91 (d, *J*=19.2 Hz, 1H), 5.01 (m, 2H), 3.75 (dd, *J*=4.1, 2.9 Hz, 1H), 3.62 (dt, *J*=10.0, 2.6 Hz, 1H), 3.33 (s, 1H), 2.52–2.44 (m, 1H), 2.33–2.25 (m, 1H), 1.77 (ddd, *J*=10.0, 7.1, 2.8 Hz, 1H), 1.53–1.42 (m, 6H), 1.36–1.24 (m, 6H), 1.09 (d, *J*=7.0 Hz, 3H), 1.03 (d, *J*=7.0 Hz, 3H), 0.94–0.83 (m, 25H), 0.80 (d, *J*=7.0 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 141.7, 128.8, 114.5, 80.2, 76.5, 44.9, 41.4, 41.0, 29.3, 27.4, 26.2, 19.6, 18.3, 18.1, 13.9, 12.9, 9.6, −3.9, −4.3. IR (neat) 3503, 2957, 2927, 1641, 1596, 1464, 1252 cm^{-1}; HRMS *m*/*z* for $C_{30}H_{62}O_2SiSnH$ $[M+H]^+$ calcd 603.3619, found 603.3645.

*4.2.4. (3S,4S,5S,6S,7S,E)-6-((tert-Butyldimethylsilyl)oxy)-1-iodo-3,5,7-trimethylnona-1,8-dien-4-ol (**13**).* To a solution of vinylstannane **12** (766 mg, 1.27 mmol) in Et_2O (20 mL) was added iodine (381 mg, 1.5 mmol) at room temperature. After being stirred for 1 h, the reaction was diluted with saturated aqueous $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were treated with KF/Celite (700 mg per mmol of **12**). This solution was stirred vigorously for at least 2 h and then filtered through Celite. Purification of the crude product by column chromatography (9:1 hexanes/Et_2O) provided the vinyl iodide **13** (406 mg, 73%) as a colorless oil: $[\alpha]_D$ −17.6 (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, *J*=14.6, 9.4 Hz, 1H), 6.07–5.97 (m, 2H), 5.09–4.98 (m, 2H), 4.01 (s, 1H), 3.70 (t, *J*=3.5 Hz, 1H), 3.67 (dt, *J*=10.3, 2.0 Hz, 1H), 2.56–2.47 (m, 1H), 2.33–2.24 (m, 1H), 1.85–1.75 (m, 1H), 1.10 (d, *J*=7.0 Hz, 3H), 1.05 (d, *J*=7.0 Hz, 3H), 0.93 (s, 9H), 0.79 (d, *J*=7.1 Hz, 3H), 0.13 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 141.2, 114.7, 81.4, 76.4, 74.7, 43.9, 41.2, 40.3, 26.1, 20.3, 18.3, 17.7, 13.7, −3.9, −4.5. IR (neat) 3480, 2959, 2930, 1640, 1602, 1463, 1254 cm^{-1}; HRMS *m*/*z* for $C_{18}H_{35}O_2SiIH$ $[M+H]^+$ calcd 439.1529 found 439.1525.

*4.2.5. tert-Butyl(((3S,4S,5S,6S,7S,E)-9-iodo-6-methoxy-3,5,7-trimethylnona-1,8-dien-4-yl)oxy)dimethylsilane (**3**).* To a stirred solution of freshly distilled MeOTf (0.52 mL, 4.7 mmol) in 2,6-di-*tert*-butylpyridine (2.06 mL, 9 mmol) was added alcohol **13** (110 mg, 0.25 mmol) in $CHCl_3$ (6 mL). The reaction mixture was then heated to reflux for 15 h. The reaction mixture was then cooled to room temperature and NH_4OH (2 mL, aqueous) was added. The resulting mixture was stirred for 2 h at room temperature and then was poured into 30 mL of water. Once the organic layer separated, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with 1 N HCl, brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (silica gel, 100:1 hexanes/EtOAc) provided the vinyl iodide **3** (96 mg, 81%) as a colorless oil: $[\alpha]_D$ −6.8 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (dd, *J*=14.6, 8.6 Hz, 1H), 6.00 (dd, *J*=14.6, 0.9 Hz, 1H), 5.88–5.78 (m, 1H), 5.05–4.98 (m, 2H), 3.82 (dd, *J*=4.5, 2.4 Hz, 1H), 3.44 (s, 3H), 2.90 (dd, *J*=8.6, 2.8 Hz, 1H), 2.51–2.41 (m, 1H), 2.34–2.23 (m, 1H), 1.74–1.65 (m, 1H), 1.10 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.91 (s, 9H), 0.77 (d, *J*=7.0 Hz, 3H), 0.08 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 141.5, 114.5, 87.2, 74.9, 74.8, 60.8, 44.8, 42.9, 39.3, 26.3, 18.7, 18.2, 16.7, 11.9, −3.4, −3.5. IR (neat) 2959, 2929, 1640, 1602, 1462, 1252, 1093 cm^{-1}; HRMS *m*/*z* for $C_{19}H_{37}O_2SiIH$ $[M+H]^+$ calcd 453.1686 found 453.1693.

*4.2.6. (2S,3R,E)-1-((4-Methoxybenzyl)oxy)-2-methyl-6-(tributylstannyl)hex-5-en-3-ol (**14**).* To a −78 °C solution of oxalyl chloride (0.25 mL, 2.85 mmol) in dry CH_2Cl_2 (10 mL) was added DMSO (0.47 mL, 6.5 mmol) dropwise. The mixture was stirred for 15 min, then a solution of alcohol **6** (525 mg, 2.5 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was left at −78 °C for 30 min. Diisopropylethylamine (2.3 mL, 13.2 mmol) was then added and the mixture was allowed to warm to room temperature. Et_2O (50 mL) was added and the organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The solution was filtered and then concentration under vacuum to provide the crude aldehyde as colorless oil, which was used immediately in the next step without further purification.

Generation of α-stannylallylborane (*R*)-**9** was performed following the literature procedure.[19] Finely powdered (^{l}Ipc)$_2$BH (950 mg, 3.5 mmol) was weighed into a round bottom flask containing a stir bar in a glove box. Toluene (10 mL) was added to the flask and the mixture was cooled to −40 °C. Allenylstannane **10** (1.65 g, 5 mmol) was added dropwise. This mixture was allowed to warm to −20 °C over 5 h, during which time the solid (^{l}Ipc)$_2$BH dissolved to leave a colorless solution of the reagent (*R*)-**9**.

A −78 °C solution of the aldehyde (theoretically 2.5 mmol) in 3 mL toluene was added dropwise to the freshly prepared solution

of α-stannylallylborane (*R*)-**9** in toluene. The mixture was stirred overnight at −78 °C. The reaction was then allowed to warm to 0 °C. To this mixture was added saturated aqueous $NaHCO_3$ (6 mL) followed by slow addition of 30% H_2O_2 (3 mL). This mixture was stirred vigorously for 4 h at room temperature. After separation of the two phases, the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography (silica gel neutralized with 1% Et_3N in hexanes; 85:15 hexanes/Et_2O) provided alcohol **14** (900 mg, 67% yield over two steps) as a colorless oil: $[\alpha]_D$ +2.2 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 6.91–6.84 (m, 2H), 6.10–5.96 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.63–3.56 (m, 1H), 3.55 (dd, *J*=9.2, 4.7 Hz, 1H), 3.47 (dd, *J*=9.2, 6.7 Hz, 1H), 3.08 (d, *J*=3.5 Hz, 1H), 2.48–2.40 (m, 1H), 2.30–2.21 (m, 1H), 1.92–1.81 (m, 1H), 1.53–1.44 (m, 6H), 1.33–1.26 (m, 6H), 0.92–0.85 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 145.7, 131.6, 130.3, 129.4, 114.0, 74.8, 74.4, 73.2, 55.4, 43.8, 38.0, 29.3, 27.4, 14.0, 13.9, 9.6. IR (neat) 3479, 2924, 1613, 1512, 1247 cm^{-1}; HRMS *m*/*z* for $C_{27}H_{48}O_3SnH$ $[M+H]^+$ calcd 541.2704 found 541.2711.

*4.2.7. 1-((((2S,3R,E)-6-Iodo-3-methoxy-2-methylhex-5-en-1-yl)oxy) methyl)-4-methoxybenzene (**4**).* To a solution of vinylstannane **14** (900 mg, 1.67 mmol) in Et_2O (30 mL) was added iodine (460 mg, 1.8 mmol) at room temperature. The mixture was stirred for 1 h, then saturated aqueous $Na_2S_2O_3$ was added to reduce remaining iodine. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic layers were treated with KF/Celite (700 mg per mmol of **14**). This mixture was stirred vigorously for at least 2 h and then filtered through Celite. Purification of the crude product by column chromatography (4:1 hexanes/EtOAc) provided the vinyl iodide product (618 mg, 1.64 mmol) as a colorless oil.

To a mixture of the above vinyl iodide (618 mg, 1.64 mmol) and MeI (1.05 mL, 16.4 mmol) in DMF (10 mL) was added 60% NaH in mineral oil (140 mg, 3.5 mmol). The reaction was stirred overnight at room temperature. The mixture wasp poured into 50 mL water, then the aqueous layer was separated and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (4:1 hexanes/EtOAc) provided the product **4** (524 mg, 80% yield over two steps) as a colorless oil: $[\alpha]_D$ −28.6 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.22 (m, 2H), 6.92–6.84 (m, 2H), 6.56 (dt, *J*=14.6, 7.4 Hz, 1H), 6.04 (dt, *J*=14.4, 1.3 Hz, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.38 (qd, *J*=9.1, 5.8 Hz, 2H), 3.32 (s, 3H), 3.24–3.18 (m, 1H), 2.26 (dddd, *J*=14.8, 7.1, 4.2, 1.4 Hz, 1H), 2.20–2.11 (m, 1H), 2.07–1.96 (m, 1H), 0.90 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 143.2, 130.8, 129.3, 113.9, 81.3, 76.7, 72.9, 72.0, 57.8, 55.4, 36.7, 36.4, 13.1. IR (neat) 2904, 1612, 1512, 1244, 1086 cm^{-1}; HRMS *m*/*z* for $C_{16}H_{23}O_3INa$ $[M+Na]^+$ calcd 413.0590 found 413.0592.

*4.2.8. (2S,3R,E)-6-Iodo-3-methoxy-2-methylhex-5-en-1-ol (**15**).* To a stirred 0 °C solution of **4** (548 mg, 1.41 mmol) in CH_2Cl_2 (5 mL) containing a small amount of pH 7 buffer (5% relative to CH_2Cl_2) was added DDQ (522 g, 2.3 mmol). The mixture was stirred at 0 °C for 30 min, then was allowed to warm to room temperature and stirred for another 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was added, then the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography provided the primary alcohol **15** (290 mg, 76%) as a colorless oil: $[\alpha]_D$ −41.4 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (ddd, *J*=14.7, 8.1, 6.8 Hz, 1H), 6.12 (dt, *J*=14.4, 1.4 Hz, 1H), 3.67–3.54 (m, 2H), 3.39 (s, 3H), 3.19 (dt, *J*=7.4, 4.9 Hz, 1H), 2.75 (dd, *J*=7.0, 4.3 Hz, 1H), 2.44 (dddd, *J*=15.1, 6.5, 4.8, 1.5 Hz, 1H), 2.30–2.21 (m, 1H), 1.89–1.80 (m, 1H), 0.91–0.86 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 85.1, 77.0, 66.9, 57.8, 38.0, 36.9, 13.9. IR (neat) 3405, 2928, 1606, 1083 cm^{-1}; HRMS *m*/*z* for $C_8H_{15}O_2IH$ $[M+H]^+$ calcd 271.0195 found 271.0204.

*4.2.9. (1E,4R,5S,7E,9S,10S,11S,12S,13S)-12-((tert-Butyldimethylsilyl) oxy)-1-iodo-4,10-dimethoxy-5,9,11,13-tetramethylpentadeca-1,7,14-trien-6-ol (**17**).* To a solution of Dess–Martin periodinane (154 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added alcohol **15** (81 mg, 0.3 mmol) in CH_2Cl_2 (3 mL). Once the reaction was complete (TLC monitoring), Et_2O (10 mL), saturated aqueous $NaHCO_3$ (5 mL), and $Na_2S_2O_3$ (1 mL) were added. The organic layer was separated and aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude aldehyde **16** was used immediately without purification in the next step.

t-BuLi (0.4 mmol, 0.25 mL, 1.6 M in pentane) was added dropwise to a −78 °C solution of vinyl iodide **3** (91 mg, 0.2 mmol) in THF (2 mL). The mixture was stirred for 30 min, then a solution of aldehyde **16** (prepared from 0.3 mmol of alcohol **15**) in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for additional 1.5 h, then the reaction mixture was allowed to warm to 0 °C. Saturated aqueous NH_4Cl solution was then added to terminate the reaction. The organic layer was separated and aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (9:1 hexanes/EtOAc) provided the alcohol **17** (58 mg, 50%) as a colorless oil, as a mixture of two isomers (2:1 ratio). This mixture was carried to next step without separation. ^1H NMR (400 MHz, $CDCl_3$) δ 6.63–6.48 (1H), 6.16–6.05 (1H), 5.90–5.59 (2H), 5.48–5.33 (1H), 5.03–4.92 (2H), 4.26 (1H), 3.86 (1H), 3.51–3.43 (3H), 3.39–3.33 (3H), 3.30–3.22 (1H), 2.91 (2H), 2.52–2.37 (2H), 2.33–2.17 (2H), 1.86–1.74 (1H), 1.74–1.64 (1H), 1.15–1.09 (3H), 1.01–0.96 (m, 3H), 0.90 (9H), 0.88–0.82 (m, 3H), 0.79–0.73 (m, 3H), 0.11–0.07 (m, 6H).

*4.2.10. (4R,5R,9S,10S,11S,12S,13S,E)-12-((tert-Butyldimethylsilyl) oxy)-1-iodo-4,10-dimethoxy-5,9,11,13-tetramethylpentadeca-1,14-dien-6-one (**18**).* To a solution of Dess–Martin periodinane (44 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added alcohol **17** (46 mg, 0.078 mmol) in CH_2Cl_2 (1 mL). Once the reaction was complete (TLC monitoring), Et_2O (5 mL), saturated aqueous $NaHCO_3$ (2 mL), and $Na_2S_2O_3$ (0.5 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give crude product ketone (42 mg). This crude product was used directly in the next step without purification.

To a solution of Stryker's copper hydride reagent ($[PPh_3CuH]_6$; 78 mg, 0.04 mmol) in 2 mL of degassed toluene was added the above enone as a solution in toluene (1 mL, degassed) and 1 drop of water via syringe. The mixture was stirred overnight at room temperature, then was diluted with 20 mL of CH_2Cl_2. The combined organic layers were washed with saturated aqueous NH_4Cl solution, brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (9:1 hexanes/EtOAc) provided the ketone **18** (28 mg, 60% over two steps) as a colorless oil: $[\alpha]_D$ −30.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (ddd, *J*=14.7, 8.4, 6.5 Hz, 1H), 6.12 (dt, *J*=14.5, 1.3 Hz, 1H), 5.92–5.79 (m, 1H), 5.06–4.96 (m, 2H), 3.84 (dd, *J*=4.5, 2.1 Hz, 1H), 3.45–3.41 (m, 4H), 3.27 (s, 3H), 2.88 (dd, *J*=8.3, 3.3 Hz, 1H), 2.76–2.67 (m, 1H), 2.55 (ddd, *J*=17.5, 9.2, 5.3 Hz, 1H), 2.49–2.37 (m, 2H), 2.34–2.26 (m, 1H), 2.19–2.08 (m, 1H), 1.83–1.69 (m, 2H), 1.65 (ddd, *J*=13.5, 6.8, 3.4 Hz, 1H), 1.44–1.33 (m, 1H), 1.01 (d, *J*=7.0 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=7.0 Hz, 3H), 0.91 (s, 9H), 0.81 (d, *J*=7.0 Hz,

3H), 0.09 (s, 2H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.6, 141.8, 141.7, 114.3, 88.8, 81.5, 77.1, 75.0, 60.9, 57.9, 49.1, 45.0, 41.6, 38.9, 36.4, 34.5, 26.3, 24.2, 18.7, 17.7, 16.7, 12.8, 12.3, −3.4, −3.5. IR (neat) 2959, 2931, 1716, 1462, 1253, 1095 cm^{-1}; HRMS *m*/*z* for $C_{27}H_{51}O_4SiIH$ $[M+H]^+$ calcd 595.2680 found 595.2678.

*4.2.11. N-((4R,5R,9S,10S,11S,12S,13S,E)-12-((tert-Butyldimethylsilyl) oxy)-4,10-dimethoxy-5,9,11,13-tetramethyl-6-oxopentadeca-1,14-dien-1-yl)-N-methylformamide (**2**).* *N*-Methyl formamide (0.1 mL), Cs_2CO_3 (26 mg, 0.08 mmol), CuTC (9 mg, 0.045 mmol), and 1,10-phenanthroline (16 mg, 0.09 mmol) were placed in a flame-dried 10 mL Schlenk tube with a stir bar. Vinyl iodide **18** (27 mg, 0.045 mmol) in 1 mL of anhydrous DMA was added and the system was degassed under vacuum until gas evolution ceased. The mixture was heated to 45 °C for 18 h. The reaction mixture was then diluted with Et_2O and pH 7 buffer. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (1:1 hexanes/EtOAc) provided the product **2** (12 mg, 50%, 75% based on recovered starting material) as a colorless oil. The product contains two amide rotamers at room temperature, and was a 12:1 mixture of epimers at C(32): $[\alpha]_D$ −25.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.06 (1H, 8.28 (s, 0.7H), 8.06 (s, 0.3H)), 7.18–6.51 (1H, 7.18 (d, *J*=14.6 Hz, 0.3H), 6.51 (d, *J*=14.0 Hz, 0.7H)), 5.94–5.76 (m, 1H), 5.17–4.95 (m, 3H), 3.84 (dd, *J*=4.4, 2.0 Hz, 1H), 3.49–3.39 (m, 4H), 3.29–3.28 (3H, 3.29 (s, 2H), 3.28 (s, 1H)), 3.06–3.03 (3H, 3.06 (s, 1H), 3.03 (s, 2H)), 2.88 (dd, *J*=8.3, 3.1 Hz, 1H), 2.78–2.67 (m, 1H), 2.60–2.39 (m, 3H), 2.35–2.25 (m, 1H), 2.22–2.08 (m, 1H), 1.83–1.70 (m, 2H), 1.70–1.62 (m, 1H), 1.37 (m, 1H), 0.98 (m, 9H), 0.91 (s, 9H), 0.81 (d, *J*=7.0 Hz, 3H), 0.08 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8, 162.3 (160.9), 141.8, 130.5 (126.5), 114.3, 105.7 (107.3), 88.8, 82.5, 75.0, 60.9, 57.9 (57.7), 49.0 (49.2), 45.0, 41.5 (41.3), 38.9, 34.5, 30.6 (30.5), 27.7 (33.2), 26.3, 24.2, 18.7, 17.8 (17.7), 16.7, 12.8 (13.0), 12.3, −3.4, −3.5. IR (neat) 2958, 2930, 1696, 1659, 1462, 1252, 1078 cm^{-1}; HRMS *m*/*z* for $C_{29}H_{55}O_5SiH$ $[M+H]^+$ calcd 526.3928 found 526.3925.

*4.2.12. N-((1E,4R,5S,7E,9S,10S,11S,12S,13S)-12-((tert-Butyldimethylsilyl)oxy)-6-hydroxy-4,10-dimethoxy-5,9,11,13-tetramethylpentadeca-1,7,14-trien-1-yl)-N-methylformamide (**19**).* *N*-Methyl formamide (0.2 mL), Cs_2CO_3 (49 mg, 0.15 mmol), CuTC (19 mg, 0.1 mmol), 1,10-phenanthroline (36 mg, 0.2 mmol) were placed in a flame-dried 10 mL Schlenk tube with a stir bar. A solution of vinyl iodide **17** (58 mg, 0.098 mmol) in 1 mL of anhydrous DMA was added and the system was degassed under vacuum until gas evolution ceased. The mixture was heated to 45 °C for 18 h. The reaction was then diluted with Et_2O and pH 7 buffer. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (1:4 hexanes/EtOAc) provided the product **19** (37 mg, 72%) as a colorless oil. This compound contains two isomers (alcohol epimers, deriving from **17**) and there are two rotamers for each isomer. The product was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.01 (1H), 7.21–6.45 (1H), 5.90–5.59 (2H), 5.50–5.32 (1H), 5.19–4.91 (3H), 4.29 (s, 1H), 3.86 (1H), 3.49–3.44 (3H), 3.41–3.37 (3H), 3.31–3.22 (1H), 3.07–3.00 (3H), 3.00–2.81 (2H), 2.55–2.39 (2H), 2.33–2.17 (2H), 1.88–1.78 (1H), 1.73–1.65 (1H), 1.12 (3H), 1.02–0.95 (3H), 0.93–0.88 (9H), 0.88–0.81 (3H), 0.80–0.74 (3H), 0.10–0.04 (6H).

*4.2.13. N-((4R,5R,9S,10S,11S,12S,13S,E)-12-((tert-Butyldimethylsilyl) oxy)-4,10-dimethoxy-5,9,11,13-tetramethyl-6-oxopentadeca-1,14-dien-1-yl)-N-methylformamide (**2**).* To a solution of Dess–Martin periodinane (44 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added alcohol **19** (37 mg, 0.07 mmol) in CH_2Cl_2 (1 mL). Once the reaction was complete (TLC monitoring), Et_2O (5 mL), saturated aqueous $NaHCO_3$ (2 mL), and $Na_2S_2O_3$ (0.5 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give crude product ketone (36 mg) that was used directly in the next step without purification.

To a solution of Stryker's copper hydride reagent ($[PPh_3CuH]_6$; 69 mg, 0.035 mmol) in 2 mL of degassed toluene was added a solution of the above ketone in toluene (1 mL, degassed) and 1 drop of water via syringe. This mixture was stirred overnight at room temperature, then was diluted with 20 mL of CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl solution, and brine, then dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (1:1 hexanes/EtOAc) provided product **2** (18 mg, 50% over two steps) as a colorless oil. This material was showed no evidence of C(32) epimerization, but was a mixture of formamide rotamers. Otherwise, the spectroscopic properties of this material were the same as described above.

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