JOC The Journal of Organic Chemistry

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Crotylboron-Based Synthesis of the Polypropionate Units of Chaxamycins A/D, Salinisporamycin, and Rifamycin S

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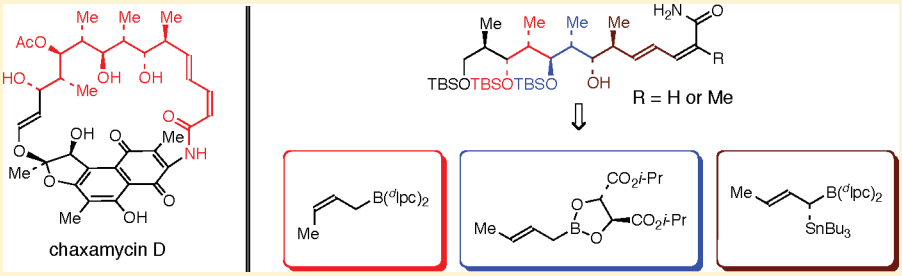
Supporting Information



ABSTRACT: Syntheses of the C(15)-C(27) fragments of chaxamycins A/D, rifamycin S, and the C(12)-C(24) fragment of salinisporamycin have been accomplished in 10 steps from commercially available starting materials. Three crotylboron reagents were utilized to construct the seven contiguous stereocenters in these fragments with excellent stereoselectivity.

INTRODUCTION

Ansamycin antibiotics, such as the rifamycins,[1] are macrolides consisting of an aromatic chromophore bridged by an aliphatic chain linking two nonadjacent positions on the aromatic moiety. In addition to their antimicrobial activities against many Gram-positive and some Gram-negative bacteria, many ansamycins also exhibit antiviral activities.[1] Furthermore, it is well documented that some members of the ansamycin family selectively interact with the ATP-binding pocket in the N-terminal domain of the heat shock protein 90 (Hsp90) and demonstrate antitumor activity.[2]

Because of the structural complexities coupled with diverse biological activities, extensive efforts have been devoted to the syntheses of ansamycin natural products. In 1980, Kishi and co-workers reported the first total synthesis of rifamycin S.[3] Following his landmark work, many strategies have been developed for the synthesis of the polyketide ansa chain of rifamycin S.[4]

Recently, salinisporamycin[5,6] and several new members of the ansamycin antibiotic family, chaxamycins A–D,[7] were reported (Figure 1). Salinisporamycin was isolated in 2009 from *Salinispora arenicola*. Subsequent biological studies revealed that salinisporamycin not only showed antimicrobial activity but also inhibited the growth of A549 cells (the human lung adenocarcinoma cell line) with an IC_{50} value of 3 μg/mL.[5] Chaxamycins A–D were isolated from *Streptomyces* sp. strain C34 obtained from soil collected in the hyperarid Chilean Atacama Desert.[7] Among the chaxamycins, chaxamycin D displayed a highly selective antibacterial activity against *S. aureus* ATCC 25923 with an IC_{50} value of 0.05 μg/mL.

As illustrated in Figure 1, chaxamycins A and D have ansa chains that are very similar to the analogous fragments of salinisporamycin and rifamycin S (shown in red in Figure 1).

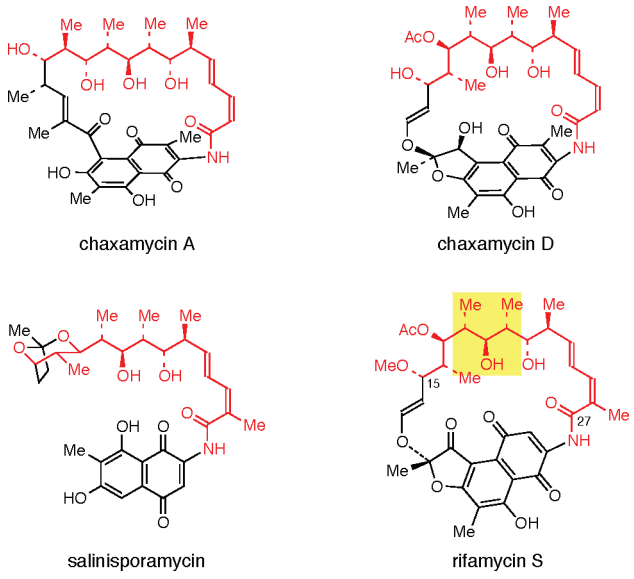


Figure 1. Structures of chaxamycins A and D, salinisporamycin, and rifamycin S.

One intriguing structural feature of these natural products is the *anti,anti*-stereotriad embedded in the polyketide chain (highlighted in yellow in Figure 1). To access this requisite *anti,anti*-stereotriad,[8] many creative approaches, including epoxide ring-opening reactions,[3,4k] the desymmetrization of *meso* interme-

Special Issue: Robert Ireland Memorial Issue

Received: April 23, 2012
Published: June 15, 2012

dx.doi.org/10.1021/jo3008226 | J. Org. Chem. 2013, 78, 3–8

diates,[4d,l,m] or elaboration of intermediates derived from hetero-Diels–Alder reactions,[4f] have been developed.

In 1987, our laboratory reported a stereoselective synthesis of the ansa chain of rifamycin S[4g,j] using the tartrate-based crotylboronate reagents.[9] In initial studies, we attempted a mismatched double asymmetric crotylboration[10] of the *β*-branched chiral aldehyde **1** using our tartrate ester modified crotylboronate reagent for the synthesis of the *anti,anti*-stereotriad **A**. However, the tartrate-based crotylboronate reagent failed to override the intrinsic diastereofacial selectivity of the chiral aldehyde, and a mixture of diastereomers was obtained with the desired *anti,anti*-stereotriad **A** only as a minor product. Therefore, we pursued an alternative strategy in which the *anti,anti*-stereotriad **2**, which can be prepared with good selectivity,[4g] was used at the starting point for the synthesis (Figure 2a).

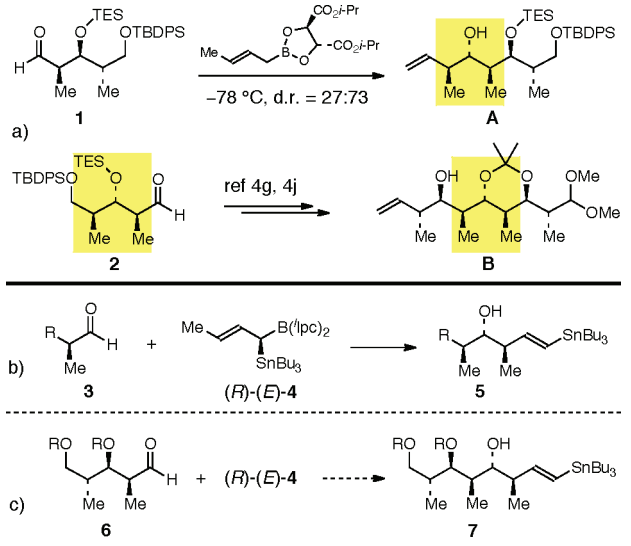


Figure 2. Strategy for synthesis of the *anti,anti*-stereotriad 7.

Recently, we described highly diastereoselective syntheses of *anti,anti*-stereotriads, such as **5**, using mismatched double asymmetric *δ*-stannylcrotylboration reactions[11] of chiral aldehydes with the chiral crotylborane reagents (*R*)-(*E*)-**4** or (*S*)-(*E*)-**4**[12] (Figure 2b). Because of the exceptional enantiofacial selectivity of reagents (*S*)-(*E*)-**4** and (*R*)-(*E*)-**4**, we were intrigued whether the *anti,anti*-stereotriad within the polyketide chain segment of the structures in Figure 1 could be prepared using reagent (*R*)-(*E*)-**4** (Figure 2c). This would enable these syntheses to be accomplished in a more direct, stepwise efficient manner without resorting to the pseudo-two-directional chain synthesis approach in our first generation synthesis of the rifamycin S ansa chain.[4j] The results of this study are reported in this article.

RESULTS AND DISCUSSION

Our retrosynthetic analysis for synthesis of the polypropionate units **8** and **9** is summarized in Figure 3. We envisioned that **8** and **9** could be assembled from aldehyde **10**, crotylborane (*S*)-(*E*)-**4**,[12] and vinyl iodides **11**.[6a,13] To access the *anti,anti*-stereotriad embedded in aldehyde **10**, we planned to utilize the mismatched double asymmetric *δ*-stannylcrotylboration of aldehyde **13** with the chiral crotylborane reagent (*R*)-(*E*)-**4**.[11,12]

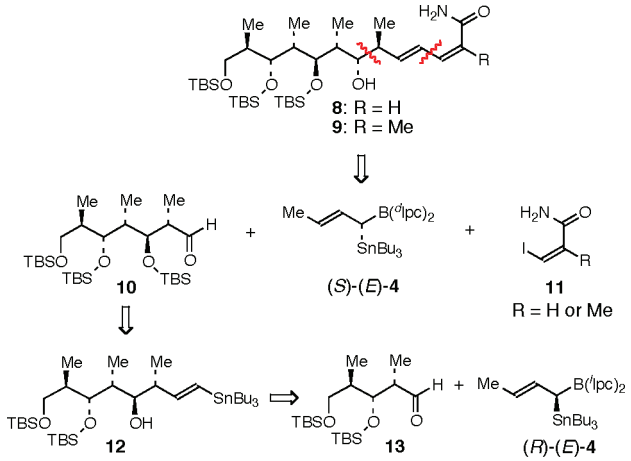
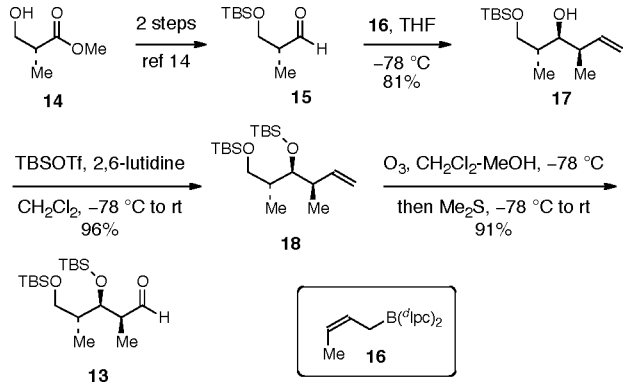


Figure 3. Retrosynthetic analysis of stereoheptads **8** and **9**.

Scheme 1. Synthesis of Aldehyde 13



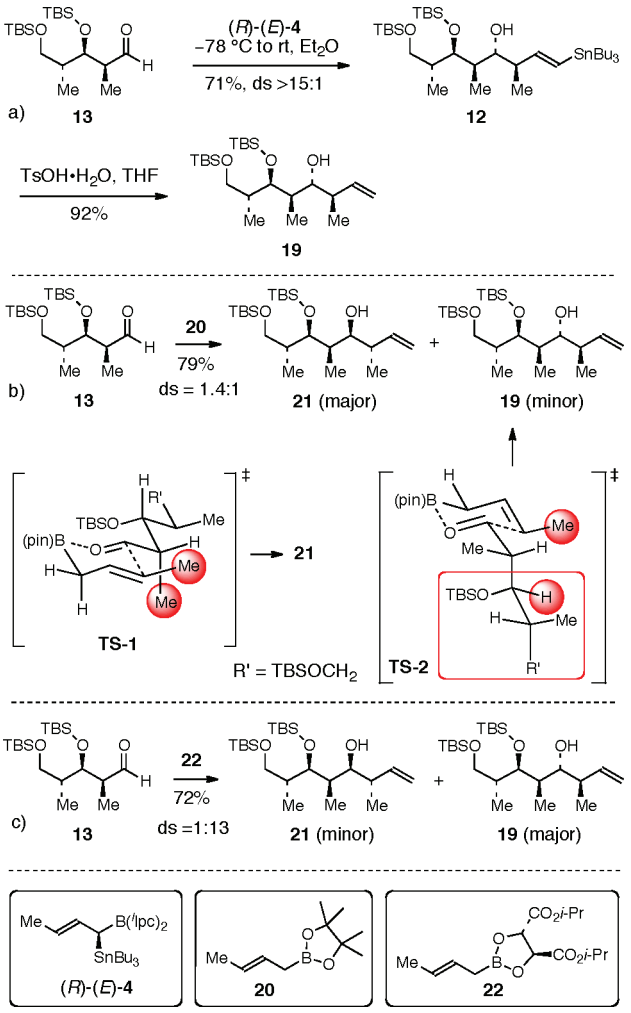
The synthesis of aldehyde **13** is summarized in Scheme 1. Commercially available ester **14** was converted into aldehyde **15** in two steps according to known procedures.[14] Crotylboration of **15** using Brown's (*Z*)-crotylborane reagent **16** gave homoallylic alcohol **17** in 81% yield.[15] Protection of the secondary alcohol of **17** (TBSOTf, 2,6-lutidine) gave the known TBS ether **18** in near quantitative yield.[16] Subsequent ozonolysis reaction of **18** provided aldehyde **13** in 91% yield.

Addition of aldehyde **13** to a solution of (*R*)-(*E*)-**4** (generated as described previously[11,12]) at −78 °C, followed by warming the reaction mixture to ambient temperature, provided the targeted *anti,anti*-stereotriad **12** in 71% yield and with >15:1 diastereoselectivity (Scheme 2a). Subsequent protodestannylation of **12** under acidic conditions (TsOH·H_2O)[12b] provided alcohol **19** in 92% yield.

The intrinsic diastereofacial preference of aldehyde **13** was assessed by using the crotylboration reaction with the achiral pinacol (*E*)-crotylboronate **20** (Scheme 2b). Interestingly, formation of the major isomer 3,4-*anti*-4,5-*syn*-stereotriad **21** was only slightly favored (~1.4:1) over the *anti,anti*-stereotriad **19**. The stereochemistry of the major product **21** was assigned following ozonolysis with reductive workup using $NaBH_4$, followed by conversion of the 1,3-diol to the corresponding acetonide, the 2,3-stereochemistry of which was easily assigned by ^1H NMR analysis as summarized in the Supporting Information. The ratio of **21** and **19** suggests that the two competing transition states, **TS-1** and **TS-2**, which lead to the formation of **21** and **19**, respectively, must be relatively close in energy.

dx.doi.org/10.1021/jo3008226 | J. Org. Chem. 2013, 78, 3–8

Scheme 2. Crotylboration Reactions of Aldehyde 13



As shown in Scheme 2b, the slightly favored transition state **TS-1** proceeds under substrate/Felkin−Anh[17] control to give the 3,4-*anti*-4,5-*syn*-stereotriad **21**. A relatively minor gauche-pentane interaction[18] between the methyl group of the crotyl unit and the methyl group of aldehyde **13** occurs in **TS-1** (shown in red). On the other hand, the competing *anti*-Felkin−Anh transition state **TS-2** gives *anti,anti*-stereotriad **19**. Gauche-pentane interactions[18] between the methyl group of the crotylboronate reagent and the side chain of aldehyde **13** (indicated in the red box in **TS-2**, Scheme 2b) should develop in **TS-2**. Close examination of **TS-2** reveals that the side chain of aldehyde **13** can adopt a conformation such that the secondary OTBS group is positioned away from the methyl group of the crotylboronate and only a hydrogen atom is within close proximity to the methyl group of the crotyl unit (shown in red in **TS-2**). Consequently, it appears that the Felkin−Anh **TS-1** and the *anti*-Felkin−Anh **TS-2** have comparable non-bonded steric interactions between aldehyde **13** and the achiral pinacol crotylboronate **20**. This analysis is consistent with experimental results that the two competing transition states for the crotylboration reaction are close in energy.

It is well documented that many classical chiral crotylating reagents have demonstrated an ability to overcome modest intrinsic diastereofacial selectivities (e.g., <3−4:1 ds) of chiral aldehydes.[4j,19] Indeed, when aldehyde **13** was treated with the tartrate-derived chiral crotylboronate reagent **22**,[9] the *anti,anti*-stereotriad **19** was obtained in 72% yield and with 13:1 diastereoselectivity (Scheme 2c).

It is appreciated that the intrinsic diastereofacial selectivity preferences of chiral aldehydes in reactions with achiral crotylboron reagents (as well as with other crotylmetal reagents) is dependent on the stereochemistry of the chiral aldehyde substrate as well as the protecting groups included in the substrates (e.g., compare results of mismatched double asymmetric reactions of **1** and **13** with the tartrate ester crotylboronate **22** presented above).[19d] Indeed, as summarized in Scheme 3, the crotylboration reactions of aldehydes **23**, **24**, and **25**, which are diastereomers of **13**, with achiral pinacol crotylboronate (**20**) provide product mixtures ranging from 3:1 (for **23**) to >100:1 (for **25**). The β-alcohol protecting groups of aldehydes **24** and **25** project into space occupied by the (*E*)-methyl group of the crotylborane reagent in transition states **TS-4** and **TS-5** (which lead to the minor *anti,anti*-stereotriads **29** and **31**, respectively), thereby destabilizing these transition states and making it difficult to access structures like **29** and **31**.[20] Therefore, while conventional chiral crotylmetal reagents may be capable of overriding the intrinsic diastereofacial preference of substrates, such as **13** and **23**, in mismatched double asymmetric reactions,[19] a much more highly enantioselective reagent, such as **4**, is required to achieve acceptable stereochemical control in mismatched double asymmetric reactions with chiral aldehydes with intrinsic diastereofacial selectivities > 5:1 (and especially > 10:1).[11]

Completion of the syntheses of **8** and **9** is summarized in Scheme 4. The secondary alcohol of stereopentad **19** was protected as a TBS ether under standard conditions (TBSOTf, 2,6-lutidine). Ozonolysis of TBS ether **32** gave aldehyde **10** in 88% yield. Matched double asymmetric crotylboration of **10** with (*S*)-(*E*)-**4** provided δ-stannyl-homoallylic alcohol **33** in 78% yield and with >15:1 diastereoselectivity. Other diastereomers were not detected in the reaction mixture. The *anti*-relative stereochemistry of two newly formed stereocenters in **33** was supported by the coupling constant analysis of the acetonide derivative **34** that was prepared from **33** by protiodestannylation, ozonolysis, reductive workup of the ozonoide using $NaBH_4$, and then acetonide formation (please see the Supporting Information for details). Finally, a Pd-catalyzed Stille coupling[21] of vinyl stannane **33** with vinyl iodide **11a**[13] provided **8** in 61% yield. Similarly, coupling of vinyl stannane **33** with vinyl iodide **11b**[6a] afforded **9** in 68% yield under analogous reaction conditions.

CONCLUSION

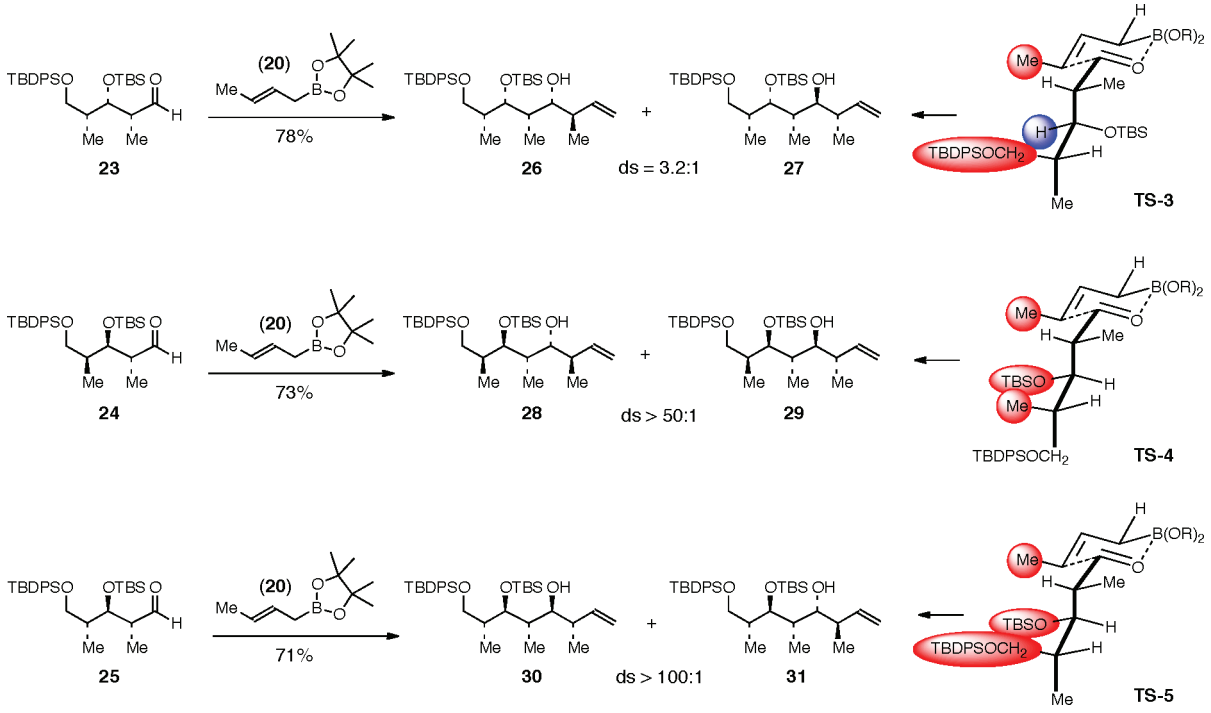
Syntheses of the polypropionate fragments of chaxamycins A/D, salinisporamycin, and rifamycin S were accomplished in 10 steps from commercially available starting materials. Three crotylboron reagents were utilized to construct the seven contiguous stereocenters in these polypropionate units. The vinylstannane unit of alcohol **33** derived from the matched double asymmetric crotylboration of aldehyde **10** with crotylborane (*S*)-(*E*)-**4** allowed direct C−C bond formation using a subsequent Stille coupling reaction.[21] Other synthetic applications of crotylborane reagents (*S*)-(*E*)-**4** and (*R*)-(*E*)-**4** will be reported in due course.

EXPERIMENTAL SECTION[22]

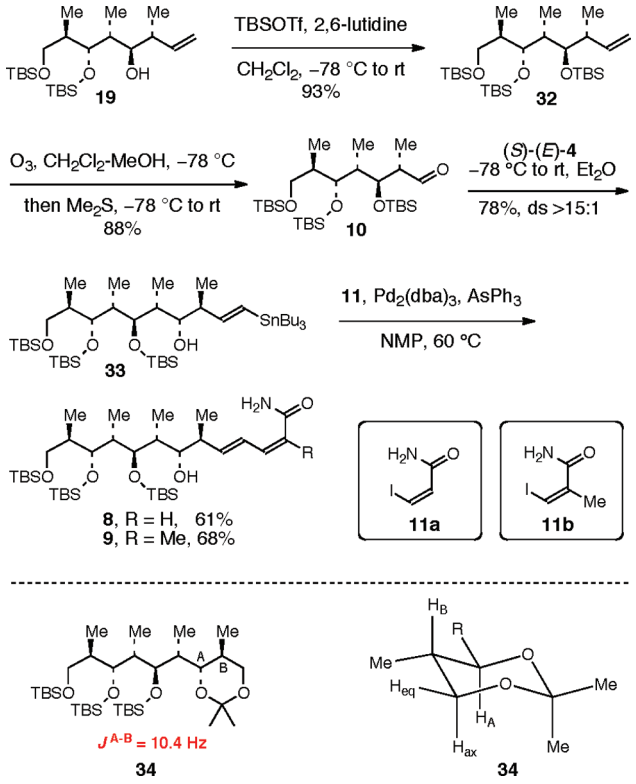
(3*R*,4*R*,5*R*,6*R*,7*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-3,5,7-trimethyloct-1-en-4-ol (19). A 50-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with 4 Å

dx.doi.org/10.1021/jo3008226 | J. Org. Chem. 2013, 78, 3−8

Scheme 3. Intrinsic Diastereofacial Selectivity of Chiral Aldehydes Related to 13 Is Dependent on Stereochemistry of the Aldehyde Substrate



Scheme 4. Completion of the Syntheses of 8 and 9



molecular sieves (freshly activated under vacuum, 200 mg) and anhydrous toluene (15 mL). To this flask was added a solution of aldehyde **13** (750 mg, 2.0 mmol, prepared in five steps from commercially available ester **14** according to known precedures[14−16]) in anhydrous toluene (5 mL). The mixture was then cooled to −78 °C, and a solution of (*E*)-crotylboronate **22**[9] in toluene (3.8 mL, ∼0.8 M, 3.0 mmol, 1.5 equiv) was added. The mixture was kept at −78 °C and stirred for 24 h. The reaction was quenched by addition of aqueous 3 N NaOH (5 mL) and stirred vigorously for 2 h. Brine (5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (gradient elution, hexane−Et_2O = 100:1 to 10:1), which provided *anti*,*anti*-stereotriad **19** (620 mg, 72% yield; ds = 13:1) as a colorless oil: $[\alpha]_D^{28.5}$ = +15.8° (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 16.8, 10.4, 8.4 Hz, 1H), 5.02−5.08 (m, 2H), 3.85 (dd, *J* = 6.4, 2.0 Hz, 1H), 3.74 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.50 (ddd, *J* = 10.4, 4.0, 2.4 Hz, 1H), 3.45 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.09 (bs, 1H), 2.29−2.37 (m, 1H), 1.88−1.98 (m, 1H), 1.71−1.79 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 18H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 115.7, 76.8, 76.7, 66.1, 40.9, 40.8, 39.7, 26.33, 26.32, 18.7, 18.5, 18.4, 15.4, 13.0, −3.9, −4.2, −4.9, −5.0; IR (neat) 3501, 2959, 2932, 2887, 2859, 1472, 1464, 1390, 1362, 1257, 1084, 1024, 1006, 913, 837, 776, 672 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{23}H_{51}O_3Si_2$ $[M + H]^+$ calcd 431.3377, found 431.3371.

(2*Z*,4*E*,6*S*,7*S*,8*R*,9*R*,10*S*,11*R*,12*R*)-9,11,13-Tris((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-6,8,10,12-tetramethyltrideca-2,4-dienamide (8). A 50-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with alcohol **19** (600 mg, 1.4 mmol) and anhydrous CH_2Cl_2 (15 mL). The solution was cooled to −78 °C, and 2,6-lutidine (300 mg, 2.8 mmol) was added. After 10 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (555 mg, 2.1 mmol) was added at −78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 8 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL) and stirred for 1 h. Brine (5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (gradient elution, hexane/Et_2O = 500:1 to 50:1), which provided TBS ether **32** (708 mg, 93% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 18.0, 10.8, 8.0 Hz, 1H),

dx.doi.org/10.1021/jo3008226 | J. Org. Chem. 2013, 78, 3−8

4.93−4.99 (m, 2H), 3.76 (dd, J = 4.0, 4.0 Hz, 1H), 3.67 (dd, J = 10.0, 5.2 Hz, 1H), 3.57 (dd, J = 6.8, 2.4 Hz, 1H), 3.39 (dd, J = 10.0, 8.0 Hz, 1H), 2.38−2.45 (m, 1H), 1.73−1.82 (m, 2H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.89 (s, 18H), 0.81 (d, J = 7.2 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.043 (s, 3H), 0.039 (s, 3H).

A stream of ozone in O_2 was bubbled through a solution (initially light red, with Sudan III as the indicator) of TBS ether **32** (270 mg, 0.5 mmol) in dichloromethane (4 mL) and MeOH (1 mL) at −78 °C until the light red solution became colorless. The solution was sparged with nitrogen to remove any excess ozone; then dimethylsulfide (5 mL) was added at −78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 24 h. The reaction mixture was filtrated through a pad of Celite. The solution was concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (gradient elution, hexane/Et_2O = 100:1 to 10:1), which provided aldehyde **10** (240 mg, 88% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, J = 1.6 Hz, 1H), 3.90 (dd, J = 6.4, 2.0 Hz, 1H), 3.81 (dd, J = 4.0, 3.2 Hz, 1H), 3.57 (dd, J = 10.4, 6.8 Hz, 1H), 3.39 (dd, J = 10.0, 6.8 Hz, 1H), 2.59 (qdd, J = 7.2, 1.6, 1.6 Hz, 1H), 1.79−1.93 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.894 (s, 9H), 0.89 (s, 9H), 0.87 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H).

Crystalline (^{d}Ipc)$_2$BH (286 mg, 1.0 mmol) was weighed into a round-bottom flask containing a stir bar in a glovebox. (Note: The crystalline borane should be crushed and pulverized to a fine powder with a glass rod in order to ensure efficient allene hydroboration.) The flask was capped with a rubber septum and removed from the glovebox and placed in a cold bath (0 °C). Ether (1.5 mL) was added slowly to the flask, and the mixture (suspension) was cooled to 0 °C. Racemic 1-stannyl-1,2-butadiene (344 mg, 1.0 mmol) was added neat via a microliter syringe. 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. The reaction mixture was cooled to −78 °C, and aldehyde **10** (218 mg in 500 μL of dry ether, 0.4 mmol) was added dropwise to the reaction mixture via a microliter syringe at −78 °C. The cold bath was removed, and the mixture was allowed to warm to ambient temperature and stirred for 24 h. The reaction was cooled to 0 °C. To the 0 °C mixture was added saturated $NaHCO_3$ (1.0 mL), followed by slow addition of 30% H_2O_2 (2.0 mL). The reaction was stirred vigorously for ∼5 h at room temperature. Brine (5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (silica gel neutralized with 1% Et_3N in hexane; gradient elution, hexane/Et_2O = 100:1 to 10:1), which provided stereoheptad **33** (280 mg, 78% yield; ds > 15:1) as a colorless oil, contaminated with small amounts of isopinocamphenol. This intermediate was used directly in the following reaction without future purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (dd, J = 19.2, 6.8 Hz, 1H), 5.95 (d, J = 19.2 Hz, 1H), 3.69−3.81 (m, 4H), 3.49 (bs, 1H), 3.43 (dd, J = 10.0, 8.4 Hz, 1H), 2.22−2.30 (m, 1H), 1.98−2.05 (m, 1H), 1.76−1.88 (m, 2H), 1.41−1.58 (m, 6H), 1.25−1.34 (m, 6H), 0.58−0.99 (m, 54H), 0.134 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.044 (s, 3H), 0.040 (s, 3H).

To a mixture of iodide **11a**[13] (12 mg, 60 μmol), vinyl stannane **33** (45 mg, 50 μmol), tris-(dibenzylideneacetone)-dipalladium(0) (2.3 mg, 2.5 μmol), and triphenylarsine (6 mg, 20 μmol) was added NMP (1.0 mL, freshly degassed by several freeze−thaw cycles under Ar). The resultant suspension was protected from light, warmed to 60 °C, and stirred for 12 h. The reaction mixture (brown) was then cooled to ambient temperature and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (gradient elution, hexane/EtOAc = 20:1 to 1:2), which provided **8** (21 mg, 61%) as a colorless oil: $[\alpha]_D^{29.2}$ = −12.5° (c 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 15.2, 11.2 Hz, 1H), 6.50 (dd, J = 11.6, 11.6 Hz, 1H), 6.19 (dd, J = 15.6, 8.0 Hz, 1H), 5.53 (d, J = 11.2 Hz, 1H), 5.39 (bs, 1H), 5.27 (bs, 1H), 3.87 (d, J = 8.8 Hz, 1H), 3.79 (dd, J = 6.8, 2.0 Hz, 1H), 3.73 (dd, J = 4.8, 4.4 Hz, 1H), 3.69 (dd, J = 10.0, 5.2 Hz, 1H), 3.61 (s, 1H), 3.43 (dd, J = 10.0, 8.0 Hz, 1H), 2.39−2.48 (m, 1H), 1.97−2.05 (m, 1H), 1.76−1.87 (m, 2H), 1.02 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.915 (s, 9H), 0.903 (s, 9H), 0.896 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.044 (s, 3H), 0.041 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 148.1, 143.3, 126.5, 117.8, 81.4, 75.8, 75.3, 65.1, 42.2, 41.4, 41.0, 35.1, 26.6, 26.5, 26.3, 19.0, 18.7, 18.6, 16.9, 14.9, 13.0, 12.3, −2.7,−2.9, −3.1,−3.8, −5.0; IR (neat) 3501, 2958, 2931, 2859, 1668, 1593, 1464, 1389, 1323, 1257, 1086, 1027, 1004, 836, 775 cm^{-1}; HRMS (ESI) m/z for $C_{35}H_{74}NO_5Si_3$ [M + H]$^+$ calcd 672.4875, found 672.4869.

(2*Z*,4*E*,6*S*,7*S*,8*R*,9*R*,10*S*,11*R*,12*R*)-9,11,13-Tris((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-2,6,8,10,12-pentamethyltrideca-2,4-dienamide (9). To a mixture of iodide **11b**[6a] (13 mg, 60 μmol), vinyl stannane **33** (45 mg, 50 μmol), tris-(dibenzylideneacetone)-dipalladium(0) (2.3 mg, 2.5 μmol), and triphenylarsine (6 mg, 20 μmol) was added NMP (1.0 mL, freshly degassed by several freeze−thaw cycles under Ar). The resultant suspension was protected from light, warmed to 60 °C, and stirred for 12 h. The reaction mixture (brown) was cooled to ambient temperature and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by flash column chromatography (gradient elution, hexane/EtOAc = 20:1 to 1:2), which provided **9** (23 mg, 61%) as a colorless oil: $[\alpha]_D^{29.2}$ = +11.2° (c 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 15.2, 10.8 Hz, 1H), 6.24 (d, J = 10.8 Hz, 1H), 5.93 (dd, J = 15.2, 8.0 Hz, 1H), 5.72 (bs, 1H), 5.54 (bs, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.79 (dd, J = 6.8, 2.0 Hz, 1H), 3.71 (dd, J = 4.8, 4.8 Hz, 1H), 3.69 (dd, J = 10.0, 4.8 Hz, 1H), 3.67 (s, 1H), 3.42 (dd, J = 10.0, 8.0 Hz, 1H), 2.29−2.38 (m, 1H), 1.97−2.05 (m, 1H), 1.95 (d, J = 0.8 Hz, 3H), 1.73−1.86 (m, 2H), 1.01 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.042 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8, 143.2, 135.2, 128.8, 126.6, 81.3, 75.8, 75.3, 65.1, 42.2, 41.4, 41.0, 35.0, 26.6, 26.5, 26.3, 21.2, 19.0, 18.7, 18.6, 17.2, 14.9, 13.0, 12.3, −2.7,−2.9, −3.1,−3.8, −4.95, −4.96; IR (neat) 3368, 2958, 2931, 2859, 1662, 1599, 1464, 1386, 1257, 1086, 1030, 836, 775 cm^{-1}; HRMS (ESI) m/z for $C_{36}H_{76}NO_5Si_3$ [M + H]$^+$ calcd 686.5031, found 686.5027.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of stereochemical assignments and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This manuscript is dedicated to the memory of Professor Robert E. Ireland, an inspirational and visionary colleague and professional mentor whose impact on the field was profound. Financial support provided by the NIH (GM038436) and a predoctoral fellowship to M.C. from Eli Lilly is gratefully acknowledged.

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