JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

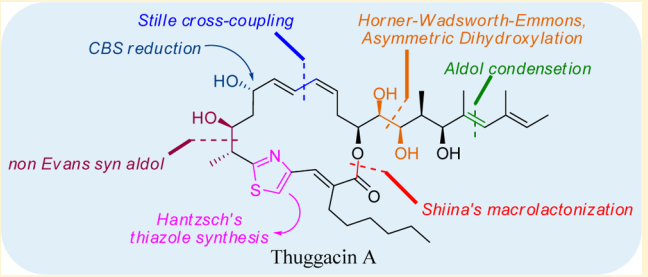
Total Synthesis of a Diacetonide Derivative of Thuggacin A

Jhillu S. Yadav* and Palash Dutta

Academy of Scientific and Innovative Research, Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India

Supporting Information

ABSTRACT: A highly stereoselective total synthesis of the diacetonide derivative of the antibiotic thuggacin A has been described. The synthesis features the stereoselective Stille cross-coupling reaction to set up the whole carbon framework, aldol condensation to construct the highly substituted conjugated diene, non-Evans *syn* aldol, CBS reduction, Hantzsch's thiazole synthesis, Horner–Wadsworth–Emmons reaction, and Shiina's macrolactonization.



INTRODUCTION

Thuggacin A (**1**), B (**2**) and C (**3**) (Figure 1) represent polyketide macrolides from myxobacterium *Sorangium cellulosum* So ce895.[1] Isolation and preliminary structural assignments of thuggacins were made by Jansen and associates in 2007. Subsequently, with the help of synthetic derivatization, degradation, and NMR spectroscopic data, complete stereochemical determination was accomplished by Kirschning et al. in 2008.[2] The unique structure of thuggacin A comprises a 17-membered α,β-unsaturated macrolactone having a thiazole ring and an *E,Z*-conjugated diene unit within it. The carbon skeleton contains 8 stereogenic centers of which 5 are contiguous at C16–C20. The macrolactone ring contains an *n*-hexyl side chain at C2 and a highly substituted conjugated diene unit in the C16 side chain. Thuggacin B and C both have the similar structural features as thuggacin A except in the ring size; however, they easily interconvert by transacylation in methanol.[1,2] These compounds are found to display strong antibiotic activity against various organisms including *Mycobacterium tuberculosis* (MTB). Tuberculosis (TB), the second most fatal infectious disease after AIDS, can no longer be sufficiently treated by currently available antibiotic therapy because of the mounting multidrug resistance of *Mycobacterium tuberculosis* and its capability to sustain as a latent infection.[3,4] Consequently, the demand for novel TB drugs has become essential for the medication with new modes of action. Thuggacins are found to be active against MTB by targeting the bacterial respiratory system.[1] This feature along with its unique structural complexity have stimulated numerous synthetic endeavors. In the past, two total syntheses of thuggacin B[5,6] have been reported, but to date, specifically, there is no report for the total synthesis of thuggacin A.[7] In continuation of our studies on total synthesis of natural[8] macrolides, herein we describe the synthesis of the immediate precursor diacetonide derivative **4** of thuggacin A (Figure 1).

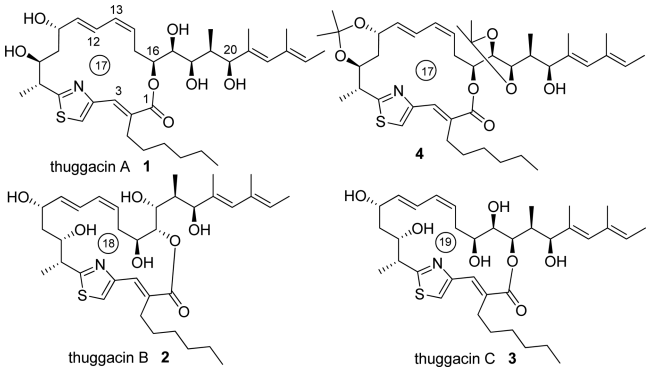


Figure 1. Structures of thuggacin A–C and diacetonide derivative of thuggacin A.

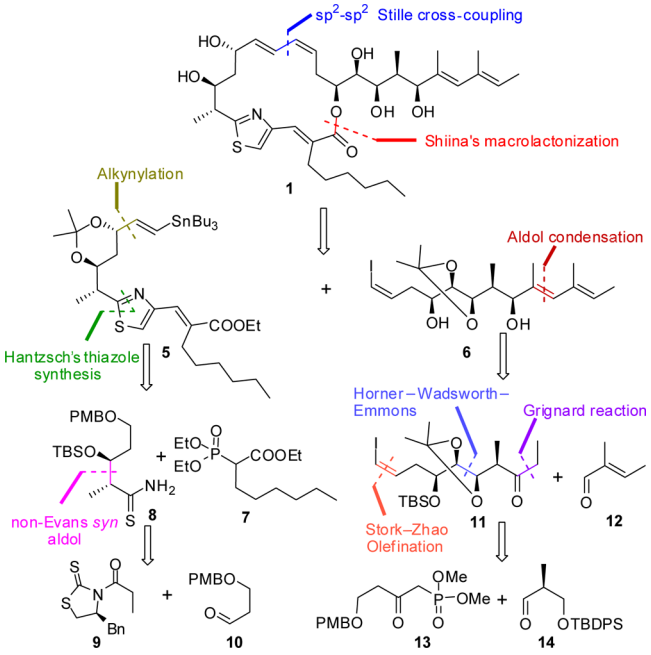
RETROSYNTHETIC ANALYSIS

The conjugated *E/Z* diene motif of thuggacin A led us to consider an sp^2–sp^2 σ-bond disconnection between C12–C13, wherein we would construct the medial σ-bond of diene via a palladium-catalyzed Stille cross-coupling reaction of two key building blocks **5** and **6** in addition to macrolactonization to achieve the 17-membered macrocyclic core structure of the molecule (Scheme 1). The key fragment **5** was further disconnected into phosphonate fragments **7** and thioamide unit **8**, which could be obtained from known aldehyde **10**. The other main fragment **6** was thought to be synthesized by the aldol elimination reaction of tiglic aldehyde **12** and subfragment **11**, which, in turn, could be obtained from phosphonate fragment **13** and aldehyde **14** via Horner–Wadsworth–Emmons reaction (HWE) (Scheme 1).

Received: October 26, 2015
Published: February 9, 2016

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786–1797

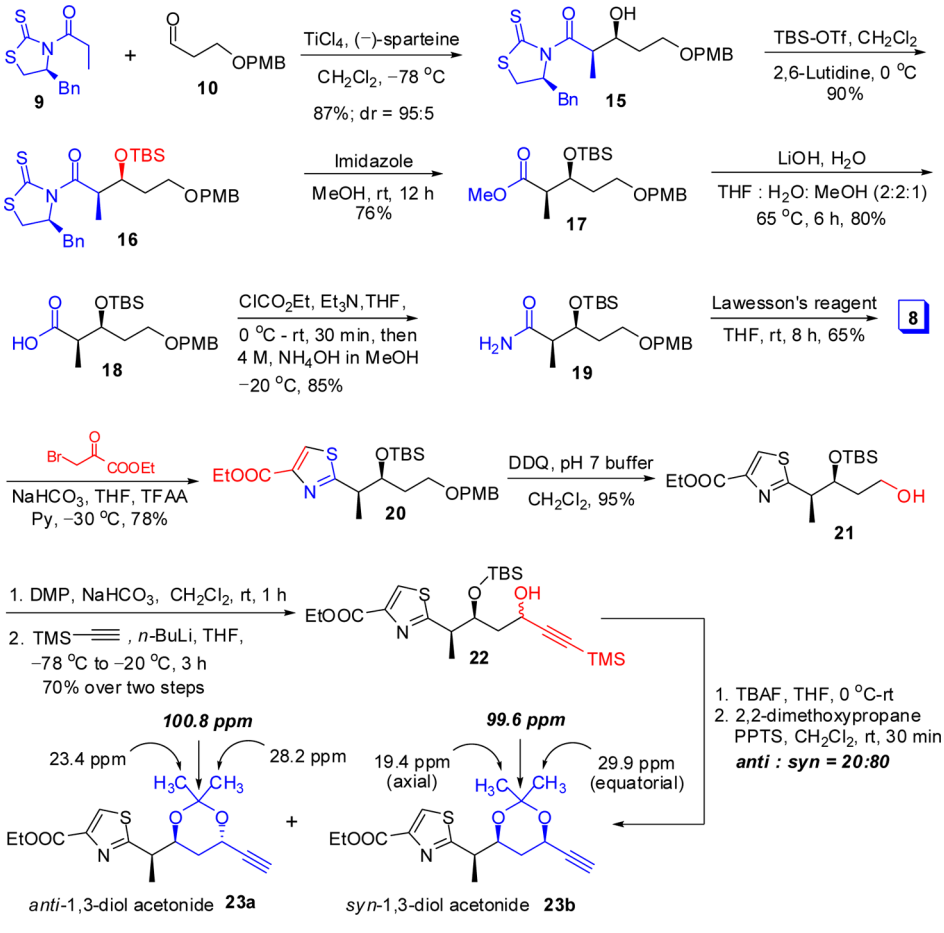
Scheme 1. Retrosynthetic Analysis of Thuggacin A



RESULTS AND DISCUSSION

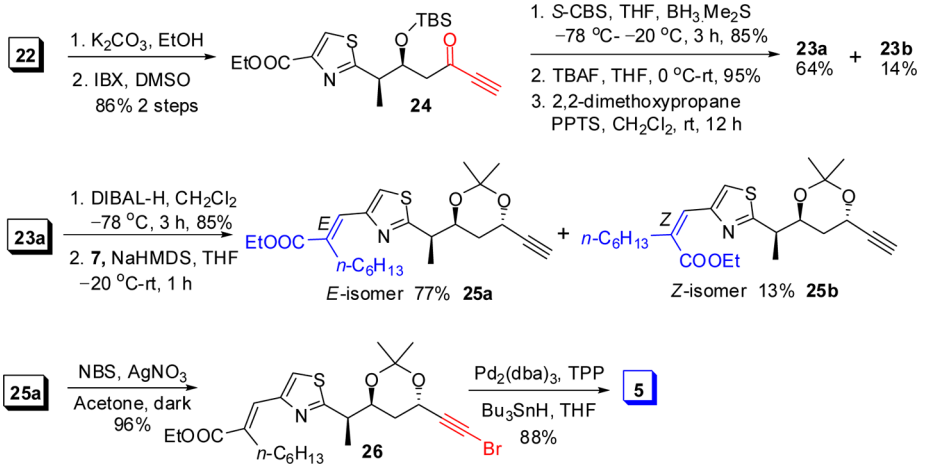
The synthesis of the C1−C12 fragment commenced with an asymmetric aldol addition reaction of *N*-propionylthiazolidinethione **9**[9] with aldehyde **10**[10] using $TiCl_4$ and (−)-sparteine as the base to produce non-Evans *syn* aldol adduct **15** in 87% yield in >95:5 diastereoselectivity. The secondary hydroxy group in the aldol product **15** was silylated using TBSOTf and 2,6-lutidine to afford the required product **16** in good yield. Methanolysis[11] of thioimide **16** yielded methyl ester **17**, which, upon saponification[12] with LiOH at 65 °C, produced carboxylic acid **18**. The acid functionality was converted to amide **19** via ethyl carbonic anhydride, followed by the treatment of Lawesson's reagent[13] in THF to furnish thioamide **8**. Hantzsch's methodology[14] was employed to construct the thiazole ring; accordingly, thioamide **8** was treated with 3 equiv of ethyl bromopyruvate (Scheme 2) at room temperature, followed by treatment of the resulting thiozoline intermediate with trifluoroacetic anhydride (TFAA) and pyridine at −30 °C to provide thiazole **20** in 78% yield (Scheme 2). PMB ether in **20** was cleaved by DDQ treatment in DCM buffered with pH 7 to afford primary alcohol **21**, which was further oxidized to the corresponding aldehyde with Dess−Martin periodinane (DMP) in good yield. Alkynylation of the aldehyde by Li-acetylide, derived from trimethylsilylacetylene furnished diastereomeric alcohol **22** as an inseparable mixture (Scheme 2). The ratio was determined after desilylation of **22** by the treatment of TBAF, and successive acetonide protection with 2,2-dimethoxypropane produced column chromatographically separable two diastereomers **23a** and **23b**. The *syn* and *anti* acetonide protected compounds were characterized based on Rychnovsky's protocol (Scheme 2).[15] Since the alkynylation

Scheme 2. Synthesis of Precursors to Vinyl Stannane 5

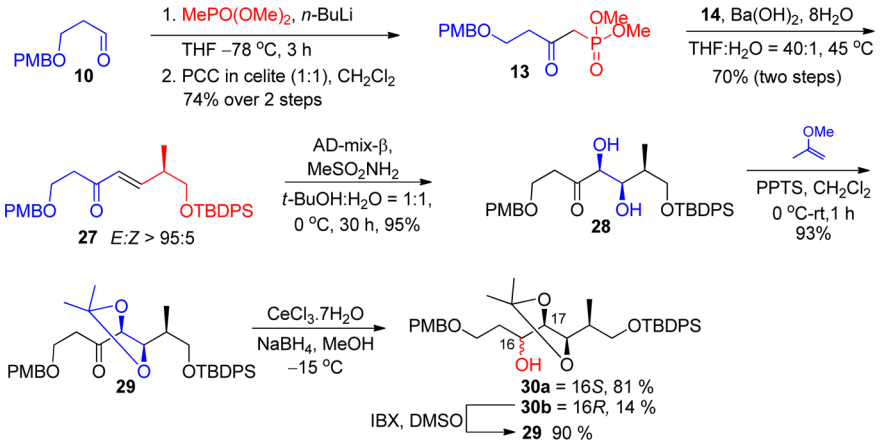


DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

Scheme 3. Synthesis of Vinyl Stannane Fragment 5



Scheme 4. Synthesis of Precursors to Vinyl Iodide 30



step did not produce our requisite diastereomer as the major product, we had to carry out an oxidation reduction sequence. In doing so, the TMS protection was removed from **22** by the treatment of potassium carbonate in ethanol, followed by IBX oxidation to furnish the propargyl ketone **24** (Scheme 3).[16a] Diastereoselective reduction of the propargylic ketone **23** was achieved by Corey's method[16b] using *S*-CBS catalyst and BH_3·Me_2S as the hydride source to obtain the inseparable diastereomeric mixture in 85% yield. TBS deprotection, followed by acetonide protection with 2,2-dimethoxypropane, furnished the desired product **23a** in 64% yield along with the undesired diastereomer **23b** in 14% yield (Scheme 3). Conversion of the ester functionality of **23a** into its corresponding aldehyde was effected by DIBAL-H. Homologation of the corresponding aldehyde by Horner−Wadsworth−Emmons reaction with phosphonate **7** afforded α,β-unsaturated ester **25a** as the major *E*-isomer and **25b** as the minor *Z*-isomer (Scheme 3).[6] The alkyne functionality in **25a** was transformed to 1-bromoalkyne **26** with NBS/acetone catalyzed by $AgNO_3$ in the absence of light. Palladium-catalyzed hydrostannylation of the 1-bromoalkyne **26** furnished exclusively *E*-vinyl stannane **5**.[17]

Toward the synthesis of vinyl iodide fragment **6**, aldehyde **10** was treated with lithiated methyldimethyl phosphonate using *n*-BuLi at −78 °C to get the secondary alcohol (Scheme 4), which, upon oxidation with PCC, resulted in keto phosphonate **13**. The known aldehyde **14** was synthesized by following the reported procedure from commercially available (*S*)-Roche ester.[18] With both fragments **13** and **14** in hand, we could investigate the Horner−Wadsworth−Emmons (HWE) reaction (Scheme 4). A screen of HWE conditions revealed $Ba(OH)_2$ in wet THF[19] at 45 °C to be optimum, affording the enone **27** cleanly as the major product. It is noteworthy that a slightly warm condition was necessary to acquire almost exclusively the *E*-geometrical isomer. The olefin compound **27** was hydroxylated[20] using AD-mix-β, which provided **28** as a single stereoisomer as observed in both ^1H and ^{13}C NMR. Isopropylidene protection of the vicinal diol using 2-methoxypropene produced the corresponding acetonide **29**. Luche reduction[21] of ketone **29** generated secondary alcohols **30a** and **30b** (Scheme 4) as the major and minor diastereoisomers, respectively. The undesired minor diastereomer **30b** was utilized further by oxidation and reduction. The good diastereoselectivity for **30a** is attributed to the tight transition state (TS) (Figure 2) which discriminates the diastereotopic face of the ketone **29**. Absolute configuration of the C16 carbinol carbon was confirmed by Mosher ester analysis (see the Supporting Information, Table S1).[22]

After successful installation of four continuous stereogenic centers in the northern fragment **6**, we proceeded further with the silyl protection of secondary alcohol in **30a** using TBSCl/imidazole in DMF solvent, but reaction at room temperature was unproductive. Additional amounts of TBSCl and imidazole were used at elevated temperature to get an excellent yield of

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

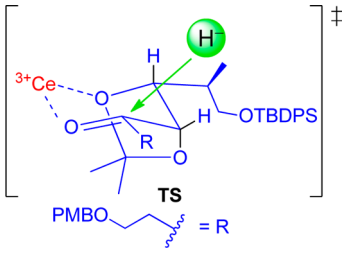


Figure 2. Chelated TS for the reduction of ketone **29**.

31 (Scheme 5). Removal of *p*-methoxybenzyl (PMB) ether gave intermediate **32** in good yield. Dess–Martin periodinane oxidation of primary alcohol furnished the analogous aldehyde which was subjected to Stork–Zhao olefination[23] that produced the desired vinyl iodide **33** in 78% yield and *Z*/*E* = 15:1 selectivity. Deprotection of primary TBDPS ether was carried out using ammonium fluoride in MeOH at 60 °C to afford primary alcohol **34** (Scheme 5) in 77% yield. Dess–Martin periodinane oxidation of alcohol **34** produced the corresponding aldehyde that was converted into ethyl ketone **11** by Grignard reaction, followed by DMP oxidation. The stereoselective aldol addition reaction of ethyl ketone **11** and aldehyde **12** was effected by using $TiCl_4$ and Et_3N along with 4 Å MS to provide **35** in 75% yield with 10:1 diastereoselectivity (see Table 1 for other conditions investigated).[24] The stereochemical preference of the aldol reaction is a consequence of the six-membered cyclic chelated transition state from kinetic *Z*-enolate where the two newly formed stereocenters bear a *syn* relationship to each other and to the methyl substituent on the other side of the ketone in the aldol adduct **35**[24] (Scheme 5).

We then attempted an *anti*-dehydration of **35** using Mitsunobu conditions[25] to obtain the dienone **36**. Reduction of the dienone **36** by $CeCl_3{\cdot}7H_2O$ and $NaBH_4$ in methanol proceeded well, but the diastereomeric ratio was not in accordance with our anticipation (Scheme 5, Table 2, entry 1).

Table 1. Aldol Reaction Conditions between 11 and 12

Entry	Reaction conditions	Yield (d.r.)
1	LDA, THF, then **12**, 3 h	trace
2	Bu_2BOTf, DIPEA, CH_2Cl_2, then **12**, 2 h	0
3	$TiCl_4$, DIPEA, CH_2Cl_2, then **12**, 1 h	30% (10:1)
4	$TiCl_4$, Et_3N, CH_2Cl_2, then **12**, 1 h	30% (10:1)
5	$TiCl_4$, Et_3N, CH_2Cl_2, 4 Å MS, then **12**, 20 min	75% (10:1)

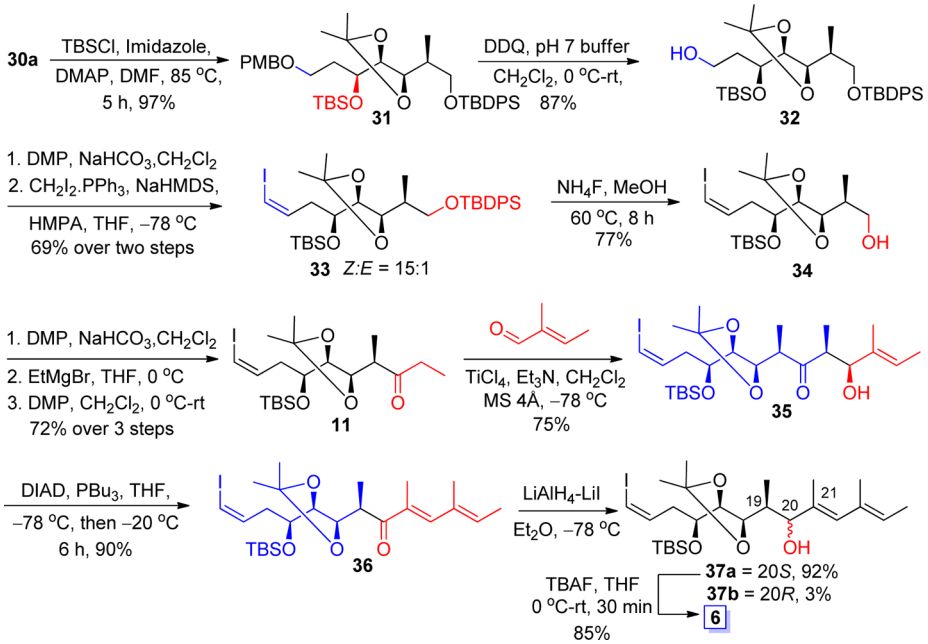
Table 2. Optimization of Dienone 36 Reduction

Entry	Reaction conditions	dr **37a:37b**	Yield (%)
1	$NaBH_4$, $CeCl_3.7H_2O$, MeOH, –78 °C	60:40	82
2	$Zn(BH_4)_2$, ether, –20 °C	10:90	85
3	$LiAlH_4$–LiI, ether, –78 °C	2:98	95
4	*S*-CBS cat., $BH_3.Me_2S$, THF, –78 °C	No reaction	--

Presumably, this may be attributed to preferential reduction through a Felkin transition state.[26] However, excellent diastereoselectivity (49:1) for reduction to the desired *syn* 1,3-diol derivative could readily be achieved with the chelating agents LiI and $LiAlH_4$ as the hydride source (entry 3).[27] This is most likely accredited to preferential reduction through bidentate chelation of reagent with substrate along with axial hydride de1ivery (Figure 3). The absolute configuration of the newly formed stereogenic center at C20 was assigned by transforming the more polar major isomer **37a** into the corresponding (*R*)- and (*S*)-Mosher esters (see the Supporting Information, Table S2).[22] After successful creation of all consecutive five chiral centers, the C16 hydroxyl group was made free by the action of TBAF to deliver northern fragment **6** in 85% yield.

An investigation of intermolecular Stille reaction[28] began with 10 mol % of $PdCl_2(MeCN)_2$ in DMF at room temperature, which did not produce any Stille cross-coupling product **38** (Scheme 6). After screening of several Stille cross-

Scheme 5. Synthesis of Vinyl Iodide Fragment 6



DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786–1797

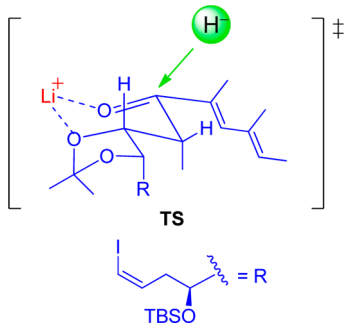
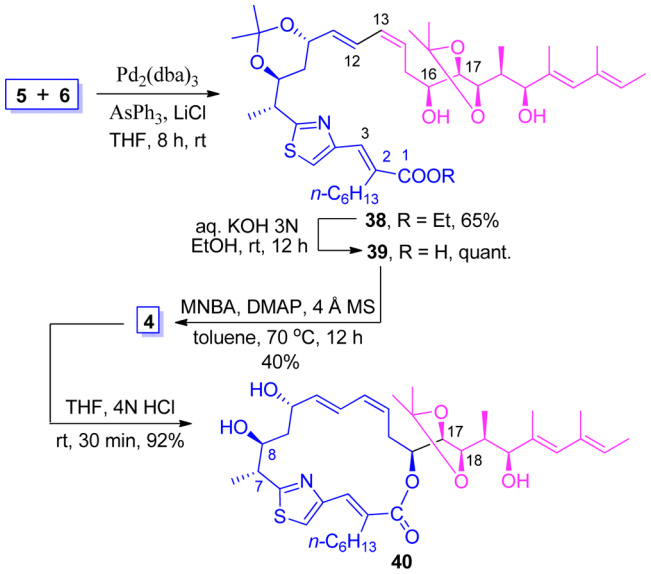


Figure 3. Chelated TS for the reduction of dienone **36**.

Scheme 6. Coupling of Fragments 5 and 6



coupling reaction conditions involving various palladium catalysts [$Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$] and solvents (DMF, NMP, THF), at last success was achieved with 10 mol % $Pd_2(dba)_3$, transmetalation ligand $AsPh_3$, and additive LiCl to produce required product **38** in THF solvent with 65% yield. Saponification of the ester functionality produced *seco*-acid **39** (Scheme 6) with quantitative yield. The crude mixture was subjected to macrocyclization, utilizing Shiina's protocol.[29] Ring closure occurred smoothly and selectively with the 16-hydroxy group according to our anticipation. Formation of the 17-membered macrolactone **4** was fully characterized by ^1H and ^{13}C NMR spectrum data, which were identical to those of an authentic sample.[2] Specific rotation of the diacetonide derivative of thuggacin A was found to be $[\alpha]_D^{20}$ = +108.5 (*c* 0.16, MeOH).[30] Final deprotection of **4** produced thuggacin A monoacetonide **40** within 30 min, but extending the reaction time produced a complex mixture.[5] The most probable reasons for the deterioration of monoacetonide **40** may be the water elimination at C7/C8 as well as the lability of the terminal diene unit, as reported by Kirschning.[31] In our case (for thuggacin A diacetonide), the presence of the free hydroxy at C20, adjacent to the terminal conjugated diene functionality, also may increase its instability.[5,6] To circumvent this deprotection problem, an easily cleavable silyl protecting group may be introduced to protect the C17 and C18 hydroxy groups at the very initial stage.

CONCLUSIONS

In conclusion, the stereoselective synthesis of the thuggacin A precursors **4** and **40** was accomplished with an overall yield of 0.55% in 24 steps and 0.5% yield in 25 steps (longest linear sequence). Intermolecular Stille cross-coupling reaction was optimized successfully for the construction of the complete carbon backbone. Substrate controlled aldol reaction and Mitsunobu elimination furnished a highly substituted conjugated diene. Final macrolactonization occurred to produce the diacetonide derivative of thuggacin A exclusively.

EXPERIMENTAL SECTION

Dry reactions were performed under an inert atmosphere using argon or nitrogen. All glassware apparatus used for reactions are perfectly oven/flame-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (230−400 mesh) unless otherwise mentioned. Analytical thin-layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wavenumber (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High-resolution mass spectra (HRMS) [ESI$^+$] were obtained using either a TOF or a double focusing spectrometer. ^1H NMR spectra were recorded at 300 or 400 or 500 MHz and ^{13}C NMR spectra at 75 or 100 or 125 MHz in $CDCl_3$ or C_6D_6 or CD_3OD with the residual solvent signal as internal standard unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane, and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quientet, sext = sextet, m = multiplet, br = broad.

(2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2-methylpentan-1-one (15). To a dry 1 L round-bottom flask, under a nitrogen atmosphere, was added *N*-propionylthiazolidinethione **9** (12.0 g, 45.36 mmol) in DCM (226 mL, 0.2 M with respect to thione). The solution was cooled to 0 °C and titanium tetrachloride (5.4 mL, 49.47 mmol) was then added to the solution dropwise. The thick suspension was stirred for 5 min, upon which (−)-sparteine (10.4 mL, 45.36 mmol) was added via syringe. The dark red solution was stirred for 30 min at 0 °C. The reaction mixture was then cooled to −78 °C, and aldehyde **10** (8.0 g, 41.23 mmol) was added in DCM (30 and 5 mL rinse) via cannula. The reaction mixture was stirred for 1 h at −78 °C; TLC analysis indicated complete consumption of starting material. Then, the reaction mixture was directly poured into a separatory funnel containing a solution of saturated aqueous ammonium chloride (200 mL). The layers were separated, and the aqueous layer was extracted with DCM (150 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc:PE = 15:85) to obtain the aldol adduct **15** (16.46 g, 87%) as a yellow oil. R_f = 0.4 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = +93.1 (*c* 0.12, $CHCl_3$); IR (neat): 3481, 2931, 2860, 1689, 1512, 1342, 1250, 1161, 1136, 1032, 747, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (d, *J* = 7.0 Hz, 3H), 1.68−1.77 (m, 1H), 1.83−1.92 (m, 1H), 2.87 (d, *J* = 11.6 Hz, 1H), 3.02 (dd, *J* = 10.5, 13.3 Hz, 1H), 3.18−3.26 (m, 2H), 3.35 (dd, *J* = 7.2, 11.6 Hz, 1H), 3.59−3.71 (m, 2H), 3.79 (s, 3H), 4.24−4.29 (m, 1H), 4.45 (s, 2H), 4.72 (qd, *J* = 3.5, 7.1 Hz, 1H), 5.80 (ddd, *J* = 4.1, 7.0,10.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.24−7.30 (m, 5H), 7.31−7.36 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 31.7, 33.6, 36.9, 43.1, 55.2, 68.0, 68.9, 70.1, 72.9, 113.8, 127.2, 128.9, 129.3, 129.4, 130.1, 136.4, 159.1, 177.5, 201.3 ppm; ESI-HRMS: *m*/*z* calculated for $C_{24}H_{29}O_4NNaS_2$ [M + Na]$^+$: 482.1430, found: 482.1416.

(2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methyl-

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

pentan-1-one (16). 2,6-Lutidine (4.8 mL, 41.6 mmol) was added at 0 °C to a solution of secondary alcohol **15** (12.3 g, 26.8 mmol) in dry DCM (80 mL) at 0 °C, and the mixture was stirred at 0 °C under a N_2 atmosphere. After 15 min, TBSOTf (9.0 mL, 39.6 mmol) was added dropwise, and the mixture was stirred at 0 °C for 10 min. TLC analysis indicated complete consumption of starting material; afterward, the reaction was quenched with H_2O (20 mL) and the mixture was extracted with DCM (30 mL × 2). Organic extracts were combined and washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:PE = 5:95) to give silyl ether **16** (13.8 g, 90%) as a yellow liquid. R_f = 0.3 (EtOAc:PE = 5:95). $[\alpha]_D^{20}$ = +25.7 (*c* 0.13, $CHCl_3$); IR (neat): 2930, 2856, 1649, 1612, 1512, 1251, 1094, 1030, 834, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.21 (d, *J* = 7.6 Hz, 3H), 1.79−2.04 (m, 2H), 2.71−2.83 (m, 2H), 3.11 (dd, *J* = 3.8, 12.8 Hz, 1H), 3.27 (dd, *J* = 7.6, 11.3 Hz, 1H), 3.44−3.63 (m, 2H), 3.79 (s, 3H), 4.19−4.27 (m, 1H), 4.39 (dd, *J* = 11.3, 17.4 Hz, 2H), 4.75 (p, *J* = 6.8 Hz, 1H), 5.25−5.36 (m, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.20−7.37 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, −4.3, 14.8, 18.1, 25.9, 31.3, 35.2, 36.8, 43.8, 55.2, 66.0, 69.0, 70.9, 72.8, 113.7, 127.1, 128.8, 129.3, 129.5, 130.6, 136.8, 159.0, 176.5, 200.8 ppm; ESI-HRMS: *m*/*z* calculated for $C_{30}H_{43}O_4NNaS_2Si$ $[M + Na]^+$: 596.2295, found: 596.2281.

(2*R*,3*S*)-Methyl-3-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methylpentanoate (17). Compound **16** (13.8 g, 24.0 mmol) was dissolved in methanol (100 mL), and to that was added imidazole (4.9 g, 72.0 mmol) in one portion. The resulting mixture was stirred at room temperature for 12 h, and then methanol solvent was removed in a rotary evaporator. The residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:PE = 5:95) to give methyl ester **17** (7.2 g, 76%) as a light yellow liquid. R_f = 0.3 (EtOAc:PE = 5:95). $[\alpha]_D^{20}$ = −18.2 (*c* 0.3, $CHCl_3$); IR (neat): 2952, 2857, 1737, 1513, 1463, 1250, 1095, 1038, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.80 (dd, *J* = 6.6, 13.0 Hz, 2H), 2.56 (dq, *J* = 4.4, 7.0 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 4.18 (td, *J* = 4.6, 6.1 Hz, 1H), 4.41 (dd, *J* = 11.4, 22.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.8, −4.5, 11.1, 18.0, 25.7, 34.8, 44.8, 51.4, 55.2, 66.4, 70.6, 72.6, 113.7, 129.2, 130.5, 159.1, 175.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{21}H_{36}O_5NaSi$ $[M + Na]^+$: 419.2224, found 419.2219.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methylpentanoic Acid (18). To a solution of the methyl ester **17** (8.16 g, 20.6 mmol) in MeOH (15 mL), THF (30 mL) and H_2O (30 mL) was added solid $LiOH·H_2O$ (4.3 g, 103.0 mmol) at room temperature, and the mixture was heated for 6 h at 65 °C. After completion of reaction, it was allowed to cool to room temperature, and the red color reaction mixture was quenched with dropwise addition of 5% citric acid aqueous solution until a permanent yellow color appeared (pH = 6). The mixture was extracted with ethyl acetate (100 mL × 3); then, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:PE = 20:80) to produce the desired acid **18** (6.3 g, 80%) as a light yellow liquid. R_f = 0.3 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = −21.1 (*c* 0.46, $CHCl_3$); IR (neat): 2953, 2931, 2957, 1708, 1513, 1249, 1096, 1037, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.89 (s, 9H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.70−1.89 (m, 2H), 2.60−2.68 (m, 1H), 3.48−3.56 (m, 2H), 3.81 (s, 3H), 4.14 (dt, *J* = 4.6, 7.3 Hz, 1H), 4.42 (dd, *J* = 11.4, 23.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.8, −4.7, 11.3, 18.0, 25.7, 34.1, 44.9, 55.2, 66.0, 70.8, 72.6, 113.8, 129.3, 130.2, 159.2, 178.8 ppm; ESI-HRMS: *m*/*z* calculated for $C_{20}H_{34}O_5NaSi$ $[M + Na]^+$: 405.2068, found: 405.2058.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methylpentanamide (19). To an ice-cold solution of acid **18** (6.0 g, 15.68 mmol) in dry THF (60 mL) were added ethyl chloroformate (1.9 mL, 20.39 mmol) and triethylamine (3.0 mL, 21.96 mmol). The reaction mixture was stirred at the same temperature for 30 min before the ice bath was replaced by a −20 °C bath; then, a methanolic solution of aqueous ammonia (39.2 mL, 150.8 mmol, 4.0 M) was added via syringe. After that, the reaction mixture was stirred at −20 °C for another 1 h and diluted with ethyl acetate (100 mL), layers were separated, and aqueous layer was extracted with ethyl acetate (70 mL × 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered; solvent was removed *in vacuo*; and the residue was purified by flash chromatography (EtOAc:PE = 35:65) to afford the amide **19** (5.0 g, 85%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 40:60). $[\alpha]_D^{20}$ = −16.8 (*c* 0.4, $CHCl_3$); IR (neat): 3345, 3194, 2953, 2931, 2857, 1674, 1513, 1250, 1094, 1038, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.70−1.93 (m, 2H), 2.59 (dq, *J* = 5.0, 7.2 Hz, 1H), 3.45−3.64 (m, 2H), 3.81 (s, 3H), 3.89−3.98 (m, 1H), 4.41 (dd, *J* = 11.3, 14.0 Hz, 2H), 5.36 (br. s, 1H, amide NH), 6.50 (br. s, 1H, amide NH), 6.88 (d, *J* = 8.5 Hz, 2H), 7.21−7.26 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.7, 13.1, 17.9, 25.8, 32.6, 45.5, 55.1, 65.9, 71.6, 72.5, 113.7, 129.2, 130.2, 159.0, 176.7 ppm; ESI-HRMS: *m*/*z* calculated for $C_{20}H_{35}O_4NNaSi$ $[M + Na]^+$: 404.2227, found: 404.2223.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methylpentanethioamide (8). To a solution of amide **19** (3.0 g, 7.87 mmol) in THF (30 mL) was added Lawesson's reagent (1.91 g, 4.72 mmol) at room temperature. After stirring for 8 h, a saturated aqueous NaCl solution (30 mL) was added. After extraction with Et_2O, the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (EtOAc:PE = 20:80) furnished thioamide **8** (2.0 g, 65%) as a colorless oil. R_f = 0.4 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = +9.1 (*c* 0.48, $CHCl_3$); IR (neat): 3305, 3183, 2953, 2931, 2857, 1612, 1513, 1249, 1090, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.71−1.88 (m, 2H), 2.95 (quint, *J* = 6.7 Hz, 1H), 3.49 (ddd, *J* = 4.3, 6.4, 9.5 Hz, 1H), 3.71 (ddd, *J* = 4.3, 7.8, 9.5 Hz, 1H), 3.81 (s, 3H), 3.98 (dt, *J* = 4.9, 6.4 Hz, 1H), 4.41 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.41 (br. s, 1H amide NH), 7.96 (br. s, 1H, amide NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.6, −4.6, 17.2, 18.0, 25.8, 32.9, 51.7, 55.2, 65.8, 72.8, 73.5, 113.8, 129.3, 130.0, 159.2, 212.9 ppm; ESI-HRMS: *m*/*z* calculated for $C_{20}H_{36}O_3NSSi$ $[M + H]^+$: 398.2179, found: 398.2170.

Ethyl-2-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentan-2-yl)thiazole-4-carboxylate (20). To a cold (0 °C) solution of thioamide **8** (1.3 g, 3.27 mmol) in dry THF (15 mL) was added solid $NaHCO_3$ (1.37 g, 16.37 mmol), followed by ethyl bromopyruvate (1.2 mL, 9.82 mmol). The reaction mixture was warmed to 25 °C and stirred for 45 min; at that time, TLC analysis indicated the absence of thioamide. After recooling the solution to −30 °C, pyridine (1.9 mL, 22.92 mmol) and trifluoroacetic anhydride (1.9 mL, 13.0 mmol) were added sequentially. After 1 h, the solution was diluted with DCM (15 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the orange liquid by flash chromatography (EtOAc:PE = 15:85) furnished thiazole **20** (1.25 g, 78%) as a colorless liquid. R_f = 0.6 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = −8.9 (*c* 0.4, $CHCl_3$); IR (neat): 2931, 2856, 1728, 1245, 1213, 1094, 1028, 836, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.19 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.40 (d, *J* = 7.0 Hz, 3H), 1.58−1.75 (m, 1H), 1.79−1.95 (m, 1H), 3.37 (qd, *J* = 3.8, 7.0 Hz, 1H), 3.49 (t, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 4.22 (td, *J* = 3.8, 6.0 Hz, 1H), 4.34−4.49 (m, 4H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.6, 14.3, 14.5, 18.0, 25.9, 34.2, 43.8, 55.2, 61.2, 66.4, 72.6, 113.7, 127.0, 129.2, 130.4, 146.2, 159.0, 161.6, 174.7 ppm; ESI-HRMS: *m*/*z* calculated for $C_{25}H_{40}O_5NSSi$ $[M + H]^+$: 494.2391, found: 494.2378.

Ethyl-2-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxypentan-2-yl)thiazole-4-carboxylate (21). To a solution of *p*-methoxybenzyl (PMB) ether **20** (2.39 g, 4.84 mmol) in DCM (30 mL) and pH 7 phosphate buffer (1.5 mL) was added 2,3-dichloro-5,6-

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

dicyanobenzoquinone (1.62 g, 7.27 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature before being quenched with saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with DCM (50 mL × 3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude brown oil. Purification of the crude product by flash column chromatography (EtOAc:PE = 30:70) gave the alcohol **21** (1.71 g, 95%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 30:70). $[\alpha]_D^{20}$ = +3.2 (*c* 0.38, $CHCl_3$); IR (neat): 3416, 2932, 1725, 1471, 1217, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.14 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.55−1.88 (m, 2H), 3.43 (qd, *J* = 4.7, 7.0 Hz, 1H), 3.73 (t, *J* = 6.2 Hz, 2H), 4.20−4.28 (m, 1H), 4.40 (qd, *J* = 1.5, 7.2 Hz, 2H), 8.06 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): −5.0, −4.6, 14.3, 14.8, 18.0, 25.8, 36.6, 43.4, 59.2, 61.3, 73.2, 126.8, 146.2, 161.4, 174.9 ppm; ESI-HRMS: *m*/*z* calculated for $C_{17}H_{32}O_4NSSi$ $[M + H]^+$: 374.1816, found: 374.1813.

Ethyl-2-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-oxohept-6-yn-2-yl)thiazole-4-carboxylate (24). A solution of the alcohol **21** (0.714 g, 1.91 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere was cooled down to 0 °C, before Dess−Martin periodinane (1.22 g, 2.87 mmol) was added. The resulting solution was stirred for 1 h at room temperature and quenched by addition of saturated aqueous Na_2SO_3 solution (8 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) afterward. The organic layer was separated, and the aqueous phase was re-extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (EtOAc:PE = 15:85) to afford the corresponding aldehyde (0.62 g, 88%) as a colorless oil. R_f = 0.6 (EtOAc:PE = 30:70). The aldehyde was immediately used for the next step. To a solution of trimethylsilylacetylene (0.3 mL, 2.22 mmol) in THF (5 mL) at −78 °C was added dropwise *n*-butyllithium (1.2 mL, 1.6 M in hexanes, 1.88 mmol). After 1 h of stirring, a solution of the previously obtained aldehyde (0.62 g, 1.68 mmol) in THF (3 and 1 mL rinse) was added via cannula. The resulting mixture was slowly warmed up to −20 °C and stirred for 4 h. It was then quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude red-colored oil was purified by flash column chromatography (EtOAc:PE = 12:88). R_f = 0.6 (EtOAc:PE = 20:80). The desired product came as an inseparable mixture of two diastereoisomeric alcohols **22** (0.59 g, 75%) as a colorless liquid. To a solution of secondary alcohol **22** (0.2 g, 0.43 mmol) in absolute ethanol (15 mL) was added K_2CO_3 (0.59 g, 4.26 mmol). The mixture was stirred at room temperature for 10 h before it was poured into a saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water (40 mL) and brine (40 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc:PE = 20:80) to give TMS deprotected prorargyl alcohol (0.16 g, 95%) as a colorless oil. R_f = 0.3 (EtOAc:PE = 20:80). To a magnetically stirred solution of the alcohol (0.16 g, 0.403 mmol) in DMSO (2 mL) under an argon atmosphere was added IBX (169 mg, 0.61 mmol). After 2 h, the resulting solution was carefully poured into a vigorously stirred mixture of water (3 mL) and Et_2O (3 mL) and then filtered. The filtrate was diluted with Et_2O (3 mL), and the layers were separated. The organic layer was washed with water (5 mL) and brine (5 mL) and dried over Na_2SO_4. Ether was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:PE = 15:85) to afford the ketone **24** (143 mg, 90%) as a colorless liquid. R_f = 0.5 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = −27.6 (*c* 1.36, EtOAc); IR (neat): 2932, 2853, 1720, 1680, 1480, 1240, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.10 (s, 3H), 0.02 (s, 3H), 0.81 (s, 9H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.43 (d, *J* = 7.2 Hz, 3H), 2.65 (dd, *J* = 7.2, 16.0 Hz, 1H), 2.78 (dd, *J* = 4.5, 16.0 Hz, 1H), 3.30 (s, 1H), 3.37 (qd, *J* = 4.2, 7.2 Hz, 1H), 4.31−4.43 (m, 2H), 4.64 (dt, *J* = 4.3, 7.2 Hz, 1H), 8.06 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.8, 14.3, 15.0, 17.9, 25.7, 44.2, 50.1, 61.2, 71.1, 79.4, 81.6, 127.2, 146.4, 161.4, 172.7, 184.6 ppm; ESI-HRMS: *m*/*z* calculated for $C_{19}H_{29}O_4NNaSSi$ $[M + Na]^+$: 418.1478, found: 418.14559.

Ethyl-2-((*R*)-1-((4*S*,6*S*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazole-4-carboxylate (23a). To a stirred solution of eynone **24** (304 mg, 0.769 mmol) in THF (2 mL) at −78 °C was added (*S*)-Me-CBS catalyst (1 M solution in toluene, 0.15 mL, 0.153 mmol) and $BH_3{\cdot}SMe_2$ (1 M in THF, 1.15 mL, 1.15 mmol), and the solution was stirred for 4 h at the same temperature. The reaction was carefully quenched at −78 °C by the dropwise addition of saturated aqueous ammonium chloride solution (3 mL) and allowed to warm to room temperature. The reaction mixture was extracted with Et_2O (10 mL × 3), and combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:PE = 20:80) to obtain the inseparable mixture of two diastereomeric propargyl alcohols (260 mg, 85%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 20:80). To a cooled (0 °C) solution of propargyl alcohol (0.26 g, 0.65 mmol) in anhydrous THF (5 mL) was added a 1 M solution of TBAF in THF (0.98 mL, 0.98 mmol). The mixture was stirred for 30 min at 0 °C before the reaction was quenched with addition of saturated aq NH_4Cl solution (2 mL). The mixture was extracted with Et_2O (5 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc:PE = 50:50) to produce the diol compound (175 mg, 95%) as a colorless liquid. R_f = 0.2 (EtOAc:PE = 50:50). The diol compound (175 mg, 0.62 mmol), obtained in the previous step, was dissolved in 2,2-DMP (5 mL) and treated with PPTS (15 mg) and stirred for 12 h. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted three times with DCM (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (EtOAc:PE = 10:90) to afford the desired major diastereomer **23a** (128 mg, 64%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 20:80) and minor diastereomer **23b** (32 mg, 14%) as a white solid. R_f = 0.2 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = −0.13 (*c* 0.28, $CHCl_3$); IR (neat): 3297, 2929, 1723, 1217, 1099, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.38−1.45 (m, 9H), 1.56 (s, 3H), 1.67−1.74 (m, 1H), 2.0 (ddd, *J* = 6.3, 10.7, 13.0 Hz, 1H), 2.47 (d, *J* = 2.3 Hz, 1H), 3.38−3.45 (m, 1H), 4.31 (dt, *J* = 4.4, 10.8 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 4.71 (td, *J* = 2.3, 5.5 Hz, 1H), 8.10 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 15.8, 23.4, 28.2, 33.9, 43.2, 59.1, 61.3, 68.1, 74.1, 83.6, 100.8, 127.6, 146.1, 161.5, 173.4 ppm; ESI-HRMS: *m*/*z* calculated for $C_{16}H_{21}NO_4NaS$ $[M + Na]^+$: 346.10835, found 346.10678.

Ethyl-2-((*R*)-1-((4*S*,6*R*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazole-4-carboxylate (23b). $[\alpha]_D^{20}$ = −3.5 (*c* 0.34, $CHCl_3$); mp: 52−55 °C; IR (neat): 3280, 2921, 1740, 1210, 1155, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.38−1.45 (m, 9H), 1.48 (s, 3H), 1.59−1.64 (m, 1H), 1.69−1.79 (m, 1H), 2.46, (d, *J* = 2.1 Hz, 1H), 3.35 (qd, *J* = 5.2, 7.0 Hz, 1H), 4.13 (ddd, *J* = 2.4, 5.0, 7.5 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.62−4.67 (m, 1H), 8.08 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 15.6, 19.4, 29.9, 34.2, 43.4, 60.0, 61.3, 70.9, 72.9, 82.2, 99.6, 127.4, 146.3, 161.5, 173.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{16}H_{21}NO_4NaS$ $[M + Na]^+$: 346.10835 found 346.10678.

(*E*)-Ethyl-2-((2-((*R*)-1-((4*S*,6*S*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)octanoate (25a). To a solution of **23a** (100 mg, 0.309 mmol) in DCM (1.5 mL) at −78 °C was added DIBAL-H (0.2 mL, 0.371 mmol, 25% in toluene) under an argon atmosphere. The reaction mixture was stirred for 2 h and quenched by careful addition of saturated aqueous Rochelle salt solution (3 mL). The layers were separated, and the aqueous phase was extracted with DCM (4 mL × 3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc:PE = 30:70) to produce the corresponding aldehyde (73 mg, 85%) as a colorless oil. R_f = 0.2 (EtOAc:PE = 10:90). To a solution of phosphonate **7** (0.2 g, 0.655 mmol) in dry THF (2.5 mL) at −20 °C was added NaHMDS (0.9 mL, 0.524 mmol, 0.6 M in toluene) dropwise. After being stirred for

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

30 min, a solution of aldehyde (73 mg, 0.262 mmol) in THF (1 mL) was added via a cannula. The reaction mixture was then stirred at −20 °C for 30 min before it was quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (EtOAc:PE = 5:95) afforded required major *E*-compound **25a** (85 mg, 77%) as a colorless liquid, R_f = 0.4 (EtOAc:PE = 10:90) and minor *Z*-compound **25b** (17 mg, 13%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = −6.2 (*c* 0.33, $CHCl_3$); IR (neat): 3304, 2927, 2857, 1704, 1377, 1228, 1128 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.24−1.36 (m, 7H), 1.37−1.43 (m, 5H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.47−1.56 (m, 2H), 1.59 (s, 3H), 1.72 (ddd, *J* = 4.1, 5.3, 9.5 Hz, 1H), 1.91 (ddd, *J* = 6.3, 10.5, 13.1 Hz, 1H), 2.47 (d, *J* = 2.4 Hz, 1H), 2.83−2.94 (m, 2H), 3.25−3.32 (m, 1H), 4.23−4.33 (m, 3H), 4.67 (td, *J* = 2.4, 5.8 Hz, 1H), 7.29 (s, 1H), 7.53 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 14.3, 16.4, 22.7, 23.5, 27.9, 28.1, 29.2, 29.6, 31.8, 34.1, 43.4, 59.1, 60.7, 68.8, 74.0, 83.6, 100.8, 121.4, 129.8, 134.0, 151.5, 168.7, 171.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{24}H_{36}NO_4S$ $[M + H]^+$: 434.2359 found: 434.2363.

(*Z*)-Ethyl-2-((2-((*R*)-1-((4*S*,6*S*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)octanoate (25b). $[\alpha]_D^{20}$ = +7.3 (*c* 0.51, $CHCl_3$); IR (neat): 2923, 2853, 1678, 1379, 1260, 1099, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.21−1.45 (m, 15H), 1.45−1.62 (m, 5H), 1.65−1.75 (m, 1H), 1.91 (ddd, *J* = 6.4, 10.6, 13.0 Hz, 1H), 2.35−2.44 (m, 2H), 2.47 (d, *J* = 2.3 Hz, 1H), 3.22 (m, 1H), 4.14−4.37 (m, 3H), 4.62−4.71 (m, 1H), 6.47 (s, 1H), 7.22, (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1, 16.4, 22.5, 23.4, 27.9, 28.7, 31.5, 34.2, 35.3, 43.3, 59.0, 60.6, 68.7, 74.0, 83.5, 100.7, 117.1, 123.0, 136.0, 150.2, 170.2, 170.8 ppm; ESI-HRMS: *m*/*z* calculated for $C_{24}H_{36}NO_4S$ $[M + H]^+$: 434.23596, found 434.23630.

(*E*)-Ethyl-2-((2-((*R*)-1-((4*S*,6*S*)-6-(bromoethynyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)octanoate (26). To a solution of alkyne **25a** (25 mg, 57 μmol) in acetone (1 mL) were added *N*-bromosuccinimide (20 mg, 115 μmol) and silver nitrate (1 mg, 5.7 μmol) sequentially in the absence of light. The mixture was stirred for 30 min at room temperature in the dark before it was diluted with DCM (3 mL) and water (3 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 mL × 2). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a colorless oil. The crude product was purified by flash column chromatography (EtOAc:PE = 8:92) to produce the desired bromoalkyne **26** (28 mg, 96%) as a colorless oil. R_f = 0.5 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +10.0 (*c* 0.36, $CHCl_3$); IR (neat): 3429, 2927, 2855, 1704, 1635, 1226, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.27−1.37 (m, 7H), 1.37−1.47 (m, 8H), 1.48−1.57 (m, 2H), 1.59 (s, 3H), 1.70 (ddd, *J* = 4.1, 5.2, 9.2 Hz, 1H), 1.89 (ddd, *J* = 6.1, 10.5, 13.1 Hz, 1H), 2.84−2.94 (m, 2H), 3.24−3.31 (m, 1H), 4.22−4.33 (m, 3H), 4.67−4.72 (m, 1H), 7.29 (s, 1H), 7.54 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 14.3, 16.4, 22.6, 23.3, 27.8, 28.1, 29.2, 29.6, 31.7, 33.9, 43.4, 46.1, 60.2, 60.7, 68.8, 79.7, 100.6, 121.3, 129.8, 134.0, 151.5, 168.7, 171.1 ppm; ESI-HRMS: *m*/*z* calculated for $C_{24}H_{35}BrNO_4S$ $[M + H]^+$: 514.14377 found 514.14551.

(*E*)-Ethyl-2-((2-((*R*)-1-((4*S*,6*S*)-2,2-dimethyl-6-((*E*)-2-(tributylstannyl)vinyl)-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)-octanoate (5). To a stirred solution of bromoalkyne **26** (104 mg, 203 μmol) in dry THF (1.5 mL) were added $Pd_2(dba)_3$ (1 mg, 1.1 μmol) and PPh_3 (2 mg, 8.1 μmol) at 0 °C, and the dark brown solution was stirred for 2 min. Then, nBu_3SnH (0.12 mL, 447 μmol) was added into the reaction mixture, which was again stirred at the same temperature for 30 min. TLC analysis indicated completion of reaction; afterward, the solvent was evaporated and the residue obtained was purified by neutral alumina column chromatography (EtOAc:PE = 8:92) to produce the desired vinyl stannane **5** (129.7 mg, 88%) as a colorless liquid. R_f = 0.7 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = −44.0 (*c* 0.28, $CHCl_3$); IR (neat): 2854, 1740, 1680, 1230, 1050, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.79−0.98 (m, 15H), 1.20−1.58 (m, 35H), 1.58−1.85 (m, 2H), 2.83−2.94 (m, 2H), 3.39 (quint, *J* = 6.8 Hz, 1H), 4.03−4.15 (m, 1H), 4.18−4.33 (m, 3H), 5.86−6.19 (m, 2H), 7.29 (s, 1H), 7.54 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3, 13.6, 14.1, 14.3, 19.6, 22.7, 24.6, 25.5, 27.2, 27.9, 29.0, 29.2, 29.6, 31.7, 34.6, 43.5, 60.7, 69.4, 70.5, 100.7, 121.4, 129.0, 129.9, 133.8, 147.9, 151.3, 168.7, 171.7 ppm; ESI-HRMS: *m*/*z* calculated for $C_{36}H_{64}NO_4SSn$ $[M + H]^+$: 726.35725, found 726.35975.

Dimethyl-(4-((4-methoxybenzyl)oxy)-2-oxobutyl)phosphonate (13). To a stirred solution of methyl dimethylphosphonate (7.1 mL, 67.0 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (48.9 mL, 1.6 M solution in hexanes, 67.0 mmol). After 30 min, a solution of aldehyde **10** (10.0 g, 51.54 mmol) in THF (40 mL) was added via cannula. The reaction mixture was stirred for a further 30 min before quenching with saturated NH_4Cl aq solution (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL × 3). The organic layers were combined and dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification by flash chromatography (EtOAc:PE = 60:40, then 100% EtOAc) afforded the desired secondary alcohol (15.2 g, 93%) as a yellow oil. R_f = 0.2 (EtOAc 100%). To the alcohol were added anhydrous DCM (200 mL) and pyridinium chlorochromate in Celite (50% w/w, 30.9 g, 71.9 mmol). The reaction mixture was then stirred for overnight; TLC analysis indicated complete consumption of starting material. The black reaction mass was filtered through Celite, and the filtrate was concentrated under reduced pressure and purified by flash column chromatography (EtOAc:PE = 70:30) to afford β-keto phosphonate **13** (12.1 g, 80%) as a pale yellow oil. R_f = 0.3 (EtOAc 100%). IR (Neat): 3445, 2957, 1717, 1514, 1249, 1049, 1030, 821, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (t, *J* = 6.0 Hz, 2H), 3.14 (d, $^2J(^{31}P,^1H)$ = 22.7 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 3.78−3.82 (m, 6H), 4.44 (s, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.4 (d, $^1J(^{31}P,^{13}C)$ = 129.5 Hz), 43.9, 52.8, 52.9, 55.0, 64.4, 72.6, 113.6, 129.1, 131.4, 159.0, 200.2 ppm; ESI-HRMS: *m*/*z* calcd for $C_{14}H_{21}O6NaP$ $[M + Na]^+$: 339.0968, found: 339.0964.

(*R*,*E*)-7-((*tert*-Butyldiphenylsilyl)oxy)-1-((4-methoxybenzyl)-oxy)-6-methylhept-4-en-3-one (27). To a 250 mL round-bottom flask charged with $Ba(OH)_2{\cdot}8H_2O$ (5.14 g, 16.31 mmol) was introduced anhydrous THF (40 mL); to that was added keto phosphonate **12** (4.42 g, 13.98 mmol) in THF (20 mL) via cannula at 0 °C. The mixture, which was allowed to warm to room temperature, became dark brown, indicating generation of phosphonate anion. After 45 min, a solution of aldehyde **13** (4.0 g, 12.26 mmol) in THF (18.5 mL) and H_2O (0.5 mL) was added via cannula at 45 °C (water bath), and the reaction mixture was stirred for a further period of 2 h. The reaction mixture was quenched with saturated NH_4Cl aq solution, extracted with Et_2O (50 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography (EtOAc:PE = 7:93) afforded enone **27** (4.45 g, 70%) as a light yellow oil. R_f = 0.3 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +9.3 (*c* 0.19, $CHCl_3$); IR (Neat): 2929, 2857, 1627, 1428, 1248, 1112, 802, 702, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 2.49−2.63 (m, 1H), 2,78 (t, *J* = 6.6 Hz, 2H), 3.59 (d, *J* = 6.2 Hz, 2H), 3.71 (t, *J* = 6.6 Hz, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 6.07 (dd, *J* = 1.3, 16.1 Hz, 1H), 6.72−6.84 (m, 3H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.32−7.42 (m, 6H), 7.59−7.65 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 19.2, 26.8, 39.3, 40.0, 55.2, 65.1, 67.5, 72.8, 113.7, 127.6, 129.3, 129.7, 130.1, 130.3, 133.4, 135.5, 150.0, 159.1, 198.5 ppm; ESI-HRMS: *m*/*z* calculated for $C_{32}H_{40}O_4NaSi$ $[M + Na]^+$: 539.2588, found: 539.2573.

(4*S*,5*R*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-4,5-dihydroxy-1-((4-methoxybenzyl)-oxy)-6-methylheptan-3-one (28). AD-Mix β (20.34 g) was added in one portion to a stirring mixture of enone **27** (7.5 g, 14.53 mmol), ^{t}BuOH (72 mL), and H_2O (72 mL) at 0 °C. After being stirred for 15 min at the same temperature, methanesulfonamide (1.36 g, 14.3 mmol) was added. The resulting yellow mixture was stirred at 0 °C for 24 h. Solid Na_2SO_3 was added, and the mixture was stirred for 30 min at room temperature. During that period, the yellow solution became colorless. The reaction mixture was then extracted with EtOAc (100 mL × 2), and the combined

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

organic extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (EtOAc:PE = 20:80) furnished the desired diol **28** as a single diastereomer (crude ^{1}H NMR) (7.6 g, 95%) as a colorless oil. R_f = 0.3 (EtOAc:PE = 30:70). $[\alpha]_D^{20}$ = +16.8 (*c* 0.23, $CHCl_3$); IR (Neat): 3432, 2930, 1717, 1427, 1247, 1111, 1036, 768, 702, 504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.94−2.08 (m, 1H), 2.70−2.95 (m, 2H), 3.71−3.82 (m, 7H), 4.09−4.18 (m, 1H), 4.22−4.28 (m, 1H), 4.43 (s, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.34−7.48 (m, 6H), 7.63−7.71 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 19.3, 26.8, 38.3, 38.6, 55.1, 64.9, 66.5, 72.9, 72.9, 113.7, 127.7, 129.3, 129.7, 133.0, 133.2, 135.4, 135.6, 159.2, 209.8 ppm; ESI-HRMS: *m*/*z* calculated for $C_{32}H_{43}O_6Si$ $[M + H]^+$: 551.2823, found: 551.2821.

1-((4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-propan-1-one (29). 2-Methoxypropene (2.0 mL, 21.81 mmol) was added at 0 °C to a solution of diol **28** (4.0 g, 7.27 mmol) in dry DCM (40 mL). After 5 min, PPTS (0.18 g, 0.72 mmol) was added in one portion. The reaction mixture was quenched with solid $NaHCO_3$ at 0 °C after being stirred at room temperature for 1 h. Organic solvent was removed, and the crude residue was purified by flash chromatography (Et OAc: PE = 10:90) to furnish the desired acetonide compound **29** (4.0 g, 93%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +3.8 (*c* 0.32, $CHCl_3$); IR (Neat): 3453, 2932, 1720, 1612, 1513, 1248, 1111, 772, 702, 505 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 1.37 (s, 3H), 1.41 (s, 3H), 1.97−2.05 (m, 1H), 2.89−2.95 (m, 2H), 3.55−3.66 (m, 2H), 3.72 (t, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 4.18 (d, *J* = 8.1 Hz, 1H), 4.28−4.33 (m, 1H), 4.42 (s, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 7.22 (d, *J* = 8.05 Hz, 2H), 7.33−7.44 (m, 6H), 7.63−7.70 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.5, 19.2, 26.1, 26.8, 37.4, 38.8, 55.2, 64.3, 66.0, 72.8, 77.4, 82.6, 110.0, 113.7, 127.6, 129.2, 129.5, 130.1, 133.6, 135.5, 159.1, 208.7 ppm; ESI-HRMS: *m*/*z* calculated for $C_{35}H_{46}O_6NaSi$ $[M + Na]^+$: 613.2955, found: 613.2939.

(*S*)-1-((4*R*,5*R*)-5-((*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-propan-1-ol (30a). To a stirred suspension of the ketone **29** (3.2 g, 5.42 mmol) and cerium(III) chloride (4.04 g, 10.84 mmol) in methanol (30 mL) was added $NaBH_4$ (103 mg, 2.71 mmol) portionwise at −15 °C, and the resulting solution was stirred for 1 h at same temperature. The reaction was terminated by the addition of 5% aq citric acid, then MeOH was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (50 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The organic solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:PE = 10:90) to afford the desired major diastereomer **30a** (2.59 g, 81%) as a colorless liquid, R_f = 0.3 (EtOAc:PE = 20:80) and minor diastereomer **30b** (0.46 g, 14%) also as a colorless liquid, R_f = 0.4 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = +5.9 (*c* 0.21, $CHCl_3$); IR (Neat): 2922, 2853, 1461, 1259, 1093, 1021, 800, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 1.65−1.87 (m, 3H), 3.48−3.73 (m, 6H), 3.77 (s, 3H), 4.11−4.20 (m, 1H), 4.41 (dd, *J* = 1.5, 11.9 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.27−7.41 (m, 6H), 7.57−7.68 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7, 19.2, 26.9, 27.2, 27.3, 34.1, 37.5, 55.2, 66.5, 67.5, 69.3, 72.8, 76.9, 81.1, 108.5, 113.8, 127.6, 129.3, 129.6, 130.3, 133.6, 133.7, 135.6, 159.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{35}H_{49}O_6Si$ $[M + H]^+$: 593.3292, found: 593.3285.

(*R*)-1-((4*R*,5*R*)-5-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-methoxybenzyloxy)-propan-1-ol (30b). $[\alpha]_D^{20}$ = +4.5 (*c* 0.66, $CHCl_3$); IR (Neat): 2923, 1614, 1249, 1089, 807, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.35 (s, 6H), 1.64−2.09 (m, 3H), 3.18 (s, 1H), 3.51−3.89 (m, 9H), 4.23 (dd, *J* = 3.0, 7.6 Hz, 1H), 4.45 (s, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 7.21−7.30 (m, 2H), 7.32−7.47 (m, 6H), 7.60−7.75 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 19.2, 26.8, 27.2, 32.6, 37.7, 55.2, 66.8, 68.8, 72.7, 73.0, 78.5, 80.2, 108.4, 113.8, 127.5, 127.6, 129.3, 129.5, 129.9, 133.8, 133.9, 135.6, 135.6, 159.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{35}H_{49}O_6Si$ $[M + H]^+$: 593.3292, found: 593.3287.

1-((4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((4-methoxybenzyl)oxy)-propan-1-one (29 from 30b). To a magnetically stirred solution of the alcohol **30b** (0.46 g, 0.777 mmol) in DMSO (5 mL) under an argon atmosphere was added IBX (0.326 g, 1.165 mmol). After 5 h, the resulting solution was carefully poured into a vigorously stirred mixture of water (10 mL) and Et_2O (10 mL) and then filtered. The filtrate was diluted with Et_2O (10 mL), and the layers were separated. The organic layer was washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. Ether was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc: PE = 10:90) to afford the ketone **29** (0.412 g, 90%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 10:90).

***tert*-Butyl((*S*)-2-((4*R*,5*S*)-5-((*S*)-1-((*tert*-butyldimethylsilyl)-oxy)-3-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propoxy)diphenylsilane (31).** To a solution of the alcohol **30a** (4.0 g, 6.75 mmol) and imidazole (1.37 g, 20.27 mmol,) in dry DMF (20 mL) were added TBSCl (3.0 g, 20.27 mmol) and DMAP (0.41 g, 3.37 mmol). The reaction mixture was heated at 85 °C for 5 h and then allowed to cool down to room temperature. The mixture was slowly added to vigorously stirred cold water (200 mL). The product was extracted with Et_2O (50 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. After flash chromatography (EtOAc:PE = 5:95), TBS-ether **31** (4.62 g, 97%) was obtained as a colorless liquid. R_f = 0.6 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +0.8 (*c* 0.24, $CHCl_3$); IR (Neat): 2924, 2854, 1462, 1250, 1106, 804, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H), 1.05 (s, 9H), 1.33 (s, 3H), 1.35 (s, 3H), 1.63−1.71 (m, 1H), 1.89−1.98 (m, 1H), 1.98−2.06 (m, 1H), 3.50−3.57 (m, 3H), 3.64 (dd, *J* = 7.9, 9.8 Hz, 1H), 3.76 (dd, *J* = 4.9, 8.7 Hz, 1H), 3.79 (s, 3H), 3.91−3.96 (m, 1H), 4.17 (dd, *J* = 2.0, 8.7 Hz, 1H), 4.40 (dd, *J* = 11.6, 28.2 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.32−7.43 (m, 6H), 7.64−7.69 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.9, −4.0, 9.9, 18.2, 19.2, 26.0, 26.8, 27.2, 33.1, 36.8, 55.2, 66.5, 67.0, 70.0, 72.5, 75.9, 79.9, 107.9, 113.7, 127.6, 127.6, 129.3, 129.5, 130.6, 133.8, 133.9, 135.5, 135.6, 159.1 ppm; ESI-HRMS: *m*/*z* calculated for $C_{41}H_{62}O_6NaSi_2$ $[M + Na]^+$: 729.3977, found: 729.3974.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-3-((4*S*,5*R*)-5-((*S*)-1-((*tert*-butyldiphenylsilyl)-oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (32). To a solution of the PMB ether **31** (1.6 g, 2.26 mmol) in DCM (20 mL) and pH 7 phosphate buffer (1.2 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.77 g, 3.39 mmol) at 0 °C. The mixture was stirred for 30 min at rt before being quenched with saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with DCM (20 mL × 3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Purification of the crude product by flash column chromatography (EtOAc:PE = 8:92) afforded the requisite alcohol **32** (1.16 g, 87%) as a colorless oil. R_f = 0.4 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +7.4 (*c* 0.16, $CHCl_3$); IR (Neat): 2924, 2855, 1462, 1255, 1106, 803, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.36 (s, 3H), 1.38 (s, 3H), 1.60−1.75 (m, 1H), 1.83−2.03 (m, 2H), 3.51−3.74 (m, 3H), 3.74−3.87 (m, 2H), 3.90−3.99 (m, 1H), 4.16 (dd, *J* = 2.3, 9.1 Hz, 1H), 7.31−7.47 (m, 6H), 7.6−7.7 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.3, 10.1, 18.1, 19.2, 25.8, 26.8, 27.0, 27.2, 36.2, 36.9, 58.9, 66.9, 70.2, 76.3, 80.1, 108.2, 127.5, 129.5, 133.7, 135.5 ppm; ESI-HRMS: *m*/*z* calculated for $C_{33}H_{54}O_5NaSi_2$ $[M + Na]^+$: 609.3402, found: 609.3399.

***tert*-Butyl((*S*)-2-((4*R*,5*S*)-5-((*S*,*Z*)-1-((*tert*-butyldimethylsilyl)-oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-propoxy)diphenylsilane (33).** A solution of the alcohol **32** (1.0 g, 1.75 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere was cooled down to 0 °C, before $NaHCO_3$ (0.37 g, 4.37 mmol) and Dess−Martin periodinane (1.0 g, 2.45 mmol) were added. The resulting solution was stirred for 30 min at room temperature. The mixture was filtered through Celite, and the residue was thoroughly washed with DCM. The organic layer was washed with water and brine and dried

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

over Na_2SO_4. DCM was evaporated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc:PE = 5:95), which gave the corresponding aldehyde (0.98 g, 95%) as a colorless liquid. R_f = 0.5 (EtOAc:PE = 10:90). In the absence of light, a 25 mL flask was charged with iodomethyl-triphenyl-phosphonium iodide (391 mg, 0.74 mmol) and THF (4 mL). A solution of NaHMDS (0.74 mL, 1.0 M in THF, 0.74 mmol) was added at 10 °C (ice−water bath), and the resulting yellow solution was stirred for 1 min before cooling to −78 °C, whereupon anhydrous HMPA (0.25 mL, 1.48 mmol) was added. Afterward, aldehyde (287 mg, 0.492 mmol) in THF (2 mL) was added via cannula. The reaction was stirred for 30 min and quenched by the addition of saturated aqueous NH_4Cl (3 mL). The reaction was warmed to 25 °C and filtered through Celite using EtOAc as the eluent. The solution was washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (EtOAc:PE = 5:95) to provide **33** (266 mg, 78%, *Z*:*E* = 15:1) as a colorless liquid. R_f = 0.6 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +8.5 (*c* 0.37, $CHCl_3$); IR (Neat): 2956, 2926, 2756, 1465, 1256, 1108, 807, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.85−0.95 (m, 12H), 1.06 (s, 9H), 1.36 (s, 3H), 1.39 (s, 3H), 1.96−2.11 (m, 1H), 2.29−2.52 (m, 2H), 3.50−3.71 (m, 2H), 3.74−3.95 (m, 2H), 4.21 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.22−6.38 (m, 2H), 7.32−7.48 (m, 6H), 7.63−7.74 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.5, −4.2, 10.1, 18.1, 19.3, 25.9, 26.9, 27.2, 27.3, 37.0, 38.7, 66.9, 71.3, 76.1, 79.7, 84.3, 108.1, 127.7, 129.5, 133.8, 135.6, 137.9 ppm; ESI-HRMS: *m*/*z* calculated for $C_{34}H_{53}IO_4NaSi_2$ $[M + Na]^+$: 731.2419, found: 731.2425.

(*S*)-2-((4*R*,5*S*)-5-((*S*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (34). In a 10 mL single-necked round-bottom flask, TBDPS ether **33** (308 mg, 0.434 mmol) was taken; to that was introduced MeOH (5 mL). Finally, NH_4F (96.4 mg, 2.60 mmol) was added in one portion, and the mixture was heated at 60 °C for 8 h. The reaction was allowed to cool down to room temperature; methanol was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (10 mL × 2), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (EtOAc:PE = 10:90) to provide alcohol **34** (157 mg, 77%) as a colorless liquid. The small amount of *E*-vinyl iodide compound was separated in this step. R_f = 0.3 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = +25.3 (*c* 0.25, $CHCl_3$); IR (Neat): 2956, 1464, 1376, 1258, 1088, 1019, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.0 (d, *J* = 7.0 Hz, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.84−1.96 (m, 1H), 2.30−2.54 (m, 2H), 3.58−3.74 (m, 2H), 3.74−3.93 (m, 2H), 4.15 (dd, *J* = 2.6, 8.3 Hz, 1H), 6.29−6.40 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.5, −4.4, 10.4, 18.1, 25.9, 27.1, 36.2, 39.0, 66.9, 70.6, 78.1, 79.9, 84.4, 108.4, 137.6 ppm; ESI-HRMS: *m*/*z* calculated for $C_{18}H_{35}IO_4NaSi$ $[M + Na]^+$: 493.1241, found: 493.1232.

(*R*)-2-((4*R*,5*S*)-5-((*S*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-3-one (11). A solution of the primary alcohol **34** (420 mg, 0.893 mmol) in DCM (12.5 mL) was treated with DMP (568 mg, 1.34 mmol) in one portion at 0 °C, and the resulting solution was stirred for 1 h. The reaction mixture was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and stirring continued until two layers were clearly visible. After extraction with DCM (10 mL × 2), the combined organic layers were dried over Na_2SO_4 and filtered and the solvent was removed under reduced pressure. Purification by a short column (EtOAc:PE = 10:90) afforded the corresponding aldehyde (376 mg, 0.803 mmol, 90%) as a colorless oil. R_f = 0.5 (EtOAc:PE = 10:90). The aldehyde was immediately utilized for the next step. To a stirred 0 °C solution of aldehyde (376 mg, 0.803 mmol) in THF (6 mL) was added EtMgBr (1.6 mL, 1.0 M in THF, 1.6 mmol). The solution was stirred at 0 °C for 10 min, then diluted with diethyl ether (10 mL) and washed with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with diethyl ether (10 mL × 2), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to flash column chromatography (EtOAc:PE = 7:97), which gave the diastereomeric alcohol (351 mg, 88%) as a colorless oil. R_f = 0.4 (EtOAc:PE = 10:90). To a solution of the secondary alcohol (351 mg, 0.706 mmol) in CH_2Cl_2 were added $NaHCO_3$ (177 mg, 2.11 mmol) and DMP (449 mg, 1.05 mmol) simultaneously at 0 °C. The reaction was allowed to stir for 30 min before being filtered through Celite, and the filtrate was washed with water and brine and dried over Na_2SO_4. The organic layer was filtered through cotton and concentrated by rotary evaporation. The residue was subjected to flash column chromatography (EtOAc:PE = 10:90), which gave ketone **11** (318 mg, 91%) as a colorless oil. R_f = 0.6 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +19.5 (*c* 0.2, $CHCl_3$); IR (Neat): 2924, 2854, 1710, 1463, 1257, 1060, 1020, 834, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.91 (s, 9H), 1.05 (t, *J* = 7.6 Hz, 3H), 1.17 (d, *J* = 7.6 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 2.34−2.58 (m, 4H), 2.75 (qd, *J* = 4.5, 6.8 Hz, 1H), 3.74 (dd, *J* = 3.8, 7.6 Hz, 1H), 3.81−3.88 (m, 1H), 4.33 (dd, *J* = 4.5, 8.3 Hz, 1H), 6.29−6.37 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, −4.4, 7.7, 11.0, 18.1, 25.8, 27.1, 27.3, 34.7, 39.2, 48.0, 70.4, 76.3, 80.5, 84.5, 108.9, 137.4, 212.2 ppm; ESI-HRMS: *m*/*z* calculated for $C_{20}H_{37}IO_4NaSi$ $[M + Na]^+$: 519.1398, found: 519.1406.

(2*R*,5*S*,*E*)-2-((4*R*,5*S*)-5-((*S*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-hydroxy-4,6-dimethyloct-6-en-3-one (35). A solution of ethyl ketone **11** (119 mg, 0.239 mmol) in CH_2Cl_2 (1.5 mL) was added to a 10 mL round-bottom flask containing activated 4 Å molecular sieves and cooled to −78 °C while $TiCl_4$ solution (0.3 mL, 1.0 M in CH_2Cl_2, 0.3 mmol) was added dropwise via syringe. The resulting dark orange solution was stirred at −78 °C for 1 min, and then Et_3N (43 μL, 0.31 mmol) was added dropwise. The resulting maroon solution was stirred at −78 °C for an additional 10 min. Tiglic aldehyde **12** (0.12 mL, 1.2 mmol) was added, and the mixture was stirred at −78 °C for 15 min. Then, the acetone−dry ice bath was replaced with an ice bath and the reaction mixture was stirred at 0 °C for an additional 5 min. The reaction mixture was poured into 2 mL of saturated aqueous NH_4Cl solution and diluted with 5 mL of CH_2Cl_2. The reaction mixture was then filtered through Celite and thoroughly washed with CH_2Cl_2. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL), and the combined organic layers were washed with and dried over Na_2SO_4, filtered, and concentrated to afford the crude aldol adduct as a yellow oil (dr 10:1 by ^1H NMR analysis). Flash column chromatography (EtOAc:PE = 8:92) provided aldol adduct **35** (104 mg, 75%) as a colorless liquid. R_f = 0.3 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +23.2 (*c* 0.16, $CHCl_3$); IR (Neat): 2924, 1720, 1461, 1360, 1258, 1080, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.14 (s, 6H), 0.91 (s, 9H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.59 (s, 3H), 1.63 (d, *J* = 6.7 Hz, 3H), 2.37−2.44 (m, 1H), 2.50 (ddd, *J* = 4.3, 6.7, 11.1 Hz, 1H), 2.83 (d, *J* = 2.4 Hz, 1H), 2.94−3.02 (m, 2H), 3.80 (dd, *J* = 3.6, 7.6 Hz, 1H), 3.86−3.93 (m, 1H), 4.30−4.36 (m, 2H), 5.59 (q, *J* = 6.7 Hz, 1H), 6.30−6.37 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.4, −4.4, 10.2, 11.1, 13.0, 13.3, 18.1, 25.9, 27.1, 27.5, 39.2, 46.7, 47.3, 70.4, 74.8, 76.2, 80.2, 84.6, 109.0, 120.6, 133.9, 137.4, 216.6 ppm; ESI-HRMS: *m*/*z* calculated for $C_{25}H_{45}IO_5NaSi$ $[M + Na]^+$: 603.1973, found: 603.1962.

(2*S*,3*S*,4*E*,6*E*)-2-((4*R*,5*S*)-5-((*S*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,6-dimethylocta-4,6-dien-3-ol (37a). To a stirring solution of the aldol adduct **35** (75 mg, 0.129 mmol) in THF (1.5 mL) at −78 °C were added PBu_3 (0.16 mL, 0.646 mmol) and diisopropylazodicarboxylate (0.13 mL, 0.646 mmol). The reaction mixture was allowed to warm up to −20 °C and stirred for 6 h. TLC analysis indicated complete consumption of starting material. THF was removed under reduced pressure, and the crude residue was subjected to flash column chromatography (EtOAc:PE = 3:97), which gave dienone **36** (65 mg, 90%) as a colorless oil. R_f = 0.7 (EtOAc:PE = 10:90). To a stirred solution of dienone **36** (65 mg, 0.115 mmol) in dry ether (3.0 mL) was added LiI (155 mg, 1.15 mmol), and the resulting mixture was stirred at −40 °C for 5 min. After this period, the mixture was cooled to −78 °C and $LiAlH_4$ (44 mg, 1.15 mmol) was added in one portion. The reaction was stirred for 30 min and quenched with aqueous 10% potassium sodium tartrate solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:PE = 7:93) to afford the major diastereomer **37a** (60 mg, 92%) as a colorless oil. R_f = 0.4 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = +10.4 (*c* 0.2, EtOAc); IR (Neat): 2940, 2920, 1485, 1244, 1082, 815, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.89 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.73 (s, 3H), 1.75 (s, 3H), 1.93−2.00 (m, 1H), 2.32−2.39 (m, 1H), 2.43−2.51 (m, 1H), 3.80 (dd, *J* = 4.3, 8.7 Hz, 1H), 3.90−3.95 (m, 1H), 4.11 (dd, *J* = 2.1, 8.7 Hz, 1H), 4.14 (d, *J* = 3.8 Hz, 1H), 5.40 (q, *J* = 6.9 Hz, 1H), 6.01 (s, 1H), 6.30−6.36 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5, −4.3, 6.4, 13.7, 15.1, 16.8, 18.1, 25.9, 27.1, 27.1, 36.2, 38.6, 70.6, 79.5, 79.6, 79.9, 84.4, 108.5, 123.9, 129.6, 133.2, 133.5, 137.7 ppm; ESI-HRMS: *m*/*z* calculated for $C_{25}H_{45}IO_4NaSi$ $[M + Na]^+$: 587.2024, found: 587.2026.

(2*S*,3*S*,4*E*,6*E*)-2-((4*R*,5*R*)-5-((*S*,*Z*)-1-Hydroxy-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,6-dimethylocta-4,6-dien-3-ol (6). To a cooled solution (0 °C) of silyl ether **37a** (85 mg, 0.15 mmol) in 2 mL of anhydrous THF was added a 1 M solution of TBAF in THF (0.22 mL, 0.22 mmol). The mixture was stirred for 30 min at 0 °C before the reaction was quenched with addition of saturated aq NH_4Cl solution (1 mL). The mixture was extracted with Et_2O (5 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc:PE = 5:95) to afford the diol **6** (57 mg, 85%) as a colorless liquid. R_f = 0.4 (EtOAc:PE = 10:90). $[\alpha]_D^{20}$ = −13.0 (*c* 0.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.9 Hz, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.72 (s, 3H), 1.74 (s, 3H), 1.81−1.90 (m, 1H), 2.35−2.45 (m, 2H), 3.63−3.70 (m, 1H), 3.78 (dd, *J* = 3.2, 8.2 Hz, 1H), 4.09 (dd, *J* = 2.6, 8.2 Hz, 1H), 4.13 (d, *J* = 4.0 Hz, 1H), 5.39 (q, *J* = 6.9 Hz, 1H), 5.99 (s, 1H), 6.34−6.42 (m, 2H) ppm; ^{13}C NMR (125 MHz, C_6D_6): δ 8.3, 13.7, 14.7, 16.9, 27.1, 27.3, 37.3, 40.6, 69.2, 79.3, 79.5, 80.8, 84.5, 108.9, 124.1, 130.5, 133.6, 134.8, 138.0 ppm; ESI-HRMS: *m*/*z* calculated for $C_{19}H_{31}O_4INa$ $[M + Na]^+$: 473.1159, found: 473.1151.

(*E*)-Ethyl-2-((2-((*R*)-1-((4*S*,6*S*)-6-((*S*,1*E*,3*Z*)-6-hydroxy-6-((4*R*,5*R*)-5-((2*S*,3*S*,4*E*,6*E*)-3-hydroxy-4,6-dimethylocta-4,6-dien-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexa-1,3-dienyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)-octanoate (38). Vinyl iodide **6** (20 mg, 44 μmol) and vinyl stannane **5** (50 mg, 66 μmol) were taken in a 10 mL round-bottom flask; to that was introduced dry THF (2.5 mL). The solution was degassed using an argon balloon for 15 min. After that, simultaneously $Pd_2(dba)_3$ (8 mg, 8 μmol; dba = dibenzylideneacetone), $AsPh_3$ (28 mg, 80 μmol), and lithium chloride (6 mg, 132 μmol) were added at room temperature, and the mixture was allowed to stir for 8 h. TLC analysis indicated completion of reaction, whereupon it was quenched with saturated aqueous NH_4Cl solution (1 mL) and extracted with EtOAc (5 mL × 2). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The residue that was obtained after evaporation of the solvent was purified by flash column chromatography (EtOAc:PE = 20:80) to afford colorless compound **38** (20 mg, 65%). R_f = 0.4 (EtOAc:PE = 20:80). $[\alpha]_D^{20}$ = −47.0 (*c* 0.36, EtOAc); ^1H NMR (300 MHz, CD_3OD): δ 0.89 (t, *J* = 6.6 Hz, 3H), 0.99, (d, *J* = 6.8 Hz, 3H), 1.22−1.58 (m, 29H), 1.57−1.90 (m, 10H), 2.27−2.57 (m, 2H), 2.84−3.20 (m, 2H), 3.44−3.56 (m, 1H), 3.74 (dd, *J* = 2.5, 8.7 Hz, 1H), 3.86 (d, *J* = 7.9 Hz, 1H), 4.00 (dd, *J* = 2.5, 8.7 Hz, 1H), 4.11−4.37 (m, 4H). 5.38 (q, *J* = 6.8 Hz, 1H), 5.51 (dd, *J* = 7.9, 18.3 Hz, 1H), 5.62 (dd, *J* = 6.2, 15.3 Hz, 1H), 5.86 (s, 1H), 6.05 (t, *J* = 11.0 Hz, 1H), 6.48 (dd, *J* = 11.0, 15.3 Hz, 1H), 7.53 (s, 1H), 7.60 (s, 1H) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 9.8, 13.7, 13.8, 14.1, 14.6, 14.7, 17.1, 23.8, 25.0, 25.9, 27.3, 27.7, 28.8, 29.2, 30.5, 30.8, 33.0, 34.0, 36.4, 38.1, 44.7, 62.0, 69.2, 70.8, 78.3, 80.9, 81.2, 102.0, 109.3, 123.9, 124.8, 127.1, 129.1, 131.3, 131.3, 132.4, 134.4, 134.6, 134.9, 136.1, 152.7, 170.4, 173.5 ppm; ESI-HRMS: *m*/*z* calculated for $C_{43}H_{67}O_8NNaS$ $[M + Na]^+$: 780.4469, found: 780.4470.

(*E*)-2-((2-((*R*)-1-((4*S*,6*S*)-6-((*S*,1*E*,3*Z*)-6-Hydroxy-6-((4*R*,5*R*)-5-((2*S*,3*S*,4*E*,6*E*)-3-hydroxy-4,6-dimethylocta-4,6-dien-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexa-1,3-dienyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thiazol-4-yl)methylene)octanoic Acid (39). To a solution of **38** (20 mg, 26 μmol) in EtOH (2 mL) was added 3 M KOH aq. (1.2 mL) at 0 °C. After stirring at rt for overnight, the reaction mixture was cooled to 0 °C and 1 N HCl was added until pH = 4. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration, dihydroxyacid **39** (19 mg, 26 μmol, quant.) was obtained as a colorless foam. R_f = 0.3 (EtOAc:PE = 30:70). This compound was used in the next step without further purification.

Thuggacin A Diacetonide (4). The mixture obtained above was dissolved in toluene (170 mL); then, activated MS 4 Å (200 mg) and DMAP (20 mg, 164 μmol) were added to that. The mixture was heated to 70 °C, and MNBA (28 mg, 82 μmol) was added in one portion. After 12 h of stirring at the same temperature, MS 4 Å was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography (EtOAc:PE = 20:80) to provide thuggacin A diacetonide **4** (7.4 mg, 40%) as a colorless foam. R_f = 0.6 (EtOAc:PE = 30:70). $[\alpha]_D^{20}$ = +108.5 (*c* 0.16, MeOH); For ^1H and ^{13}C NMR data, see the Supporting Information, page S4, Table S3; ESI-HRMS: *m*/*z* calculated for $C_{41}H_{62}O_7NS$ $[M + H]^+$: 712.4241, found: 712.4254.

Thuggacin A Monoacetonide (40). The diacetonide compound **4** (4 mg, 5.6 μmol) was dissolved in THF (0.5 mL), and aqueous 4 N HCl (2.8 μL, 11.2 μmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (2 mL × 4), and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (EtOAc:PE = 80:20) produced the monoacetonide **40** (3.5 mg, 92%) as a colorless foam. R_f = 0.3 (EtOAc:PE = 30:70). $[\alpha]_D^{20}$ = −86.5 (*c* 0.1, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.25−1.37 (m, 9H), 1.38−1.45 (m, 5H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.66 (d, *J* = 6.7 Hz, 3H), 1.71 (s, 3H), 1.74 (s, 3H), 1.81 (ddd, *J* = 3.8, 9.3, 13.6 Hz, 1H), 1.88−1.96 (m, 1H), 2.27 (dd, *J* = 5.3, 14.2 Hz, 1H), 2.41 (dt, *J* = 7.8, 15.1 Hz, 1H), 2.62 (dt, *J* = 7.8, 15.6 Hz, 1H), 3.03 (dt, *J* = 11.6, 13.9 Hz, 1H), 3.53−3.61 (m, 1H), 3.62−3.68 (m, 1H), 3.87 (dd, *J* = 2.3, 9.0 Hz, 2H), 4.04 (dd, *J* = 2.1, 8.7 Hz, 1H), 5.02 (dt, *J* = 1.7, 11.6 Hz, 1H), 5.07 (dd, *J* = 9.3, 9.3 Hz, 1H), 5.32−5.40 (m, 2H), 5.45 (dd, *J* = 9.3, 15.0 Hz, 1H), 5.84 (s, 1H), 5.94 (dd, *J* = 11.1, 11.1 Hz, 1H), 6.62 (dd, *J* = 11.3, 15.0 Hz, 1H), 7.63 (s, 1H), 7.97 (s, 1H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ 9.6, 13.2, 13.9, 14.5, 17.0, 17.9, 23.7, 27.1, 27.6, 28.3, 29.2, 30.3, 32.6, 32.9, 37.3, 40.8, 45.1, 71.7, 72.4, 77.9, 78.3, 80.4, 82.0, 109.7, 119.7, 124.8, 127.4, 128.7, 132.6, 132.7, 133.7, 134.3, 135.1, 136.2, 137.7, 151.2, 168.4, 173.4 ppm. ESI-HRMS: *m*/*z* calcd for $C_{38}H_{57}O_7NNaS$ $[M + Na]^+$: 694.3748, found 694.3750.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02426.

Mosher ester analyses, copies of ^1H and ^{13}C NMR spectra for all new compounds, and data comparisons (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yadavpub@gmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

P.D. thanks CSIR, New Delhi, for financial assistance in the form of a fellowship. J.S.Y. thanks CSIR and DST, New Delhi, for Bhatnagar and J. C. Bose Fellowships, respectively. This

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797

work is partly funded by CSC-0108, ORIGIN under XII Five Year Plan programme.

REFERENCES

(1) Steinmetz, H.; Irschik, H.; Kunze, B.; Reichenbach, H.; Höfle, G.; Jansen, R. *Chem.—Eur. J.* **2007**, *13*, 5822−5832.
(2) Bock, M.; Müller, K.; Buntin, K.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2308−2311.
(3) McKinney, D. *Nat. Med.* **2000**, *6*, 1330−1333.
(4) O'Brain, R. J.; Nunn, P. P. *Am. J. Respir. Crit. Care Med.* **2001**, *163*, 1055−1058.
(5) Bock, M.; Dehn, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9134−9137.
(6) Matsuzawa, A.; Opie, C. R.; Kumagai, N.; Shibasaki, M. *Chem.—Eur. J.* **2014**, *20*, 68−71.
(7) Zarate-Ruiz, G. A.; de Figueiredo, R. M.; Niel, G.; Campagne, J.-M. *Synlett* **2012**, *2012*, 219−222.
(8) (a) Yadav, J. S.; Das, S. K.; Sabitha, G. *J. Org. Chem.* **2012**, *77*, 11109−11118. (b) Yadav, J. S.; Reddy, Ch. S. *Org. Lett.* **2009**, *11*, 1705−1708.
(9) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777.
(10) (a) Chavan, S. P.; Harale, K. R. *Tetrahedron Lett.* **2012**, *53*, 4683−4686. (b) Dias, L. C.; de Oliveira, L. G.; de Sousa, M. A. *Org. Lett.* **2003**, *5*, 265−268.
(11) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.
(12) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4685−4689.
(13) Pedersen, B. S.; Lawesson, S. O. *Tetrahedron* **1979**, *35*, 2433−2437.
(14) Dondoni, A.; Merino, P. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 3, pp 432−434.
(15) Rychnovsky, S.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948.
(16) (a) Removal of TMS protection was necessary to acquire the desired diastereoselectivity. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.
(17) (a) Zhang, H. X.; Guibě, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867. (b) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417−2419.
(18) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909−5922.
(19) (a) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, *1993*, 774−776. (b) Alvarez-Ibarra, C.; Arias, S.; Bañón, G.; Fernández, M. J.; Rodríguez, M.; Sinisterra, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1509−1511.
(20) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, *1993*, 605−606.
(21) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2916−2919.
(22) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732−3738. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2449.
(23) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.
(24) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. (b) Dunetz, J. R.; Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 16407−16416. (c) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811−1834.
(25) (a) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1−28. (b) Shirokawa, S.-i.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849−852.
(26) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204.
(27) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783−8788.
(28) (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817.
(29) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822−1830.
(30) Since the optical rotation was not reported, an e-mail was communicated to Prof. Dr. Andreas Kirschning inquiring about the optical rotation of compound **4**. In response, we came to know that they did not measure the optical rotation and also the removal of the acetonides is tricky and not a clean process.
(31) Franke, J.; Bock, M.; Dehn, R.; Fohrer, J.; Mhaske, S. B.; Migliorini, A.; Kanakis, A. A.; Jansen, R.; Herrmann, J.; Müller, R.; Kirschning, A. *Chem.—Eur. J.* **2015**, *21*, 4272−4284.

DOI: 10.1021/acs.joc.5b02426
J. Org. Chem. 2016, 81, 1786−1797