JOC The Journal of Organic Chemistry

Article

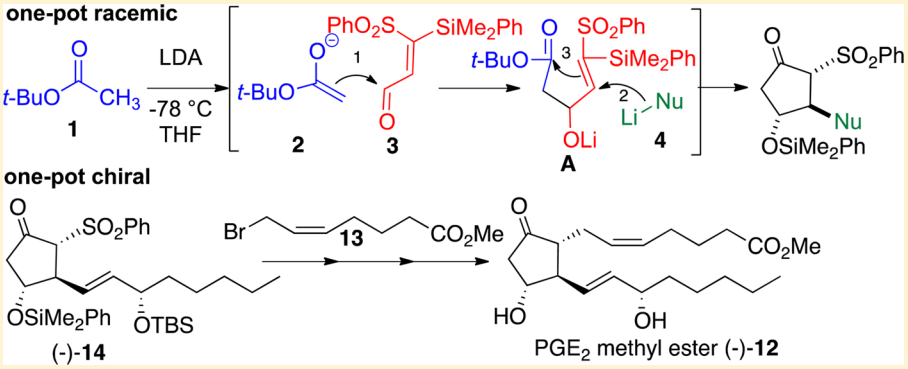
pubs.acs.org/joc

Multicomponent Strategy for the Synthesis of Prostaglandin E_2 Methyl Ester under Anion Relay Chelation Control

Kuan-Hsun Huang, Chun-Chieh Huang, and Minoru Isobe*,#

Department of Chemistry, National Tsing Hua University, Hsinchu, 30013, Taiwan (ROC)

Supporting Information



ABSTRACT: Starting with four components, the enantioselective synthesis of prostaglandin E_2 methyl ester has been achieved through a highly stereoselective heteroatom-directed conjugate addition reaction and cyclopentanone ring cyclization as the key steps. This asymmetric strategy includes (i) an asymmetric Reformatsky reaction; (ii) conjugate addition of a chiral vinyllithium reagent; (iii) cyclization to form a sulfonylated cyclopentanone in one-pot; followed by (iv) allylation of the side chain. Four carbon−carbon bond-forming processes and three stereogenic centers were established, with the steps from (ii) to (iii) being achieved in a one-pot process.

INTRODUCTION

It has been the dream of synthetic chemists to be able to create multiple carbon−carbon bonds in a chemo- and stereoselective manner in a single reaction vessel. Domino or cascade reactions have been often used for such consecutive C−C bond formations to provide the target compound in highly controlled manner.[1−9] Recently, further improvements in atom- and step-economy in domino reactions have been realized by protection-free routes.[10−12]

Prostanoids are biosynthesized in the body from arachidonic acid by the action of COX enzymes[13−15] and play various physiological roles including smooth muscle constriction or dilation, regulating inflammation, and platelet aggregation or disaggregation.[16] Since the 1960s, many efforts on the chemical synthesis of prostaglandins have been reported, including the elegant strategies designed by Corey,[17] Woodward,[18] Stork,[19] Fuchs,[20] Noyori,[21] Aggarwal,[22] Hayashi,[10] Nicolaou,[23] and others. Because of the high demand of prostaglandins as drugs, there is still a necessity for the development of more efficient routes toward this class of compounds, based on new reactions and strategies. Herein we describe a four-component strategy for a highly economical synthesis of prostaglandins.

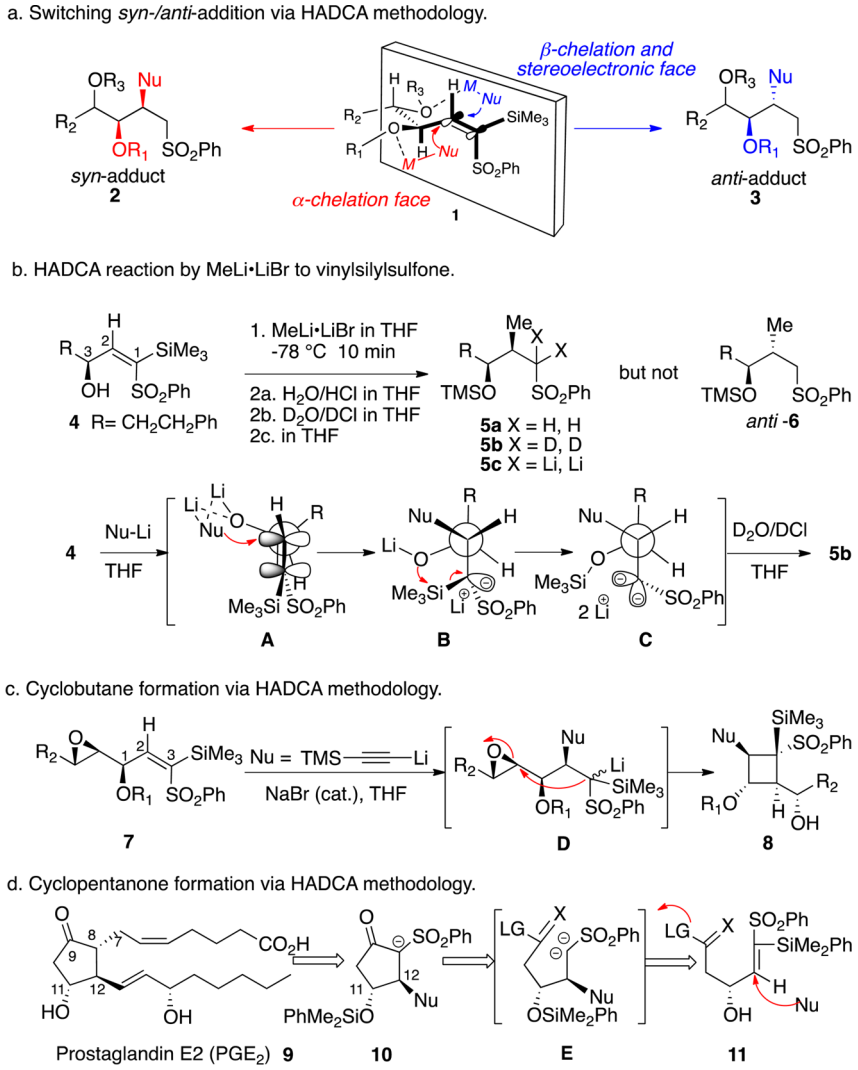
In the course of tackling the syntheses of other complex natural products, we have developed a versatile C−C bond-forming methodology that exerts acyclic stereocontrol via anion-relay, which we have coined heteroatom-directed conjugate addition (HADCA). We have utilized this HADCA methodology effectively as a key step in the stereocontrolled total syntheses of maytansine,[24] okadaic acid,[25] tautomycin,[26] and ciguatoxin.[27] Complete stereochemical control in this C−C bond-forming reaction to obtain either diastereomer can be achieved through exploiting α- or β-chelation. This HADCA methodology also has the potential to synthesize the *syn* or *anti* complementary stereochemical arrays in either enantiomeric forms from similar starting materials (Scheme 1a).[28,29] Due to allylic strain, i.e., $A^{1,3}$-strain, chiral vinyl-sulfones **4** prefer to adopt a conformation **A** in which the trisubstituted carbon−carbon double bond is coplanar with the hydrogen atom at the C_3 stereogenic carbon, in the ground state as well as in the transition state (Scheme 1b). Substrate **4** is known to react with MeLi·LiBr and undergo a subsequent Brook rearrangement (**B** → **C**), to give exclusively *syn*-product **5a** within 10 min at −78 °C, with no observable concomitant formation of *anti*-product **6**. Quenching the reaction mixture with D_2O/THF at −78 °C afforded the dideuterated compound **5b**, suggesting that the precursor was the corresponding dianionic species **5c**.

The HADCA methodology has also been further engaged to undergo a domino cyclobutane-ring cyclization. A *syn* conjugate addition to **7** generated carbanion **D**, whose reactivity was

Received: December 1, 2015
Published: January 26, 2016

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

Scheme 1. HADCA



enhanced by a salt effect, and intramolecularly attacked the epoxide in an *exo* fashion (Scheme 1c).[30−32]

Since five-membered ring formation through *endo* epoxide opening was not observed for **D** at all, to yield a cyclopentane as found in the prostaglandin nucleus, it must be obtained by reaction with a different electrophilic group. We surmised that cyclopentanone formation for the synthesis of a prostaglandin like **9** required a substrate with a *tert*-butoxy-carbonyl functionality that would not be expected to compete with the vinylsulfone group for the C-nucleophile (Scheme 1d). The construction of the C_{12} stereocenter in a *syn* manner by HADCA could be directed by the neighboring C_{11}-oxygen functionality through α-chelation. The reaction of carbanion intermediate **E** should terminate with C_8−C_9 bond formation to yield a cyclopentanone to access the synthesis of prostaglandins.

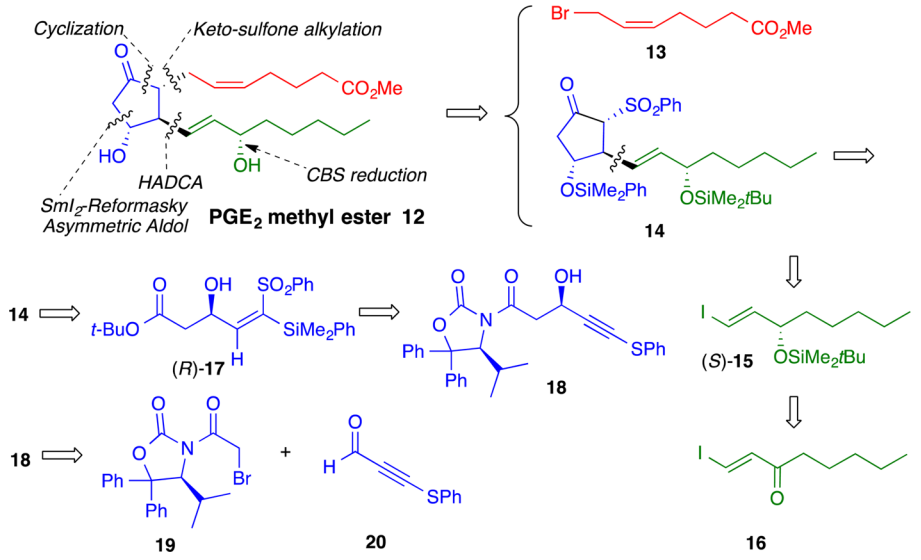
Using HADCA as the central concept of a plan for the asymmetric synthesis of prostaglandin E_2 (PGE_2) methyl ester **12** is shown in Scheme 2. The alkylation of ketosulfone **14** with allylic halide **13** was envisioned to be the last C−C bond-forming event. Cyclopentanone **14** with the correct stereochemistry would be expected to be obtained from alcohol **17** via HADCA of a vinyllithium reagent. The lithium alkoxide generated from the deprotonation of the hydroxyl group of **17** should direct the addition of the vinyllithium derived from **15** through α-chelation control, leading to a *syn*-stereochemistry of **14**. An asymmetric reduction of enone **16** is known to provide optically enriched **15**.[33] Vinylsulfone **17** could be synthesized from thioacetylene **18** via hydrosilylation.[34] An asymmetric Reformatsky-type reaction would generate **18** from oxazolidinone **19** and aldehyde **20**.

■ RESULTS AND DISCUSSION

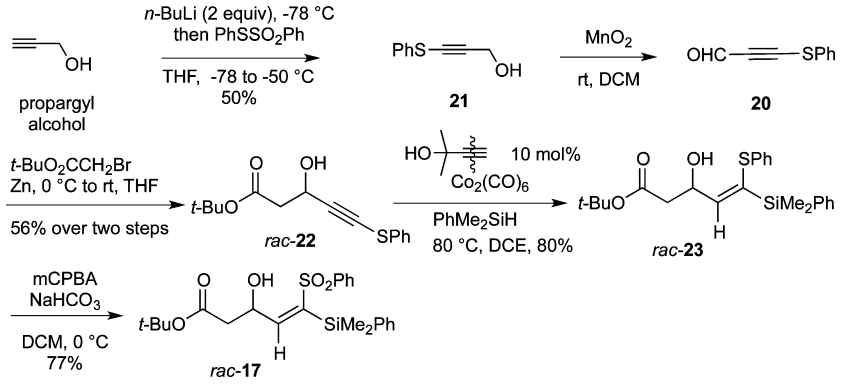
First, to examine the proposed syntheic plan, racemic **17** was prepared in five steps from commercially available propargyl alcohol without any protection steps (Scheme 3). The dianion of propargyl alcohol was generated and trapped with thiosulfonate to provide **21**, and the hydroxyl group of which was oxidized to the corresponding aldehyde. Since aldehyde **20** was not so stable, it was subjected directly to the Reformatsky reaction with *t*-butyl bromoacetate to produce *rac*-**22**. Alkyne *rac*-**22** was converted to vinyl(silyl)sulfide *rac*-**23** in a regio- and stereoselective manner using a dicobalt complex catalyst,[34] and the sulfide was further oxidized to provide the racemic sulfone *rac*-**17** (Scheme 3). The bulky *tert*-butoxycarbonyl group of *rac*-**17** was installed to deter the nucleophile from attacking the carbonyl group as well as discouraging α-deprotonation, which might result in the elimination of the hydroxyl group, but the

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

Scheme 2. Retrosynthesis of Prostaglandin E_2 Methyl Ester (PGE_2) 12



Scheme 3. Synthesis of Racemic *tert*-Butyl C_5-Ester *rac*-17



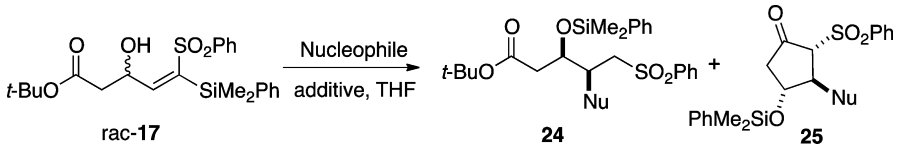
first step is deprotonation of OH so there should not be elimination.

When we examined the HADCA reaction of *rac*-**17**, we observed a significant difference in the reactivity compared with **4**. When MeLi·LiBr was employed as the nucleophile at −78 °C in THF, the reaction with **4** was 95% complete within 10 min (Scheme 1b), whereas the corresponding addition to *rac*-**17** was not incomplete even after 18 h (Table 1, entry 1). Such an enormous difference in reactivity may be attributed to the different chelation structures of the two substrates. The reaction conditions of the HADCA to *rac*-**17** were studied by changing the nucleophiles, salt additives, and temperatures, and the results are summarized in Table 1. Employing of 2.5 equiv of MeLi·LiBr in the reaction with *rac*-**17** at −78 °C provided two products: O-silylated methyl adduct **24a** and cyclization product **25a**, together with unreacted *rac*-**17** (entry 1). The addition of NaBr to the reaction mixture facilitated the cyclization slightly (entry 2). Upon raising the temperature from −78 to −20 °C, only the methyl addition and cyclization product **25a** (Nu = Me) was obtained in 86% yield (entry 3). Using MeMgBr or MeMgCl as nucleophile resulted in no reaction and the recovery of most of *rac*-**17** (entries 4, 5). The use of a vinyllithium reagent, generated from (*E*)-1-iodooct-1-ene and *t*-BuLi at −78 °C, in the presence of 0.25 equiv of NaBr afforded **25b** (Nu = −CH═CHC_6H_{13}) upon warming to −20 °C. After 12 h, some unreacted *rac*-**17** remained, but no **24b** was observed (entry 6). However, the addition of 5 equiv of LiBr and 0.1 equiv NaBr resulted in complete HADCA but with partial cyclization, to give **24b** and **25b** (entry 7). The effect of the addition of LiBr might be to enhance the rate of nucleophilic addition and promote HADCA, whereas the addition of NaBr promoted cyclization. From previous studies of this salt effect,[30,31] the optimum results were obtained with 2.5−5 equiv of LiBr and with 0.25 equiv of NaBr. In the event, the reaction of *rac*-**17** in the presence of 5 equiv of LiBr and 0.25 equiv of NaBr facilitated both HADCA and cyclization to give only **25b** in 82% yield (entry 8). Oct-1-yn-1-yllithium without NaBr as additive (MeLi·LiBr contains ca. 2.5 equiv of LiBr) reacted with *rac*-**17** for 1 h to afford a mixture of **24c**:**25c** in a 3:1 ratio (entry 9). But in the presence of NaBr as additive, a higher ratio (1:1) of cyclization product was observed (entry 10) with otherwise the same conditions. Prolonging the reaction time to 5 h at −20 °C led to complete cyclization giving exclusively **25c** in 84% yield (entry 11).

These studies of the HADCA cyclization prompted us to take on the challenge of accomplishing a one-pot, four-component synthesis (Scheme 5). This strategy required (*Z*)-silylsulfonyl enal **30**, which was synthesized in four steps from propargyl alcohol as shown in Scheme 4. The same dianion generated from propargyl alcohol was trapped with phenyldimethylchlorosilane to give **26**. Silylacetylene **26** was subjected to a hydromagnesiation reaction according to Sato's titanocene-mediated

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

Table 1. Results of HADCA on Silylvinyl-Sulfone *rac*-17

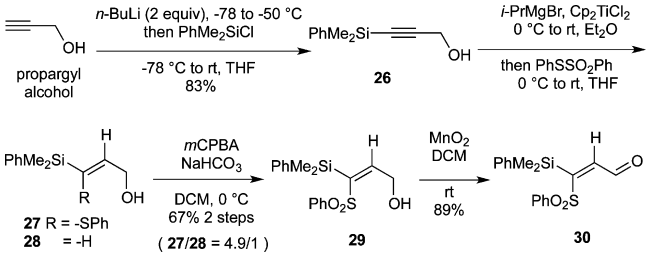


rac-17 24 25

entry	Nucleophile (eq)	additive (eq.)	Temp. (°C)	Time (h)	Products **17 / 24 / 25**	ratio (%)[a] **17 / 24 / 25**	Yield (%)[b] **17 / 24 / 25**
1	MeLi•LiBr (2.5)	---	-78	18	**17 / 24a / 25a**	29 / 55 / 16	-- / -- / --
2	MeLi•LiBr (2.5)	NaBr (0.25)	-78	18	**17 / 24a / 25a**	29 / 38 / 33	-- / -- / --
3	MeLi•LiBr (2.5)	NaBr (0.25)	-78 to -20	5	**25a**	-- / -- / >99	-- / -- / 86
4	MeMgBr(2.5)	---	-78 to -20	20	**17**	>99 / -- / --	75 / -- / --
5	MeMgCl(2.5)	---	-78 to -20	20	**17**	>99 / -- / --	80 / -- / --
6	C_6H_{13}–I (2.5) *t*-BuLi (5eq)	NaBr (0.25)	-78 to -20	12	**17 / --/ 25b**	44 / -- / 56	-- / -- / --
7	C_6H_{13}–I (2.5) *t*-BuLi (5eq)	LiBr (5) NaBr (0.10)	-78 to -20	12	**-- / 24b / 25b**	-- / 43 / 57	-- / -- / --
8	C_6H_{13}–I (2.5) *t*-BuLi (5eq)	LiBr (5) NaBr (0.25)	-78 to -20	12	**-- / -- / 25b**	-- / -- / >99	-- / -- / 82
9	C_6H_{13}–≡–H (2.5) MeLi, LiBr (2.5)	---	-78 to -20	1	**-- / 24c / 25c**	-- / 74 / 26	-- / 44 / 16
10	C_6H_{13}–≡–H (2.5) MeLi, LiBr (2.5)	NaBr (0.25)	-78 to -20	1	**-- / 24c / 25c**	-- / 48 / 52	-- / 32 / 45
11	C_6H_{13}–≡–H (2.5) MeLi, LiBr (2.5)	NaBr (0.25)	-78 to -20	5	**-- / --/ 25c**	-- / -- / >99	-- / -- / 84

[a]Determined by 1H NMR analysis of the crude product. [b]Yield of isolated product after column chromatography.

Scheme 4. Synthesis of Aldehyde 30



protocol[35] and trapped by thiosulfone to afford thioether **27**, along with **28** in a ratio of 4.9:1. Oxidation of the sulfide in the mixture with *m*-CPBA and separation afforded hydroxysulfone **29**, which was oxidized with MnO_2 to afford aldehyde **30** (Scheme 4).

The one-pot assembly of cyclopentanones was implemented as follows: First, lithium enolate **32** was prepared by the deprotonation of *t*-butyl acetate **31** at −78 °C and was treated with aldehyde **30** to give aldol intermediate **A**, which is analogous to the lithium alkoxide of *rac*-**17**. After the addition of MeLi·LiBr and a catalytic amount of NaBr at −78 °C, the reaction temperature was gradually raised to −20 °C to induce HADCA and cyclization. Protonation upon workup afforded **25a** in 57% yield. Similarly, the treatment of aldol intermediate **A** with (*E*)-oct-1-en-1-yllithium, LiBr (3 equiv), and NaBr (0.3 equiv) afforded **25b** in 53% yield. Finally, the use of oct-1-yn-1-yllithium under the same conditions provided **25c** in 58% yield (Scheme 5). In each of these one-pot reactions, three C−C bonds were constructed with excellent stereoselectivity to give the substituted cyclopentanones **25a−c** as single stereoisomers. The structure of **25b** was deduced on the basis of NMR experiments, and **25a** and **25c** were assumed to have the same relative stereochemistry (for details, see SI).

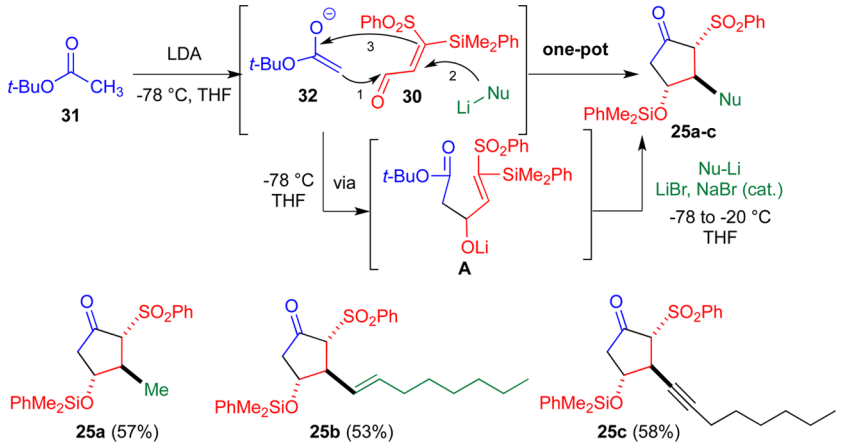
The completion of the synthesis of (±)-15-deoxy PGE_2 **36** from HADCA cyclization product **25b** is shown in Scheme 6. Alkylation of **25b** with allylic bromide **13** in the presence of K_2CO_3 and NaI (cat.) in DMF afforded a diastereomeric mixture of **33**, which was further treated with SmI_2 in mixed THF/MeOH solvent (1:1) at −78 °C to give **34** as a single isomer. It was treated with HF·pyridine in acetonitrile at 0 °C to give (±)-15-deoxy PGE_2 methyl ester **35** in 74% yield. Hydrolysis with PPL in pH 7 buffer afforded (±)-15-dehydroxy PGE_2 **36** in 85% yield. Thus, the overall yield of **36** was 42% from **25b** over four steps.

In order to understand the mechanism of the HADCA reaction of *rac*-**17** with (*E*)-oct-1-en-1-yllithium at −78 °C, the reaction was quenched with D_2O/THF after 1 h at −50 °C. The product mixture contained unreacted *rac*-**17** (20%), *α,α*-di-D-**24b** (30% yield, 93% D-incorporation) and **25b** (20%) (Scheme 7).

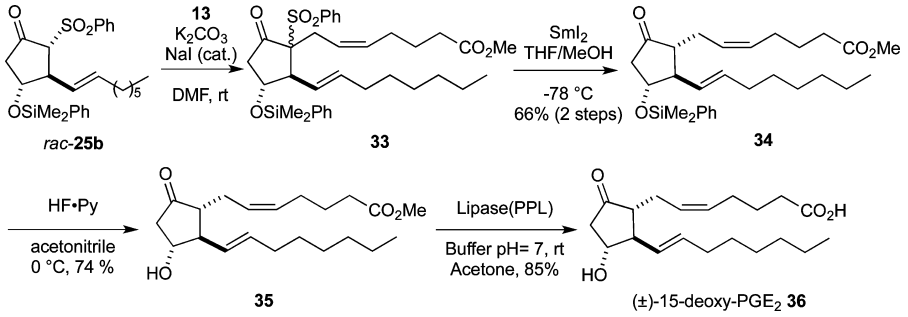
The stereoselective HADCA cyclization reaction and the effects of the salts are explained as follows: The $A^{1,3}$-strain in

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

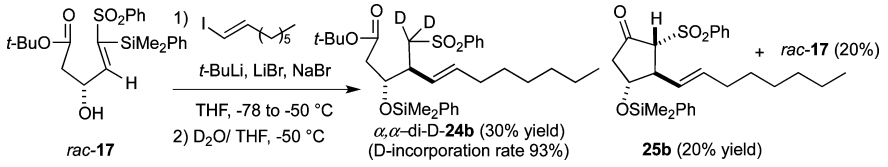
Scheme 5. Three C−C Bond Formations in One-Pot Syntheses of Racemic 25a−c



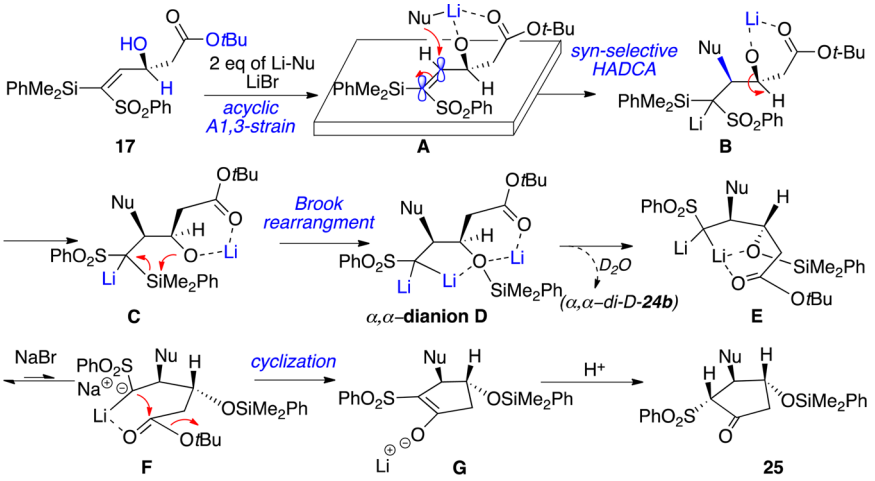
Scheme 6. Racemic Synthesis of 15-Deoxy PGE_2 36



Scheme 7. Deuterium-Labeling Experiments for HADCA Reaction



Scheme 8. A Plausible Reaction Mechanism on Salt Effect to Chelation Controlled HADCA Anion Relay Cyclization[a]

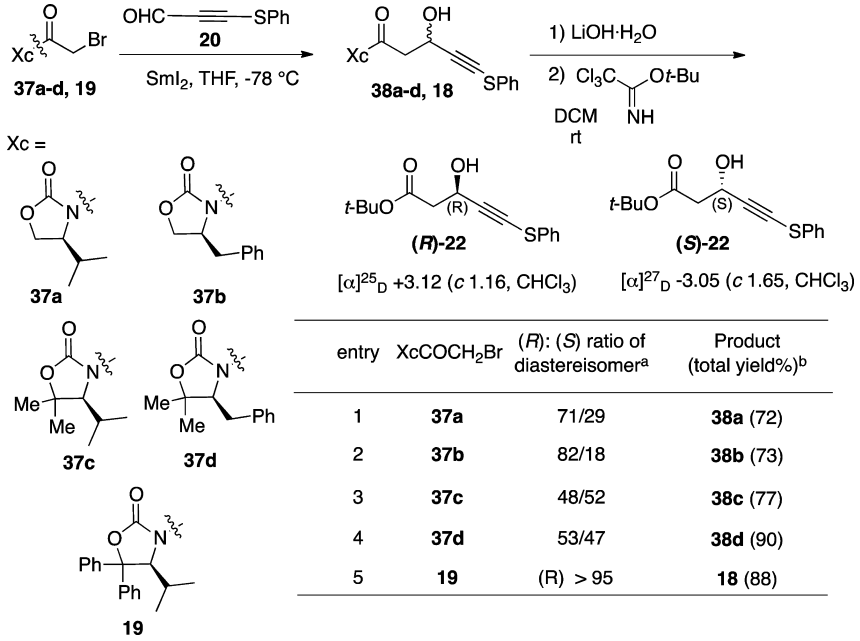


[a]The coordinations between Li and THF (solvent) are not shown.

rac-**17** facilitated high stereocontrol in the HADCA reaction, by chelation of the vinyllithium via the lithium alkoxide, such that the nucleophile added *syn* with respect to the *α*-oxygen (Scheme 8). LiBr, possibly reacting as a Lewis acid, enhanced the rate of conjugate addition to give **B**. **B** must then undergo a conformational change to **C**, in order to proceed with the

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

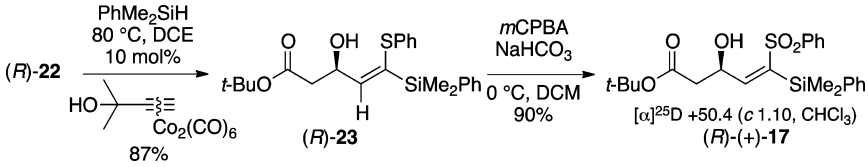
Table 2. Asymmetric Samarium-Reformatsky Reaction of Chiral α-Bromoacetyl-2-oxazolidinones 37a−e with the Aldehyde 20 To Form 38a−e, Leading to Selective Synthesis of (*R*)-Alcohol Ester (*R*)-21



entry	XcCOCH$_2$Br	(*R*): (*S*) ratio of diastereisomer[a]	Product (total yield%)[b]
1	**37a**	71/29	**38a** (72)
2	**37b**	82/18	**38b** (73)
3	**37c**	48/52	**38c** (77)
4	**37d**	53/47	**38d** (90)
5	**19**	(R) > 95	**18** (88)

[a]Ratio was determined by crude 1H NMR spectrum. [b]Yield of isolated product after column chromatrography.

Scheme 9. Synthesis of Chiral Vinylsulfone (*R*)-(+)-17 from (*R*)-22



Brook rearrangement to yield **D**. The α,α-dilithiated state of **D** found support from the deuteration experiments (Scheme 7). Because the rigid Li chelation in **E** could prevent or slow down the subsequent cyclization, the addition of Na^+ (less covalent ion than Li^+) led to metal exchange with Li^+ and promoted cyclization via **F** to give keto−enolate **G**. Work up provided cyclopentanone **25** as a single stereoisomer (Scheme 8). Unfortunately, attempts to induce the alkylation of the side chain in one pot from **G** failed to occur under these conditions.

Next, we approached the asymmetric synthesis of PGE_2 methyl ester **12**. An asymmetric samarium Reformatsky-type reaction was employed to install the C_{11} stereogenic center by using a chiral oxazolidinone and aldehyde **20**. Screening five chiral auxiliaries (Xc in Table 2) as reported by Fukuzawa[36] yielded diastereomeric products of very different ratios as found from the NMR data, summarized in Table 2. In entries 1−4, the chemical yields of the products are good, but the diastereomeric ratios of the products are low. However, in the case of 4-isopropyl-5,5-diphenyl-2-oxazolidine **19**, product **18** was obtained as a single stereoisomer in 88% yield (entry 5). The absolute configuration of **38a** was assigned using the Mosher−Kusumi protocol[37] and further confirmed by converting to the corresponding alcohol, **22**. The *t*-butyl ester derivative was deduced to be (***R***)-**22** based on the positive sign of its optical rotation and (***S***)-**22** when it has a negative rotation. Assignments of the stereochemistries of **38b−d** were based on NMR analysis and by comparison with the optical rotations of **22** (see SI).

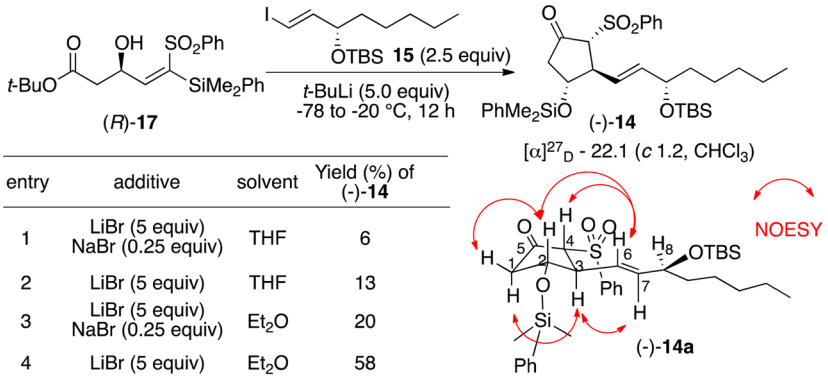
Alkyne (*R*)-**22** was hydrosilylated with phenyldimethylsilane using a cobalt−acetylene complex as a catalyst, to give (*R*)-**23** in high regio- and stereoselectivity. The sulfide was oxidized with *m*-CPBA to the corresponding sulfone (*R*)-(+)-**17** (Scheme 9).

The one-pot HADCA cyclizations of (*R*)-**17** with the vinyllithium derived from iodide (*S*)-**15** are summarized in Table 3. When this reaction was carried out in THF, low yields of (−)-**14** were obtained in the presence of LiBr, whether or not NaBr was an additive (entries 1 and 2). When the less polar Et_2O was employed as the reaction solvent and in the presence of LiBr (5 equiv) and NaBr (0.25 equiv), product (−)-**14** was obtained in 20% yield when the reaction was performed at −78 to −20 °C for 12 h (entry 3). In the absence of NaBr in Et_2O, however, (−)-**14** was obtained in an even higher yield of 58% and with the correct stereochemistry as deduced from the NOE experiments (entry 4). These LiBr-NaBr effects found in Et_2O as solvent were different from their effects on reactions conducted in THF as solvent (e.g., Table 1). Such a difference might be due to the presence of the additional oxygen atom in compound **15**, which could participate in the chelation during the HADCA cyclization reaction.

The (−)-PGE_2 methyl ester **12** was synthesized from (−)-**14** by alkylation with **13** to give **39** as shown in Scheme 10, under conditions similar to those for the preparation of **25b** (Scheme 6). Subsequent desulfonylation with SmI_2 was implemented in a mixed THF/MeOH solvent at −78 °C to give (−)-**40**. Final deprotection of the silyl ether with HF·pyridine in acetonitrile at 0 °C afforded PGE_2 methyl ester **12** in 42% overall yield from

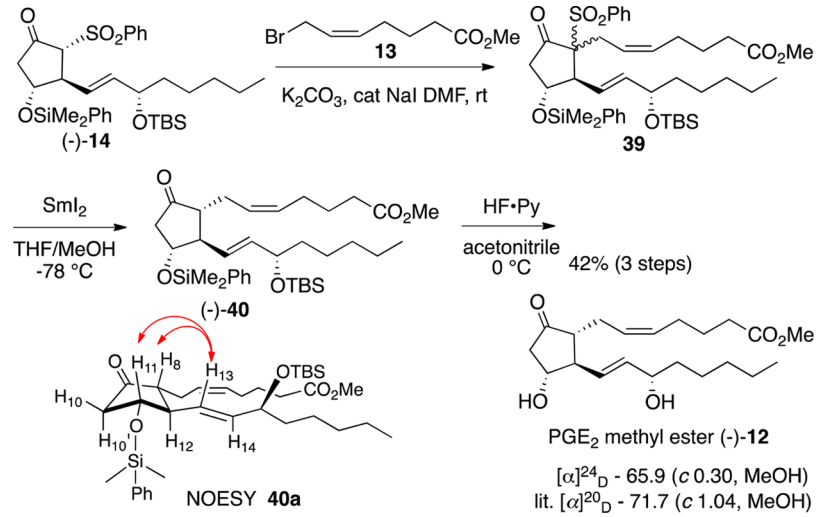
DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

Table 3. Synthesis of (−)-14 Having 15-(*S*)-Hydroxyl Group



entry	additive	solvent	Yield (%) of (-)-**14**
1	LiBr (5 equiv) NaBr (0.25 equiv)	THF	6
2	LiBr (5 equiv)	THF	13
3	LiBr (5 equiv) NaBr (0.25 equiv)	Et_2O	20
4	LiBr (5 equiv)	Et_2O	58

Scheme 10. Synthesis of PGE_2 Methyl Ester (−)-12



(−)-**14**. The stereochemistry was confirmed by NOESY as shown in **40a**, and the specific rotation of PGE_2 methyl ester **12** ($[\alpha]_D^{24}$, 65.9 (*c* 0.30, MeOH)) was in agreement with literature report ($[\alpha]_D^{24}$, 71.7 (*c* 1.04, MeOH)).[20]

CONCLUSION

The asymmetric total synthesis of PGE_2 has been achieved in a one-pot reaction plus three steps. The synthesis starts with the (*R*)-silylvinyl sulfone **17**, through (−)-**14**, to afford (−)-**12** in 4 steps and 24.4% overall yield. The key feature in this synthesis is a highly selective HADCA reaction followed by spontaneous cyclization under substrate control in one-pot reaction. All of the four C−C bond formation processes were successively implemented with high stereoselectivity starting from the four acyclic components. A strictly one-pot synthesis of prostaglandins may be realized along these lines in the future.

EXPERIMENTAL SECTION

General Information. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 400 MHz and a 600 MHz NMR spectrometer. NMR characterization is reported as follows: Chemical shifts are reported as δ values referenced to $CHCl_3$ (7.24), integration, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, br = broad, m = multiplet or unresolved, ABq = AB quartet), coupling constants in Hz, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 100 and 150 MHz spectrometers. Chemical shifts are reported as δ values and referenced to $CHCl_3$ (77.00). High-resolution mass spectra (HRMS) were recorded on a ESI/FT-MS mass spectrometer and reported in *m*/*z*. Infrared (IR) spectra were recorded on a FT-IR spectrometer and reported in wavenumbers (cm^{-1}). Optical rotations were measured on a digital polarimeter. HPLC analysis was carried out with a variable-wavelength detector. All reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Nonaqueous reagents were transferred under argon by syringe. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Reactions were monitored by thin-layer chromatography on 0.25 mm Silica Gel 60 F254 precoated glass plates using UV light to visualize or ammonium molybdate tetrahydrate solution as stain. Silica Gel 60 (particle size 40−63 μm) was used for flash column chromatography. Dry THF was distilled from sodium metal with benzophenone under an N_2 atmosphere. Dry Et_2O and CH_2Cl_2 were distilled from CaH_2 under an N_2 atmosphere. All other commercial reagents were used as received.

3-(Phenylthio)prop-2-yn-1-ol (21). A solution of propargyl alcohol (11.6 mL, 220 mmol) in THF (50 mL) was cooled to −78 °C, to which *n*-BuLi (2.4 M in hexanes, 184 mL, 440 mmol) was added dropwise. After stirring for 1 h at −78 °C, $PhSSO_2Ph$ (45.0 g, 180 mmol) in THF (50 mL) was added dropwise. The reaction was slowly warmed to −50 °C and stirred for 1 h. The reaction mixture was warmed to −20 °C and stirred for another 1 h. The reaction mixture was quenched with an ice-cooled saturated solution of NH_4Cl (500 mL). The aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexane, R_f = 0.20) to provide alcohol **21** (14.8 g, 50%) as a pale yellow oil. **21**: R_f = 0.20 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3342, 3060, 2911, 2855, 1582, 1478, 1441, 1063, 995, 737, 587;^{1}H NMR

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

(400 MHz, $CDCl_3$): δ 2.61 (1H, br), 4.47 (2H, s), 7.19−7.24 (1H, m), 7.29−7.34 (2H, m), 7.40−7.43 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9 (CH2), 7.29 (C), 97.5 (C), 126.5 (CH × 2), 126.8 (CH), 129.3 (CH × 2), 132.3 (C); HRMS (ESI): calcd for $[C_9H_8OS + H]^+$ 165.0369; found 165.0369.

***tert*-Butyl 3-hydroxy-5-(phenylthio)pent-4-ynoate (*rac*-22).** To a solution of alcohol **21** (6123 mg, 37.29 mmol) in DCM (370 mL) was added MnO_2 (64.79 g, 745 mmol) at room temperature. The reaction mixture was stirred for 2 h and filtered. The filtrate was dried over $MgSO_4$ and concentrated in vacuo to obtain the crude aldehyde product **20**. Crude aldehyde **20** was dissolved in THF (37 mL) and used in the next reaction without further purification.

To a suspension of Zn dust (18.28 g, 279.6 mmol) and a catalytic amount of I_2 in THF was added *t*-butyl bromoacetate (10.91 g, 55.93 mmol) over 30 min at room temperature under an argon atmosphere. The reaction mixture was stirred for 30 min at room temperature and then heated under reflux for 1 h. After cooling to 0 °C, aldehyde **20** in THF was added dropwise at 0 °C to the pale green solution. The reaction mixture was stirred at 0 °C for 1 h before pouring into an ice-cooled saturated solution of NH_4Cl (300 mL). The aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to provide alcohol **22** (5.89 g, 56% over two steps) as a colorless oil. **22**: R_f = 0.4 (10% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3435, 3060, 2978, 2931, 2186, 1727, 1583; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s), 2.72−2.74 (2H, m), 3.36 (1H, d, J = 6.8 Hz), 4.88 (1H, ddd, J = 6.8, 6.4, 6.4 Hz), 7.18−7.22 (1H, m), 7.29−7.33 (2H, m), 7.37−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (CH_3 × 3), 42.7 (CH_2), 59.7 (CH), 72.0 (C), 81.9 (C), 98.0 (C), 126.2 (CH × 2), 126.5 (CH), 129.1 (CH × 2), 132.1 (C), 170.5 (C); HRMS (ESI): calcd for $[C_{15}H_{18}O_3S + Na]^+$ 301.0874; found 301.0871.

***tert*-Butyl (*Z*)-5-(Dimethyl(phenyl)silyl)-3-hydroxy-5-(phenylthio)pent-4-enoate (*rac*-23).** The dicobalthexacarbonyl complex of 2-methyl-butyn-2-ol (1.0 M in DCM, 566 mL) was added to a mixture of thiophenylacetylene **22** (1.58 g, 5.67 mmol) and dimethylphenylsilane (855 mg, 6.23 mmol) in dry 1,2-dichloroethane (56 mL). The mixture was heated to 80 °C and stirred for 2 h. After the reaction mixture was cooled to room temperature, the solvent was removed in vacuo. The residue was washed with cold TBAF in water and brine, then purified by chromatography (10% EtOAc/hexane) to afford vinylsilane **23** (188 mg, 80%) as a colorless oil. **23:** R_f = 0.20 (10% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3490, 3069, 2978, 1725, 1590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.21 (3H, s), 0.24 (3H, s), 1.42 (9H, s), 2.44 (1H, d, J = 7.6 Hz), 2.45 (1H, d, J = 4.4 Hz), 3.41 (1H, d, J = 4.4 Hz), 5.13 (1H, dddd, J = 7.6, 6.8, 4.4, 4.4 Hz), 6.47 (1H, d, J = 6.8 Hz), 7.09−7.17 (3H, m), 7.26−7.36 (4H, m), 7.40−7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.6 (CH_3), −2.5 (CH_3), 28.1 (CH_3 × 3), 41.2 (CH_2), 66.9 (CH), 81.6 (C), 126.2 (CH), 127.7 (CH × 2), 128.7 (CH × 2), 129.2 (CH), 129.7 (CH × 2), 133.9 (CH × 2), 134.9 (C), 135.8 (C), 136.9 (C), 152.3 (CH), 171.7 (C); HRMS (ESI): calcd for $[C_{23}H_{30}O_3SSi + Na]^+$ 437.1577; found 437.1578.

***tert*-Butyl (*Z*)-5-(Dimethyl(phenyl)silyl)-3-hydroxy-5-(phenylsulfonyl)pent-4-enoate (*rac*-17).** To a solution of vinylsilane **23** (1.62 g, 3.91 mmol) in DCM (39 mL) at 0 °C were added *m*-CPBA (2.41 g, 9.77 mmol, 70% of purity) and $NaHCO_3$ (1.64 g, 19.54 mmol). The reaction was stirred at 0 °C for 1 h, then quenched with 1 N $Na_2S_2O_3$ (40 mL). The aqueous layer was extracted with DCM (30 mL × 3). The combined organic layers were washed with 1 N $NaHCO_3$ solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexane) to provide alcohol *rac*-**17** (1.34 g, 77%) as a white solid. *rac*-17: Mp: 83−84 °C (recrystallization from EtOAc/hexane); R_f = 0.25 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3490, 3069, 2978, 1725, 1590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.52 (6H, s), 1.41 (9H. s), 2.43 (1H, ABq, d, J = 16.7, 8.0 Hz), 2.51 (1H, ABq, d, J = 16.7, 4.0 Hz), 3.54 (1H, d, J = 4.0 Hz), 5.37 (1H, ddd, J = 8.4, 8.0, 4.0 Hz), 6.46 (1H, d, J = 8.4 Hz), 7.27−7.38(5H, m), 7.42−7.56 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.2 (CH_3), −2.1 (CH_3), 28.0 (CH_3 × 3), 41.1 (CH_2), 65.4 (CH), 81.6 (C), 126.9 (CH × 2), 127.9 (CH × 2), 128.9 (CH × 2), 129.9 (CH), 132.9 (CH), 134.3 (CH × 2), 135.0 (C), 141.9 (C), 145.4 (C), 157.7 (CH), 171.0 (C); HRMS (ESI): calcd for $[C_{23}H_{30}O_5SSi + Na]^+$ 469.1481; found 469.1474.

General procedure for HADCA of various nucleophiles to *rac*-17 (Table 1). *HADCA with MeLi·LiBr.* The *tert*-butyl ester of the vinyl silyl sulfone *rac*-**17** (1 equiv) and NaBr (equiv see Table 1) in THF (0.1 M) were added to the MeLi·LiBr complex (2.21 M in Et_2O, equiv see Table 1) at −78 °C under argon atmosphere. The reaction mixture was stirred at −78 °C or warmed to −20 °C in 1 h and stirred for 4 h at −20 °C as indicated in Table 1. The reaction mixture was poured into ice-cooled saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash column chromatography to provide the **24a** and **25a** as a colorless oil.

*tert-Butyl (3R,4S)-3-((dimethyl(phenyl)silyl)oxy)-4-methyl-5-(phenylsulfonyl)pentanoate (**24a**).* Column chromatography of the mixture (combined entries 1 and 2) afforded small amount of pure **24a** and mixture fraction. **24a**: R_f = 0.60 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2977, 2933, 1731, 1587; ^1H NMR (400 MHz, $CDCl_3$): δ 0.307 (3H, s), 0.313 (3H, s), 1.03 (3H, d, J = 7.2 Hz), 2.16−2.30 (3H, m), 2.73 (1H, dd, J = 13.9, 9.5 Hz), 3.22 (1H, dd, J = 13.9, 3.0), 4.18 (1H, ddd, J = 8.0, 4.8, 4.2 Hz), 7.30−7.38 (3H, m), 7.47−7.54 (4H, m), 7.57−7.62 (1H, m), 7.78−7.80 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.4 (CH_3), −1.3 (CH_3), 14.6 (CH_3), 28.0(CH_3 × 3), 34.1 (CH), 39.7 (CH_2), 58.5 (CH_2), 72.0 (CH), 80.8 (C), 127.79 (CH × 2), 127.80 (CH × 2), 129.7 (CH), 133.1 (CH × 2), 133.44 (CH × 2), 137.6 (C), 140.1 (C), 170.3 (C); HRMS (ESI): calcd for $[C_{24}H_{34}O_5SSi + H]^+$ 463.1969; found 463.1967.

*(2R,3S,4R)-4-((Dimethyl(phenyl)silyl)oxy)-3-methyl-2-(phenylsulfonyl)cyclopentanone (**25a**).* According to the general procedure, *rac*-**17** (130 mg) was converted to **25a** (98 mg) in 86% yield as a colorless oil (entry 3, Table 1). R_f = 0.50 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2929, 2965, 1755, 1586; ^1H NMR (400 MHz, $CDCl_3$): δ 0.370 (3H, s), 0.386 (3H, s), 1.21 (3H, d, J = 6.4 Hz), 2.35−2.37 (2H. m), 2.70−2.80 (1H, m), 3.32 (1H, d, J = 10.4 Hz), 3.68−3.74 (1H, m), 7.33−7.42 (3H, m), 7.50−7.56 (4H, m), 7.64−7.67 (1H, m), 7.83−7.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.7 (CH_3), −1.4 (CH_3), 17.5 (CH_3), 41.9 (CH), 48.4 (CH_2), 73.3 (CH), 75.8 (CH), 128.0 (CH × 2), 129.1 (CH × 2), 129.17 (C), 129.24 (CH × 2), 130.1 (CH), 133.4 (CH × 2), 134.2 (CH), 136.7 (C), 202.2 (C); HRMS (ESI): calcd for $[C_{20}H_{24}O_4SSi + H]^+$ 389.1237; found 389.1241.

HADCA with octen-1-yl Lithium. To a solution of (*E*)-1-iodooct-1-ene were added LiBr, and NaBr (equiv see Table 1) in THF (0.1 M) and *tert*-butyllithium (1.65 M in pentane, equiv see Table 1) at −78 °C over 10 min under argon atmosphere. The reaction mixture was stirred at −78 °C for additional 15 min. (Note: *tert*-butyllithium with THF form a bright yellow complex at −78 °C). The excess *tert*-butyllithium was removed by addition of one or two drops of vinyl iodide to the solution mixture. To this solution was added *tert*-butyl ester of the silylvinyl sulfone *rac*-**17** (1 equiv) in THF (1.0 M). The resulting mixture was warmed to −20 °C in 1 h and stirred for 11 h at −20 °C. The reaction mixture was poured into ice-cooled saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off and concentrated in vacuo. The residue was purified by flash column chromatography to provide **24b** and **25b** as a colorless oil.

*(3R,4S,E)-tert-Butyl-3-((dimethyl(phenyl)silyl)oxy)-4-((phenylsulfonyl)methyl)dodec-5-enoate (**24b**).* Column chromatography of the mixture (entry 7: started from 368 mg *rac*-**17**) afforded small amount of pure **24b** (46 mg) and mixture fraction. **24b**: R_f = 0.50 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2957, 2928, 2856; ^1H NMR (400 MHz, $CDCl_3$): δ 0.35 (3H, s), 0.37 (3H, s), 0.86 (3H, t, J = 6.8 Hz), 1.22−1.26 (8H, m), 1.38 (9H, s), 1.84−1.85 (2H, br), 2.18 (1H, ABq, d, J = 15.5, 7.6 Hz), 2.28 (1H, ABq, d, J = 15.5, 5.6 Hz), 2.65 (1H, m), 2.98 (1H, dd, J = 14.0, 8.8), 3.22 (1H, dd, J = 14.0, 4.0 Hz), 4.19−4.23 (1H, m), 5.05 (1H, ddt, J = 15.2, 8.8, 1.2 Hz), 5.28 (1H, dt, J = 15.2, 6.8 Hz), 7.31−7.39 (3H, m), 7.46−7.53

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

(4H, m), 7.56−7.60 (1H, m), 7.73−7.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.4 (CH_3), −1.2 (CH_3), 14.1(CH_3), 22.6 (CH_2), 28.0 ($CH_3 \times 3$), 28.8 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 40.4 (CH_2), 43.2 (CH), 57.2 (CH_2), 72.0 (CH), 80.7 (C), 125.6 (CH), 127.8 (CH × 2), 128.0 (CH × 2), 129.0 (CH × 2), 129.7 (CH), 133.3 (CH), 133.5 (CH × 2), 135.7(CH), 137.6 (C), 140.0 (C), 170.2 (C); HRMS (ESI): calcd for $[C_{31}H_{46}O_5SSi + Na]^+$ 581.2733; found 581.2731.

*(2R,3S,4R)-4-((Dimethyl(phenyl)silyl)oxy)-3-((E)-oct-1-en-1-yl)-2-(phenylsulfonyl)cyclopentanone (**25b**).* According to the general procedure, ***rac*-17** (248 mg) was converted to **25b** (220 mg) in 82% yield as a colorless oil (entry 8, Table 1). R_f = 0.38 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2956, 2927, 2855, 1756, 1586; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.332 (3H, s), 0.335 (3H, s), 0.88 (3H, t, J = 7.2 Hz), 1.23−1.28 (8H, m), 1.85−1.87 (2H, m), 2.45 (1H, ABq, d, J = 17.1, 6.9 Hz), 2.49 (1H, ABq, d, J = 17.1, 10.1 Hz), 3.21−3.25 (1H, m), 3.53 (1H, d, J = 9.8 Hz), 3.84−3.88 (1H, m), 5.10 (1H, ddt, J = 16.2, 8.4, 1.4 Hz), 5.45 (1H, dtd, J = 16.2, 6.6, 0.6 Hz), 7.33−7.40 (3H, m), 7.48−7.54 (4H, m), 7.61−7.64 (1H, m), 7.82−7.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.5 (CH_3), −1.3 (CH_3), 14.1 (CH_3), 22.6 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 32.4 (CH_2), 48.3 (CH_2), 50.0 (CH), 71.9 (CH), 74.3 (CH), 126.8 (CH), 127.9 (CH × 2), 129.0 (CH × 2), 129.1 (CH x2), 130.0 (CH), 133.5 (CH × 2), 134.0 (CH), 135.2 (CH), 136.8 (C), 138.2 (C), 201.7 (C); HRMS (ESI): calcd for $[C_{27}H_{36}O_4SSi + Na]^+$ 507.2001, found 507.1998.

HADCA with octyn-1-yl Lithium. To a mixture of oct-1-yne and NaBr (equiv see Table 1) in THF (0.1 M) was added MeLi·LiBr complex (2.21 M in Et_2O, equiv see Table 1) at −78 °C under argon atmosphere. This mixture was stirred at −78 °C for 1 h. To this solution was added *tert*-butyl ester of the silylvinyl sulfone ***rac*-17** (1 equiv) in THF (1.0 M). The resulting mixture was warmed to −20 °C in 1 h and stirred for additional 4 h at −20 °C. The reaction mixture was poured into ice-cooled saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash chromatography to provide the **24c** and **25c** as a colorless oil.

*tert-Butyl (3R,4S)-3-((dimethyl(phenyl)silyl)oxy)-4-((phenylsulfonyl)methyl)dodec-5-ynoate (**24c**).* According to the general procedure, ***rac*-17** (46 mg) was converted to **24c** (25 mg) in 44% yield and **25c** (8 mg, 16%) (entry 9, Table 1). **24c**: R_f = 0.63 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2957, 2931, 2858, 1731, 1587; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.357 (3H, s), 0.364 (3H, s), 0.86 (3H, t, J = 6.8 Hz), 1.18−1.30 (8H, m), 1.38 (9H, s), 1.84−1.88 (2H, m), 2.23 (1H, dd, J = 15.6, 8.8 Hz), 2.59 (1H, dd, J = 15.6, 3.6 Hz), 2.98−3.03 (1H, m), 3.08 (1H, dd, J = 13.6, 10.0 Hz), 3.40 (1H, dd, J = 13.6, 10.0 Hz), 4.33 (1H, ddd, J = 8.8, 3.6, 3.6 Hz), 7.32−7.38 (3H, m), 7.47−7.55 (4H, m), 7.57−7.61 (1H, m), 7.83−7.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.27 (CH_3), −1.22 (CH_3), 14.0 (CH_3), 18.6 (CH_2), 22.5 (CH_2), 28.1 ($CH_3 \times 3$), 28.4 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 33.5 (CH), 39.9 (CH_2), 56.2 (CH_2), 70.6 (CH), 76.2 (C), 80.8 (C), 85.9 (C), 127.9 (CH × 2), 128.4 (CH × 2), 129.0 (CH × 2), 129.7 (CH), 13.47 (CH), 133.52 (CH × 2), 137.4 (C), 139.8 (C), 170.3 (C); HRMS (ESI): calcd for $[C_{31}H_{44}O_5SSi + Na]^+$ 579.2570, found 579.2571.

*(2R,3S,4R)-4-((Dimethyl(phenyl)silyl)oxy)-3-(oct-1-yn-1-yl)-2-(phenylsulfonyl)cyclopentanone (**25c**).* According to the general procedure, ***rac*-17** (73 mg) was converted to **25c** (66 mg) in 84% yield (entry 11, Table 1). R_f = 0.50 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3068, 2930, 2857, 1762, 1586; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.39 (3H, s), 0.42 (3H, s), 0.88 (3H, t, J = 7.2 Hz), 1.18−1.39 (8H, m), 1.95 (2H, td, J = 6.8, 2.0 Hz), 2.46−2.49 (2H, m), 3.47 (1H, ddt, J = 9.6, 7.6, 2.0 Hz), 3.74 (1H, d, J = 9.6 Hz), 4.12 (1H, ddd, J = 9.2, 7.6, 7.6 Hz), 7.33−7.41 (3H, m), 7.52−7.56 (4H, m), 7.62−7.67 (1H, m), 7.88−7.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.6 (CH_3), −1.2 (CH_3), 14.1 (CH_3), 18.6 (CH_2), 22.5 (CH_2), 28.46 (CH_2), 28.54 (CH_2), 31.3 (CH_2), 39.5 (CH), 48.0 (CH_2), 72.9 (CH), 75.2 (CH), 77.4 (C), 84.2 (C), 127.9 (CH_2), 129.1 (CH × 2), 129.2 (CH × 2), 130.0 (CH), 133.5 (CH × 2), 134.2 (CH), 136.7 (C), 138.2 (C), 200.7 (C); HRMS (ESI): calcd for $[C_{27}H_{34}O_4SSi + Na]^+$ 505.1839; found 505.1839.

***(Z)*-3-(Dimethyl(phenyl)silyl)-3-(phenylsulfonyl)prop-2-en-1-ol (29).** Alkyne **26** was prepared from progargyl alcohol according to the literature.[38] To Cp_2TiCl_2 (2.40 g, 9.64 mmol) in dry Et_2O (50 mL) was added *i*PrMgBr (2.46 M in Et_2O, 89.0 mL, 218.0 mmol) at 0 °C, and this suspension was stirred for 15 min. The silylacetylene **26** (16.58 g, 87.12 mmol) in Et_2O (87 mL) was added via cannula at 0 °C and then warmed to room temperature with stirring for 6 h. After cooling to 0 °C, $PhSSO_2Ph$ (28.53 g, 130.7 mmol) in THF (70 mL) was added into the reaction mixture in dropwise. This mixture was then heated to reflux for 5 h before pouring into ice-cooled saturated solution of NH_4Cl (500 mL). The aqueous layer was extracted with Et_2O (200 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc/hexane) to provide the inseparable silylvinyl phenyl sulfide **27** and vinylsilane **28** in 20.0 g (ratio **27**/**28** = 4.9/1). The silylvinyl sulfide mixture in DCM (650 mL) was added to *m*-CPBA (41.0 g, 166 mmol, 70% of purity) and $NaHCO_3$ (2.80 g, 333 mmol) at 0 °C and then warmed to room temperature with stirring for 1 h. The reaction mixture was quenched with 1 N $Na_2S_2O_3$ (600 mL). The aqueous layer was extracted with DCM (200 mL × 3). The combined organic layer was washed 1 N $NaHCO_3$ solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexane) to provide the alcohol **29** (1.93 g, 67%) as a pale yellow solid. **29**: Mp: 82−83 °C (recrystallization from EtOAc/hexane); R_f = 0.25 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3501, 3069, 3002, 2958, 2902, 1589; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55 (6H, s), 4.57 (2H, d, J = 4.8 Hz), 6.62 (1H, t, J = 4.8 Hz), 7.30−7.38 (5H, m), 7.46−7.53 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.2 ($CH_3 \times 2$), 60.7 (CH_2), 126.9 (CH x2), 127.9 (CH × 2), 128.8 (CH × 2), 129.7 (CH), 132.9 (CH), 134.4 (CH), 135.1 (C), 141.7 (C), 144.9 (C), 158.8 (CH); HRMS (ESI): calcd for $[C_{17}H_{20}O_3SSi + Na]^+$ 355.0795; found 355.0797.

***(Z)*-3-(Dimethyl(phenyl)silyl)-3-(phenylsulfonyl)-acrylaldehyde (30).** To a solution of alcohol **29** (1.022 g, 3.075 mmol) in DCM (30 mL) was added MnO_2 (2.672 g, 30.70 mmol) at room temperature. The reaction mixture was stirred for 2 h and filtered. The filtrates were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexane) to yield aldehyde **30** (904 mg, 89%) as a yellow color oil, which was unstable. We used it immediately after spectra measurements. **29**: R_f = 0.35 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3070, 3002, 2959, 2901, 1684, 1583;^{1}H NMR (400 MHz, $CDCl_3$): δ 0.56 (6H, s), 6.41 (1H, d, J = 6.0 Hz), 7.29−7.33 (2H, m), 7.35−7.41 (6H, m), 7.52−7.54 (2H, m), 10.61 (1H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.6 ($CH_3 \times 2$), 127.3 (CH × 2), 128.2 (CH × 2), 129.2 (CH × 2), 130.2 (CH), 133.5 (CH), 134.3 (CH × 2), 140.8 (C), 146.6 (CH), 160.00 (C), 160.02 (C), 190.9 (CH); HRMS (ESI): calcd for $[C_{17}H_{18}O_3SSi + Na]^+$ 353.0638; found 353.0635.

Three-Components in One-Pot Reaction: Aldol/HADCA/Cyclization (Scheme 5). *Aldol/HADCA/Cyclization with MeLi·LiBr.* To a solution of diisopropylamine (59 mg, 0.581 mmol), NaBr (12 mg, 0.121 mmol) in THF (5.0 mL) at 0 °C was added *n*-BuLi (2.45 M in hexanes, 0.237 mL, 0.581 mmol) under an argon atmosphere and stirred for 15 min. Then the solution was cooled to −78 °C and was mixed with *tert*-butyl acetate **31** (62 mg, 0.53 mmol) in THF (0.5 mL), and this mixture was stirred at −78 °C for 1 h. The resulting solution of the enolate of *tert*-butyl acetate was added dropwise in a solution of aldehyde **30** (160 mg, 0.484 mmol) in THF (0.5 mL) with stirring in 30 min at −78 °C. To this mixture was further added (dropwise) the MeLi·LiBr solution (2.21 M in Et_2O, 0.438 mL, 0.968 mmol). The reaction mixture was kept at −20 °C in 1 h with stirring for 4 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (50 mL) solution, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to obtain cyclopentanone **25a** (107 mg, 57%) as a colorless oil.

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

Aldol/HADCA/Cyclization with octen-1-yl Lithium. To a solution of diisopropylamine (59 mg, 0.58 mmol), LiBr (210 mg, 2.42 mmol), NaBr (12 mg, 0.12 mmol) in THF (5.0 mL) was added *n*-BuLi (2.45 M in hexanes, 0.238, 0.581 mmol) at 0 °C under argon atmosphere with stirring for 15 min. The solution was cooled to −78 °C, and then *tert*-butyl acetate **31** (62 mg, 0.53 mmol) in THF (0.5 mL) was added dropwise with stirring at −78 °C for 1 h. To the mixture of LDA and *tert*-butyl acetate was added a solution of aldehyde **30** (150 mg, 0.484 mmol) in THF (0.5 mL) dropwise, and this mixture **A** was stirred for 30 min at −78 °C. In a separate vessel, a solution of vinyl iodide (230 mg, 0.968 mmol) in THF (5.0 mL) was mixed with *tert*-butyl lithium (1.65 M in pentane, 1.17 mL, 1.94 mmol) at −78 °C over 10 min under argon atmosphere. This reaction mixture was stirred at −78 °C for an additional 15 min, and the resulting vinyl lithium was added into the mixture **A** containing LDA/*tert*-butyl acetate/aldehyde via a cannula. The resulting mixture was gradually warmed to −20 °C in 1 h and stirred for 11 h at −20 °C. The reaction mixture was poured into ice-cooled saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash column chromatography to provide the cyclopentanone **25b** (125 mg, 53%) as a colorless oil.

Aldol/HADCA/Cyclization with octyn-1-yl Lithium. To a mixture of diisopropylamine (59 mg, 2.45 mmol) and NaBr (12 mg, 0.121 mmol) in THF (5.0 mL) was added *n*-BuLi (2.45 M in hexanes, 0.238 mL, 0.581 mmol) at 0 °C under argon atmosphere with stirring for 15 min. The solution was cooled to −78 °C, to which was added *tert*-butyl acetate **31** (62 mg, 0.532 mmol) in THF (0.5 mL) dropwise with stirring at −78 °C for 1 h. To this solution (LDA/*tert*-butyl acetate) was added a solution of aldehyde **30** (160 mg, 0.484 mmol) in THF (0.5 mL) dropwise, and the stirring was continued for 30 min at −78 °C to name as solution **A**. A mixture of octyne (107 mg, 0.968 mmol) in THF and MeLi·LiBr complex (2.21 M in Et_2O, 0.438 mL, 0.968 mmol) was kept at −78 °C for 1 h under argon atmosphere. This mixture (lithium acetylide solution) was added to the solution **A** of LDA/*tert*-butyl acetate/aldehyde via a cannula. The resulting mixture was warmed to −20 °C in 1 h and stirred for additional 4 h at −20 °C. The reaction mixture was poured into ice-cooled saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to obtain the cyclopentanone **25c** (135 mg, 58%) as a colorless oil.

(±)-15-Dehydroxy-PGE$_2$ Methyl Ester (35) (Scheme 6). To a solution of **25b** (102 mg, 0.211 mmol) and **13** (103 mg, 0.467 mmol) in DMF (2.1 mL) were added K_2CO_3 (17 mg, 0.127 mol) and NaI (3 mg, 0.021 mol) successively. The reaction mixture was stirred at room temperature for 40 min before pouring into H_2O (20 mL) and extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude allylation product was obtained (**33**), which was used for next step without further purification.

A solution of allylation crude product **33** in a mixture of MeOH (90 μL) and dry THF (0.9 mL) was added a solution of SmI_2 (0.1 M in THF, 10.0 mL) dropwise at −78 °C. The resulting solution was stirred for 15 min at −78 °C, during which time the deep blue color of the solution faded. The solution was quenched with saturated solution of NH_4Cl (10 mL), and the aqueous phase was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient elution by 5−15% EtOAc/hexane, 10% EtOAc/hexane, R_f = 0.5) to yield **34** (67 mg, 66% in two steps) as a colorless oil.

To a solution of **34** (67 mg, 0.138 mmol) in THF (2.0 mL) was added 70% hydrogen fluoride−pyridine complex (22 μL) at 0 °C. The mixture was stirred at 0 °C for 1 h before pouring into saturated aqueous $NaHCO_3$ (10 mL). The aqueous mixture was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography and eluted by 20% EtOAc/hexane to provide 15-deoxy-PGE$_2$ methyl ester **35** (36 mg, 74%) as a colorless oil. R_f = 0.13 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3463, 2926, 2954, 2855, 1741, 1458, 1244, 1158, 1078, 967; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 6.8 Hz), 1.23−1.37 (8H, m), 1.61−1.69 (3H, m), 2.00−2.09 (5H, m), 2.17 (1H, dd, J = 18.4, 9.6 Hz), 2.26−2.37 (5H, m), 2.71 (1H, dd, J = 18.4, 7.2 Hz), 3.64 (3H, s), 4.00−4.06 (1H, m), 5.26−5.41 (3H, m), 5.62 (1H, dt, J = 15.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 24.7 (CH_2), 24.9 (CH_2), 26.6 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 32.6 (CH_2), 33.4 (CH_2), 46.2 (CH_2), 51.5 (CH_3), 53.8 (CH), 54.6 (CH), 72.3 (CH), 126.6 (CH), 129.0 (CH), 130.8 (CH), 135.3 (CH), 174.1 (C), 214.5 (C); HRMS (ESI): calcd for $[C_{21}H_{34}O_4 + Na]^+$ 373.2355; found 373.2353.

(±)-15-Dehydroxy-PGE$_2$ (36). To a solution of the methyl ester **35** (21 mg, 0.060 mmol) in acetone (1.0 mL), was added porcine pancreatic lipase (PPL, EC 3.1.13, 179 mg) and phosphate buffer solution (NaH_2PO_4/Na_2HPO_4, 6 mL, pH 7) at room temperature. After stirring at room temperature for 11 h, the mixture was diluted with EtOAc (30 mL) and then acidified to pH 5 with 0.1 N HCl. The mixture was further stirred with saturated $(NH_4)_2SO_4$ solution, and the product was extracted with EtOAc (30 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient elution; 50−70% EtOAc/hexane) to provide the 15-deoxy-PGE$_2$ **36** (17 mg, 85%) as a colorless oil. **36**: R_f = 0.25 (60% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3625−2661 (br), 3422, 3010, 2955, 2926, 2855, 1710, 1456, 1242,1158,1076, 966, 724; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.2 Hz), 1.23−1.37 (8H, m), 1.66 (2H, pent, J = 7.2 Hz), 2.01−2.09 (5H, m), 2.17 (1H, dd, J = 18.4, 9.4 Hz), 2.26−2.37 (5H, m), 2.71 (1H, dd, J = 18.4, 7.2 Hz), 4.00−4.60 (1H, m), 5.26−5.41 (3H, m), 5.63 (1H, dt, J = 15.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 24.4 (CH_2), 24.9 (CH_2), 26.5 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 32.6 (CH^2), 33.3 (CH_2), 46.1 (CH_2), 53.8 (CH), 54.6 (CH), 72.3 (CH), 126.7 (CH), 128.9 (CH), 130.6 (CH), 135.4 (CH), 178.9 (C), 214.6 (C); HRMS (ESI): calcd for $[C_{20}H_{32}O_4 + Na]^+$ 359.2193; found 359.2191.

Deuterium Labeling Experiment for HADCA Reaction (Scheme 7). To a mixture of *E*-octen-1-yl-1-iodide (107 mg, 0.448 mmol), LiBr (78 mg, 0.895 mmol), and NaBr (5 mg, 0.045 mmol) in THF (4.5 mL) was added *tert*-butyl lithium (1.72 M in pentane, 520 mL, 0.895 mmol) at −78 °C over 10 min under argon atmosphere. The reaction mixture was stirred for at −78 °C for another 15 min. (Note: *tert*-butyl lithium with THF forms a bright yellow complex at −78 °C). The excess *tert*-butyl lithium was removed by addition of one or two drops of vinyl iodide to the reaction mixture. To this solution was added *tert*-butyl ester of silylvinyl sulfone *rac*-**17** (80 mg, 0.179 mmol) in THF (1.5 mL). The resulting mixture was warmed to −50 °C in 0.5 h and stirred for 2 h at −50 °C. The reaction mixture was quenched with D_2O (0.5 mL in THF 4 mL) at −50 °C and stirred for 15 min. The reaction mixture was poured into ice-cooled saturated solution of NH_4Cl (30 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (gradient elution; 8% to 20% EtOAc/hexane) provided the *tert*-butyl silylvinyl sulfone ***rac*-17** (16 mg, 30%), cyclopentanone **25b** (17 mg, 20%) and ***α,α*-diD-24b**. (30 mg, 30%) as a colorless oil. Compound ***α,α*-di-D-24b**: R_f = 0.50 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3069, 2975, 2927, 2855, 1730, 1587; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.35 (3H, s), 0.37 (3H, s), 0.86 (3H, t, J = 6.8 Hz), 1.22-.126 (9H, m), 1.38 (9H, s), 1.846−1.853 (2H, m), 2.18 (1H, ABq, d, J = 15.4, 7.6 Hz), 2.28 (1H, ABq, d, J = 15.4, 5.6 Hz), 2.64 (1H, dd, J = 8.8, 3.6 Hz), 2.97 (0.07H, d, J = 9.2 Hz), 3.20 (0.07H, d, J = 4.0 Hz), 4.19−4.23 (1H, m), 5.05 (1H, ddt, J = 15.2, 8.8, 1.2 Hz), 5.28 (1H, dt, J = 15.2, 6.4 Hz), 7.31−7.37 (3H, m), 7.46−7.53 (4H, m), 7.56−7.60 (1H, m), 7.73−7.76 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.4 (CH_3), −1.2 (CH_3), 14.1 (CH_3), 22.6 (CH_2 × 2), 28.1 (CH_3 × 3), 28.8 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 32.5 (CH_2), 40.4 (CH_2), 43.1 (CH), 71.9 (CH), 80.7 (C),

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

125.6 (CH), 127.8(CH × 2), 128.1 (CH × 2), 129.0 (CH × 2), 129.7 (CH), 133.3 (CH), 133.5 (CH × 2), 135.7 (CH), 137.6 (C), 140.0 (C), 170.2 (C); HRMS (ESI): calcd for $[C_{31}H_{44}D_2O_5SSi + Na]^+$ 583.2856; found 583.2853.

General Procedure for Samarium(II) Iodide-Mediated Reformatsky-Type Reaction (Table 2). The starting materials **37a**, **37b**, **37c**, **37d**, and **19** were prepared according to literature.[36,39−42] The following description provides a typical experimental procedure for the Reformatsky-type reaction of a chiral 3-bromoacetyl-2-oxazolidinone (**37a−d** and **19**) using **19** with aldehyde **20** as an example.

To a solution of alcohol **21** (704 mg, 4.29 mmol) in DCM (42 mL, was added MnO_2 (2.80 g, 32.2 mmol) at room temperature. The reaction mixture was stirred for 2 h and filtered. The filtrates were dried over $MgSO_4$ and concentrated in vacuo to obtain the crude aldehyde product **20**. Since this aldehyde is rather unstable, it is recommended to go successively to the next step.

Under the argon atmosphere, samarium powder (1.21 mg, 8.04 mmol) in THF (11 mL) was placed in an Schlenk tube equipped with a magnetic stirring bar. To this solution was added diiodomethane (1.44 g, 5.36 mmol). The mixture was stirred for 2 h at room temperature, and SmI_2 solution was obtained as a deep blue solution. The Schlenk tube was cooled to −78 °C, and a mixture of aldehyde **20** and chiral 3-bromoacetyl-2-oxazolidinone **19** (863 mg, 2.15 mmol) in dry THF (8.0 mL) was injected over a period of 10 min. The resulting solution was stirred at −78 °C for 0.5 h, during which time the deep green color of the solution faded. The reaction was quenched by addition of 25 mL of saturated solution of NH_4Cl, and the aqueous phase was extracted with three 20 mL portions of diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to provide the alcohol **18** (911 mg, 88%) as a colorless oil.

(S)-3-((R)-3-Hydroxy-5-(phenylthio)pent-4-ynoyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one ((R)-18). R_f = 0.13 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3470, 3060, 2966, 1784, 1703, 1582, 1530; ^1H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 7.2 Hz), 1.97 (1H, qqd, J = 7.2, 6.8, 3.2 Hz), 3.08 (1H, d, J = 6.8 Hz), 3.26 (1H, ABq, d, J = 17.5, 7.2 Hz), 3.43 (1H, ABq, d, J = 17.5, 4.0 Hz), 5.00 (1H, ddd, J = 7.2, 6.8, 4.0 Hz), 5.38 (1H, d, J = 3.2 Hz), 7.19−7.23 (1H, m), 7.25−7.46 (14H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (CH_3), 21.7 (CH_3), 29.8 (CH), 42.7 (CH_2), 59.5 (CH), 64.5 (CH), 72.3 (C), 89.8 (C), 97.8 (C), 125.5 (CH × 2), 125.8 (CH × 2), 126.2 (CH × 2), 126.5 (CH), 128.0 (CH), 128.3 (CH × 2), 128.7 (CH), 128.9 (CH × 2), 129.2 (CH × 2), 132.1 (C), 137.8 (C), 141.8 (C), 152.8 (C), 170.5 (C); HRMS (ESI): calcd for $[C_{29}H_{27}O_4NS + Na]^+$ 508.1553; found 508.1553. $[\alpha]_D^{26}$ −122.9° (c 0.75, $CHCl_3$).

(S)-3-((R)-3-Hydroxy-5-(phenylthio)pent-4-ynoyl)-4-isopropyloxazolidin-2-one ((R)-38a) and (S)-3-((S)-3-Hydroxy-5-(phenylthio)-pent-4-ynoyl)-4-isopropyloxazolidin-2-one ((S)-38a). (R)-/(S)-38a. According to the general procedure, **37a** (202 mg) was converted to (***R***)-/(***S***)-**38a** (194 mg) in 72% yield as a colorless oil (entry 1, Table 2). Column chromatography afforded pure diastereomer fraction of (***R***)-**38a** (82 mg) and (***S***)-**38a** (28 mg) and unseparable mixture (84 mg) . (***R***)-**38a**: R_f = 0.20 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3474, 3059, 2964, 2928, 2876, 1781, 1701, 1582; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, d, J = 6.0 Hz), 0.90 (3H, d, J = 6.8 Hz), 2.32−2.40 (1H, m), 3.20 (1H, d, J = 6.0 Hz), 3.39 (1H, ABq, d, J = 17.6, 4.0 Hz), 3.52 (1H, ABq, d, J = 17.6, 7.6 Hz), 4.21 (1H, ABq, d, J = 8.8, 3.2, Hz), 4.26 (1H, ABq, d, J = 8.8, 8.8 Hz), 4.43 (1H, ddd, J = 8.8, 4.0, 3.2 Hz), 5.05 (1H, ddd, J = 7.6, 6.0, 4.0 Hz), 7.18−7.22 (1H, m), 7.29−7.33 (2H, m), 7.38−7.41 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (CH_3), 17.8 (CH_3), 28.4 (CH), 42.8 (CH_2), 58.4 (CH), 59.4 (CH), 63.7 (CH_2), 72.3 (C), 97.9 (CH), 126.3 (CH × 2), 126.6 (CH), 129.2 (CH × 2), 132.1 (C), 153.9 (C), 170.6 (C); HRMS (ESI): calcd for $[C_{17}H_{19}NO_4S + Na]^+$ 356.0927; found 356.0928; $[\alpha]_D^{24}$ +63.2°(c 1.80, $CHCl_3$). (***S***)-**38a:** R_f = 0.28 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3457, 3061, 2964, 2928, 2876, 1780, 1697; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (3H, d, J = 7.0 Hz), 0.88 (3H, d, J = 7.0 Hz), 2.31−2.39 (1H, m), 3.28 (1H, dd, J = 17.4, 4.2 Hz), 3.62 (1H, dd, J = 17.4, 7.4 Hz), 4.20 (1H, ABq, d, J = 9.2, 3.2 Hz), 4.26 (1H, ABq, d, J = 9.2, 9.2 Hz), 4.43 (1H, ddd, J = 9.2, 3.6, 3.2 Hz), 5.01 (1H, dd, J = 7.4, 4.2 Hz), 7.18−7.21 (1H, m), 7.28−7.32 (2H, m), 7.37−7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (CH_3), 17.8 (CH_3), 28.4 (CH), 42.8 (CH), 58.4 (CH), 59.6 (CH), 63.7 (CH_2), 72.4 (C), 97.9 (C), 126.3 (CH × 2), 126.6 (CH), 129.2 (CH × 2), 132.1 (C), 153.9 (C), 170.8 (C); HRMS (ESI): calcd for $[C_{17}H_{19}NO_4S + Na]^+$ 356.0927; found 356.0927; $[\alpha]_D^{24}$ +38.1° (c 1.20, $CHCl_3$).

(S)-4-Benzyl-3-((R)-3-hydroxy-5-(phenylthio)pent-4-ynoyl)-oxazolidin-2-one ((R)-38b) and (S)-4-Benzyl-3-((S)-3-hydroxy-5-(phenylthio)pent-4-ynoyl)oxazolidin-2-one ((S)-38b). ((R)-/(S)-38b). According to the general procedure, **37b** (223 mg) was converted to (***R***)-/(***S***)-**38b** (208 mg) in 73% yield as a colorless oil (entry 2, Table 2). Column chromatography afforded pure diastereomer fraction of (***R***)-**38b** (117 mg) and (***S***)-**38b** (26 mg) and unseparable mixture (65 mg). (***R***)-**38b**: R_f = 0.15 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3460, 2922, 1781, 1582; ^1H NMR (400 MHz, $CDCl_3$): δ 2.78 (1H, dd, J = 13.2, 9.6 Hz), 3.28 (1H, dd, J = 13.2, 3.2 Hz), 3.40 (1H, ABq, d, J = 17.6, 4.0 Hz), 3.54 (1H, ABq, d, J = 17.6, 7.2 Hz), 4.15−4.22 (2H, m), 4.68 (1H, dddd, J = 9.6, 6.8, 3.6, 3.2 Hz), 5.09 (1H, br), 7.17−7.21 (3H, m), 7.26−7.34 (5H, m), 7.38−7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.7 (CH_2), 42.9 (CH_2), 55.0 (CH), 59.3 (CH), 66.4 (CH_2), 72.5 (C), 97.9 (C), 126.3 (CH × 2), 126.6 (CH), 127.4 (CH), 128.9 (CH × 2), 129.2 (CH × 2), 129.3 (CH × 2), 132.0 (C), 134.9 (C), 153.2 (C), 170.6 (C); HRMS (ESI): calcd for $[C_{21}H_{19}NO_4S + Na]^+$ 404.0927; found 404.0929; $[\alpha]_D^{27}$ +49.9° (c 0.90, $CHCl_3$). (***S***)-**38b**: R_f = 0.20 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3464, 3060, 3027, 2923, 2354, 1781, 1698; ^1H NMR (400 MHz, $CDCl_3$): δ 2.77 (1H, dd, J = 13.2, 9.6 Hz), 3.26 (1H, dd, J = 13.2, 3.2 Hz), 3.32 (1H, dd, J = 17.6, 4.4, Hz), 3.63 (1H, dd, J = 17.6, 7.2), 4.16 (1H, ABq, d, J = 9.2, 3.2 Hz), 4.21 (1H, ABq, d, J = 9.2, 8.8, Hz), 4.66−4.72 (1H, m), 5.06 (1H, br), 7.16−7.23 (3H, m), 7.25−7.33 (5H, m), 7.40−7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.7 (CH_2), 42.8 (CH_2), 55.0 (CH), 59.5 (CH), 66.4 (CH_2), 72.6 (C), 97.8 (C), 126.4 (CH × 2), 126.7 (CH), 127.4 (CH), 129.0 (CH), 129.2 (CH), 129.4 (CH), 132.0 (C), 134.8 (C), 153.3 (C), 170.8 (C); HRMS (ESI): calcd for $[C_{21}H_{19}NO_4S + Na]^+$ 404.0927; found 404.0927; $[\alpha]_D^{26}$ +28.8° (c 1.0, $CHCl_3$).

(S)-3-((R)-3-Hydroxy-5-(phenylthio)pent-4-ynoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one ((R)-38c) and (S)-3-((S)-3-Hydroxy-5-(phenylthio)pent-4-ynoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one ((S)-38c). ((R)-/(S)-38c). According to the general procedure, **37c** (225 mg) was converted to (***R***)-/(***S***)-**38c** (226 mg) in 77% yield as a colorless oil (entry 3, Table 2). Column chromatography afforded pure diastereomer fraction of (***R***)-**38c** (75 mg) and (***S***)-**38c** (89 mg) and unseparable mixture (62 mg). (***R***)-**38c**: R_f = 0.10 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3452, 2974, 1776, 1702, 1582; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.34 (3H, s), 1.49 (3H, s), 2.09−2.17 (1H, m), 3.23 (1H, br), 3.38 (1H, ABq, d, J = 17.2, 4.0 Hz), 3.58 (1H, ABq, d, J = 17.2, 7.2 Hz), 4.15 (1H, d, J = 3.6 Hz), 5.04 (1H, br), 7.18−7.22 (1H, m), 7.29−7.33 (2H, m), 7.38−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0 (CH_3), 21.3 (CH_3), 21.5 (CH_3), 28.7 (CH_3), 29.5 (CH), 42.6 (CH_2), 59.9 (CH), 66.5 (CH), 72.5 (C), 83.4 (C), 97.8 (C), 126.36 (CH × 2), 126.39 (CH), 129.2 (CH × 2), 129.4 (C), 132.1 (C), 153.4 (C), 171.4 (C); HRMS (ESI): calcd for $[C_{19}H_{23}NO_4S + Na]^+$ 384.1240; found 384.1243; $[\alpha]_D^{25}$ +29.9° (c 0.85, $CHCl_3$). (***S***)-**38c**: R_f = 0.15 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3463, 3059, 2973, 1774, 1701, 1582; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 6.8 Hz), 1.37 (3H, s), 1.49 (3H, s), 2.08−2.16 (1H, m), 3.31 (1H, ABq, d, J = 17.2, 4.4 Hz), 3.36 (1H, br), 3.64 (1H, ABq, d, J = 17.2, 7.6 Hz), 4.15 (1H, d, J = 3.2 Hz), 5.02 (1H, br), 7.17−7.21 (1H, m), 7.28−7.32 (2H, m), 7.38−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (CH_3), 21.3 (CH_3), 21.5 (CH_3), 28.7 (CH), 29.5 (CH_3), 42.7 (CH_2), 59.7 (CH), 66.4 (CH), 72.4 (C), 83.3 (C), 97.9 (C), 126.3 (CH × 2), 126.6 (CH), 129.2 (CH × 2), 132.0 (C), 153.4 (C), 171.3 (C), HRMS (ESI): calcd for $[C_{19}H_{23}NO_4S + Na]^+$ 384.1240; found 384.1242; $[\alpha]_D^{26}$ +17.1° (c 1.10, $CHCl_3$).

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

(S)-4-Benzyl-3-((R)-3-hydroxy-5-(phenylthio)pent-4-ynoyl)-5,5-dimethyloxazolidin-2-one ***((R)-38d)*** *and (S)-4-Benzyl-3-((S)-3-hydroxy-5-(phenylthio)pent-4-ynoyl)-5,5-dimethyloxazolidin-2-one* ***((S)-38d)****.* ***((R)-/(S)-38d)****.* According to the general procedure, **37d** (323 mg) was converted to **38d** (363 mg) in 90% yield as colorless oil (entry 4, Table 2). Column chromatography afforded pure diastereomer fraction of (***R***)-**38d** (80 mg) and (***S***)-**38d** (43 mg) and unseparable mixture (240 mg). (***R***)-**38d**): R_f = 0.30 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3449, 3060, 2980, 2928, 1783, 1697, 1582; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, s), 1.36 (3H, s), 2.86 (1H, dd, J = 14.4, 9.2 Hz), 3.12 (1H, dd, J = 14.4, 4.4 Hz), 3.31 (1H, dd, J = 17.2, 4.0 Hz), 3.57 (1H, dd, J = 17.2, 7.6 Hz), 4.51 (1H, dd, J = 9.2, 4.4 Hz), 4.99 (1H, br), 7.18−7.24 (2H, m), 7.26−7.33 (5H, m), 7.39−7.4 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1 (CH_3), 28.4 (CH_3), 35.3 (CH_2), 42.8 (CH_2), 59.6 (CH), 63.4 (CH), 72.5 (C), 82.8 (C), 97.8 (C), 126.4 (CH × 2), 126.6 (CH), 126.9 (CH), 128.7 (CH × 2), 129.0 (CH × 2), 129.2 (CH × 2), 132.1 (C), 136.6 (C), 152.4 (C), 171.0 (C); HRMS (ESI): calcd for $[C_{23}H_{23}NO_4S + Na]^+$ 432.1240; found 432.1240. $[\alpha]_D^{25}$ −12.5° (c 1.60, $CHCl_3$). (***S***)-**38d**): R_f = 0.38 (30% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3471, 3062, 3029, 2981, 2926, 1783, 1694, 1582; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.36 (3H, s), 2.84 (1H, dd, J = 14.4, 9.2 Hz), 3.10−3.15 (2H, m), 3.34 (1H, ABq, d, J = 17.6, 4.0 Hz), 3.56 (1H, ABq, d, J = 17.6, 7.2 Hz), 4.51 (1H, dd, J = 9.6, 9.2 Hz), 4.99 (1H, ddd, J = 7.2, 6.8, 4.0 Hz), 7.14−7.18 (1H, m), 7.22−7.31 (7H, m), 7.38−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22. (CH_3), 28.5 (CH_3), 35.3 (CH_2), 43.0 (CH_2), 59.5 (CH), 63.5 (CH), 72.6 (C), 82.7 (C), 97.7 (C), 126.4 (CH × 2), 126.6 (CH), 126.9 (CH), 128.7 (CH × 2), 129.0 (CH × 2), 129.2 (CH × 2), 132.1 (C), 136.6 (C), 152.4 (C), 171.1 (C); HRMS (ESI): calcd for $[C_{23}H_{23}NO_4S + Na]^+$ 432.1240; found 432.1242. $[\alpha]_D^{24}$ −34.4°(c 1.55, $CHCl_3$).

After the absolute configurations of **38a** were determined by Mosher−Kusumi protocol,[44] the rest amount [(*R*)-**38a** and (*S*)-**38a**] were separated by column chromatography. Then hydrolysis of each of them gave the corresponding free carboxylic acid, and was further converted to *tert*-butyl ester (*R*)-**22** and (*S*)-**22**, respectively. The (***R***)-**22** exhibits a positive specific rotation, and (***S***)-**22** exhibits a negative specific rotation. Absolute configurations of the alcoholic carbon in the *β*-hydroxy carboximide (**38b−d**, **18**) were assumed by converting them into the corresponding *tert*-butyl esters. From the sign of the specific rotations of the *tert*-butyl esters, the absolute configurations of those alcoholic carbons in each compound were assumed to be positive to the *R* and negative to the *S* configuration, respectively.

General Procedure for Mosher Ester. To a solution of alcohol (172 mg, 0.51 mmol) in DCM (4.0 mL) at room temperature under argon were added (*R*)- or (*S*)-MTPA (158 mg, 0.77 mmol) and DCC (158 mg, 0.77 mmol), respectively. After stirring for 20 h, the reaction mixture was poured into ice-cold, saturated, aqueous NH_4Cl. The aqueous layer was separated and extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography to give (***S***)-**MTPA-(*S*)-38a** (197 mg, 70%) and (***R***)-**MTPA-(*S*)-38a**, (182 mg, 65%) (see SI for the NMR spectra of the Mosher method).

tert*-Butyl (*R*)-3-hydroxy-5-(phenylthio)pent-4-ynoate ((*R*)-22).** To a mixture of lithium hydroxide monohydrate (33 mg, 0.780 mmol) in THF (3.0 mL) and H_2O (1.0 mL) was added hydrogen peroxide (35% in H_2O, 227 mL, 2.34 mmol) at 0 °C and stirred for 15 min. (R***)-**38a** (119 mg, 0.312 mmol) in THF (1.0 mL) was then added into this lithium peroxide solution at 0 °C and stirred for 1.5 h. The reaction mixture was diluted with water (30 mL) and extracted with DCM (10 mL × 3). The DCM layers were combined and dried over $MgSO_4$, and concentrated in vacuo to give an oxazolidone. Subsequently the aqueous solution was cooled to 0 °C, then acidified to pH = 1 by 1 *N* HCl and extracted with Et_2O (10 mL × 3). The combined organic layers was dried over $MgSO_4$, and concentrated in vacuo to afford the crude carboxyl acid (69 mg) as colorless oil. To the carboxylic acid (69 mg) in DCM (3.0 mL) was added *tert*-butyl-trichloroacetimidate (95 mg, 0.435 mmol) at room temperature. After 50 min, the solvent was evaporated in vacuo. The residue was purified by flash chromatography (10% EtOAc/hexane) to provide the ester (***R***)-**22** (43 mg, 50% over two steps) as a colorless oil. (***R***)-**22**: R_f = 0.3 (10% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3435, 3060, 2978, 2931, 1726, 1583; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (9H, s), 2.72−2.73 (2H, m), 3.38 (1H, br), 4.89 (1H, dd, J = 5.2, 5.2 Hz), 7.18−7.21 (1H, m), 7.28−7.32 (2H, m), 7.38−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (CH_3 × 3), 42.7 (CH_2), 59.8 (CH), 72.1 (C), 82.0 (C), 98.0 (C), 126.3 (CH × 2), 126.6 (CH), 129.2 (CH), 132.2 (C), 170.6 (C); HRMS (ESI): calcd for $[C_{15}H_{18}O_3S + Na]^+$ 301.0869, found 301.0869. $[\alpha]_D^{25}$ +3.12° (c 1.16, $CHCl_3$)

tert-Butyl (S)-3-hydroxy-5-(phenylthio)pent-4-ynoate ***((S)-22)****.* According to the general procedure, (***S***)-**38a** (57 mg) was converted to (***S***)-**22** (23 mg, 48% yield in two steps) as a colorless oil. The NMR spectrum was identical to (***R***)-**22**, and the specific rotation (***S***)-**22** was $[\alpha]_D^{28}$ −3.1° (c 1.65, $CHCl_3$).

(*R,Z*)-*tert*-Butyl 5-(dimethyl(phenyl)silyl)-3-hydroxy-5-(phenylthio)pent-4-enoate ((*R*)-17). The dicobalthexacarbonyl complex of 2-methyl-butyn-2-ol (0.5 M in DCM, 0.17 mL, 0.085 mmol) was added to a mixture of the solution of thiophenylacetylene (***R***)-**22** (236 mg, 0.848 mmol) and dimethylphenyl silane (0.128 mg, 0.933 mmol) in dry 1,2-dichloroethane (8.4 mL) and then heated to 80 °C and stirred for 2 h. After the reaction mixture was cooled to room temperature, the solvent was removed in vacuo. The residue was washed with cold TBAF and brine and then purified by chromatography (10% EtOAc/hexane) to afford vinylsilane (***R***)-**23** (292 mg, 87%) as a colorless liquid. The vinylsilane (***R***)-**23** (292 mg, 0.740 mmol) in DCM (7.4 mL) was added *m*-CPBA (457 mg, 1.85 mmol, 70% of purity) and $NaHCO_3$ (310 mg, 3.70 mmol) at 0 °C and stirred 1 h. The reaction mixture was quenched with 1 N $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with DCM (10 mL × 3). The combined organic layer was washed with 1 N $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, and filtered off, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexane) to yield the (*R*)-silylvinyl sulfone (***R***)-**17** (297 mg, 90% over two steps) as a white solid. (***R***)-**17**: Mp: 67−68 °C (recrystallization from EtOAc/hexane); R_f = 0.25 (20% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3494, 3070, 3002, 2978, 2929, 2852, 1726, 1590; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.52 (6H, s), 1.41 (9H, s), 2.42 (1H, ABq, d, J = 16.8, 8.0 Hz), 2.51 (1H, ABq, d, J = 16.8, 4.0 Hz), 3.51 (1H, br), 5.37 (1H, ddd, J = 8.0, 8.0, 4.0 Hz), 7.28−7.36 (5H, m), 7.42−7.48 (3H, m), 7.55−7.57 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.1 (CH_3), −2.0 (CH_3), 28.1 (CH_3 × 3), 41.1 (CH_2), 65.6 (CH), 81.8 (C), 127.0 (CH × 2), 128.0 (CH × 2), 128.9 (CH × 2), 129.8 (CH), 133.0 (CH), 134.4 (CH × 2), 135.1 (C), 142.1 (C), 145.6 (C), 157.7 (CH), 171.2 (C); HRMS (ESI): calcd for $[C_{23}H_{30}O_5SSi + Na]^+$ 469.1475; found 469.1475. $[\alpha]_D^{25}$ +50.4° (c 1.10, $CHCl_3$).

(2*R*,3*S*,4*R*)-3-((*S,E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-4-((dimethyl(phenyl)silyl)oxy)-2-(phenylsulfonyl)-cyclopentanone ((−)-14). Compound **15** was synthesized according to the literature procedure.[33] To the (*S*)-vinyl iodide **15** (255 mg, 0.693 mmol), LiBr (100 mg, 1.16 mmol) in Et_2O (0.69 mL) was added *tert*-butyl lithium (1.65 M in pentane, 0.84 mL, 1.39 mmol) at −78 °C over 10 min under argon atmosphere. After this reaction mixture was stirred at −78 °C for additional 15 min, a small amount of THF (0.3 mL) was added as indicator to observe color change; thus, *tert*-butyl lithium in THF forms a bright yellow complex at −78 °C. The excess *tert*-butyl lithium was removed by addition of one or two drops of (*S*)-vinyl iodide **15** to the reaction mixture. To this solution was added (*R*)-silyl-vinyl phenyl sulfone (*R*)-**17** (103 mg, 0.231 mmol) in Et_2O (0.20 mL). The resulting mixture was warmed to −20 °C in 1 h and stirred for further 11 h at −20 °C. The reaction mixture was poured into ice-cold saturated solution of NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residue was purified by flash column chromatography (7% EtOAc/hexane) to afford the cyclopentanone (−)-**14** (82 mg, 58%) as a colorless oil. (−)-**14**: R_f = 0.33 (10% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3034, 2996, 2977, 2928, 1726, 1590; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (3H, s), 0.03 (3H, s),

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

0.348 (3H, s), 0.359 (3H, s), 0.84−0.90 (12H, H), 1.24−1.44 (8H, m), 2.41 (1H, ABq, d, J = 17.2, 6.8 Hz), 2.48 (1H, ABq, d, J = 17.2, 10.0 Hz), 3.35−3.41 (1H, m), 3.49 (1H, d, J = 9.6 Hz), 3.94 (1H, ddd, J = 10.0, 7.2, 6.8 Hz), 4.03 (1H, td, J = 5.2, 4.8 Hz), 5.45 (1H, ABq, dd, J = 15.6, 7.6, 0.8 Hz), 5.57 (1H, ABq, d, J = 15.6, 4.8 Hz), 7.32−7.41 (3H, m), 7.49−7.55 (4H, m), 7.62−7.66 (1H, m), 7.81−7.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8 (CH_3), −4.2 (CH_3), −1.6 (CH_3), −1.1 (CH_3), 14.1 (CH_3), 18.2 (C), 22.6 (CH_2), 24.9 (CH_2), 31.8 (CH_2), 38.2 (CH_2), 48.3 (CH_2), 49.1 (CH), 71.8 (CH), 72.2 (CH), 74.5 (CH), 126.1 (CH), 128.0 (CH × 2), 129.1 (CH × 2), 129.2 (CH × 2), 130.0 (CH), 133.5 (CH × 2), 134.1 (CH), 136.8 (C), 137.8 (CH), 138.3 (C), 201.9 (C); HRMS (ESI): calcd for $[C_{33}H_{50}O_5SSi_2 + Na]^+$ 637.2810; found 637.2811. $[\alpha]_D^{27}$ −22.1° (c 1.20, $CHCl_3$).

PGE_2 Methyl Ester ((−)-12). Allyl bromide **13** was obtained from propargyl alcohol in six steps according to literature procedure.[43] To a solution of (−)-**14** (64 mg, 0.104 mmol) and **13** (69 mg, 0.312 mmol) in DMF (1.5 mL) were successively added K_2CO_3 (10 mg, 0.072 mmol) and NaI (2 mg, 0.013 mmol), and the reaction mixture was stirred at room temperature. After 40 min, the reaction mixture was quenched with H_2O (20 mL) and extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude allylation product **39** was used for next step without further purification. A solution of **39** and MeOH (90 μL) in dry THF (0.9 mL) was added SmI_2 (0.1 M in THF, 3.0 mL) dropwise. The resulting solution was stirred at −78 °C for 15 min, during which time the deep green color of the solution faded. The solution was quenched with saturated solution of NH_4Cl (10 mL), and the aqueous phase was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off, and concentrated in vacuo. The residues were purified by flash chromatography (gradient 5% to 20% EtOAc/hexane, 10% EtOAc/hexane, R_f = 0.4) and provided an inseparable mixture of **40** and allyl bromide **13**. A solution of mixture **40** and **13** in MeCN (2.0 mL) was added 70% hydrogen fluoride−pyridine complex (50 μL) at 0 °C. The mixture was stirred at 0 °C for 1 h before pouring into saturated aqueous $NaHCO_3$ (5 mL). The aqueous solution was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residues were purified by flash chromatography (gradient 50 to 80% EtOAc/hexane) and provided PGE_2 methyl ester (−)-**12** (16 mg, 42% over three steps) as a colorless oil. (−)-**12:** R_f = 0.13 (70% EtOAc/hexane); IRν_{max} (neat, cm^{-1}): 3421, 2930, 2857, 1743, 1735, 1437, 1457, 1437, 1247, 1160, 1080; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz), 1.23−1.70 (10H, m), 1.98−2.44 (9H, m), 2.73 (1H, dd, J = 18.4, 7.2 Hz), 3.65 (3H, s), 4.05−4.13 (2H, m), 5.28−5.42 (2H, m). 5.57 (1H, ABq, d, J = 15.2, 8.0 Hz), 5.67 (1H, ABq, d, J = 15.2, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 24.7 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 26.6 (CH_2), 31.7 (CH_2), 33.4 (CH_2), 37.4 (CH_2), 46.2 (CH_2), 51.6 (CH_3), 53.3 (CH), 54.5 (CH), 72.2 (CH), 72.6 (CH), 126.5 (CH), 130.2 (CH), 130.9 (CH), 137.2 (CH), 174.2 (C), 214.1 (C); HRMS (ESI): calcd for $[C_{21}H_{34}O_5 + Na]^+$ 389.2298; found 389.2300. $[\alpha]_D^{24}$ −65.9° (c 0.30, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02735.

NMR spectra and experimental details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: minoru@cri.or.th; minoru@mx.nthu.edu.tw.

Present Address

[#]Chulabhorn Research Institute, 54 Kamphaeng Phet 6 Road, Lak Si, Bangkok 10210, Thailand.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Ministry of Science and Technology (former National Science Council) Taiwan and National Tsing Hua University for financial supports of this work.

■ DEDICATION

Dedicated to Prof. Gilbert Stork of Columbia University on his 94th birthday.

■ REFERENCES

(1) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 414.
(2) Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. *Nature* **2014**, *505*, 199.
(3) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682.
(4) Chen, M. Z.; Gutierrez, O.; Smith, A. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1279.
(5) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183.
(6) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171.
(7) Green, N. J.; Sherburn, M. S. *Aust. J. Chem.* **2013**, *66*, 267.
(8) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.
(9) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
(10) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450.
(11) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.
(12) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197.
(13) Bergström, S. *Science* **1967**, *157*, 382.
(14) Samuelsson, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 805.
(15) Bergström, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 858.
(16) Smyth, E. M.; Grosser, T.; Wang, M.; Yu, Y.; FitzGerald, G. A. *J. Lipid Res.* **2009**, *50*, S423.
(17) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(18) Woodward, R. B.; Gosteli, J.; Ernest, I.; Friary, R. J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 6853.
(19) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
(20) (a) Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108. (b) Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110. (c) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112.
(21) (a) Ryoji, N.; Masaaki, S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.
(22) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278.
(23) Nicolaou, K. C.; Heretsch, P.; ElMarrouni, A.; Hale, C. R. H.; Pulukuri, K. K.; Kudva, A. K.; Narayan, V.; Prabhu, K. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 10443.
(24) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.
(25) Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737.
(26) Jiang, J.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1997**, *53*, 5103.
(27) Hamajima, A.; Isobe, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2941.
(28) Isobe, M. *Pure Appl. Chem.* **2013**, *85*, 1149.
(29) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 4727.
(30) Tsao, K.-W.; Isobe, M. *Org. Lett.* **2010**, *12*, 5338.

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584

(31) Isobe, M.; Niyomchon, S.; Cheng, C.-Y.; Hasakunpaisarn, A. *Tetrahedron Lett.* **2011**, *52*, 1847.
(32) Adachi, M.; Yamauchi, E.; Komada, T.; Isobe, M. *Synlett* **2009**, *2009*, 1157.
(33) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J.-J. *Eur. J. Org. Chem.* **1999**, *1999*, 2655.
(34) Huang, K.-H.; Isobe, M. *Eur. J. Org. Chem.* **2014**, *2014*, 4733.
(35) Sato, F.; Watanabe, H.; Tanaka, Y.; Yamaji, T.; Sato, M. *Tetrahedron Lett.* **1983**, *24*, 1041.
(36) Fukuzawa, S.-i.; Matsuzawa, H.; Yoshimitsu, S.-i. *J. Org. Chem.* **2000**, *65*, 1702.
(37) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(38) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554.
(39) Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337.
(40) Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Shyam Prasad, R.; Sanganee, H. J. *Synlett* **1998**, *1998*, 519.
(41) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387.
(42) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**, *39*, 6733.
(43) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726.
(44) Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

DOI: 10.1021/acs.joc.5b02735
J. Org. Chem. 2016, 81, 1571−1584