JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

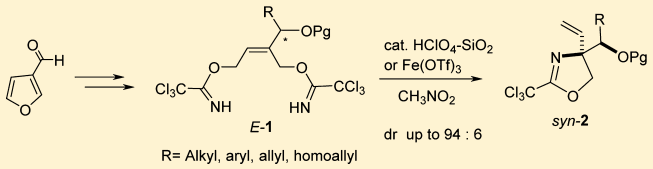
2-Vinyl Threoninol Derivatives via Acid-Catalyzed Allylic Substitution of Bisimidates

Varun Kumar, Kristine Klimovica, Dace Rasina, and Aigars Jirgensons*

Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga, Latvia LV 1006

Supporting Information

ABSTRACT: A diastereoselective synthesis of 4-vinyl oxazolines *syn*-**2** was developed based on an acid-catalyzed cyclization of bistrichloroacetimidates (*E*)-**1**. The reaction likely involves an allyl carbenium ion intermediate in which the adjacent stereocenter directs the stereoselectivity for C−N bond formation. Oxazolines *syn*-**2** were transformed to C-quaternary threoninol, threoninal, and threonine derivatives which can be further incorporated into complex natural compounds.



C-quaternary amino acids and their derivatives have a wide range of applications in both chemical and biochemical domains.[1,2] 2-Substituted threonine and allothreonine are specific types of amino acids bearing two adjacent stereocenters. Such substructures are found in many natural products and pharmaceutically relevant compounds as illustrated by lactacystin, altemicidin, mycestericin E, and HYDIA (Figure 1).[1f,3]

Stereodefined 2-vinyl threonine derivatives can be used as precursors for incorporation of these substructures into target compounds. However, stereoselective synthesis of such compounds is limited to relatively few examples. Carbery's group has demonstrated the use of the stereoselective Ireland−Claisen rearrangement to assemble 2-oxymethylthreonine, which was further transformed to the 2-vinyl threoninol derivative.[4,5] Ariza et al. have developed the synthesis of 2-vinyl threoninol via diastereoselective allylboration of chiral α-substituted aldehydes.[6] 2-Vinyl threoninol derivatives can be obtained in moderate stereoselectivity via monosaccharide or tartrate-derived allylic imidate (Overman) rearrangement and related allylic thiocyanate rearrangements.[7] Another method for the synthesis of the 2-vinyl threoninol derivative with defined structure involves the addition of a vinyl Grignard reagent to nitrone derived from L-erythrulose.[8]

Lewis acid catalyzed cyclization of allylic bisimidates via generation of allylic carbenium ions is a convenient approach for the synthesis of unsaturated amino alcohols.[9,10] Previously, we showed that this strategy can be applied for the synthesis of C-quaternary vinylglycinols.[9c,d] A reaction mechanism was proposed which involves selective abstraction of the imidate leading to the formation of a tertiary carbenium ion intermediate. We envisioned that bisimidates **1** bearing an oxy group would lead to stereodefined threoninol derivatives **2** if the stereochemistry of the C−N bond formation in the allyl carbenium ion intermediate **A** could be controlled by the adjacent stereocenter (Scheme 1).

Bisimidates (*E*)-**1a−l** were prepared in four steps starting with 3-furanaldehyde **3** (Scheme 2). The addition of Grignard reagent to aldehyde **3** gave alcohol **4**. Silyl-type protection (TBS = *tert*-butylsilyl; TIPS = triisopropylsilyl; TBDPS = *tert*-butyldiphenylsilyl) of the hydroxyl group in alcohol **4** followed by furan ring opening[11] provided monoprotected triols (*E*)-**5** which were transformed to bisimidates (*E*)-**1**.

Bisimidates (*Z*)-**1** with a *Z*-configuration double bond were more difficult to achieve; therefore, only one substrate, (*Z*)-**1b**, was prepared for comparative studies (Scheme 3). Hydrostannylation/iodination provided 2-iodobutenediol **7**[12] with the required double bond configuration (*E*/*Z* = 1:15). Diol **7** was transformed to dialkoxide followed by iodine to lithium exchange. The addition of the resulting trimetalated species to pentanal provided triol **8**.[12] Primary alcohol groups in this intermediate were protected by acylation; secondary alcohol was protected with a TBS group, and the acyl groups were cleaved off by methanolyis. The resulting monoprotected triol (*Z*)-**5b** was transformed to bisimidate (*Z*)-**1b**.

Bisimidate (*E*)-**1a** was used as a model substrate in Lewis acid catalyzed cyclization to oxazoline **2a** (Table 1). The reaction turned out to be problematic due to the formation of seven-membered imidate **9** as a byproduct along with the expected oxazoline **2a**. It should be mentioned that the prolonged exposure of byproduct **9** to Lewis acid catalyst did not afford product **2a**, but rather a mixture of the decomposition products was formed. An extensive screening of conditions revealed that the desired oxazoline **2a** can be obtained as the major product using $HClO_4$ adsorbed on silica gel[13] or $Fe(OTf)_3$ as a catalyst in nitromethane (Table 1, entries 1 and 2; see Supporting Information for the full set of results). Choice of solvent had a significant effect on the product **2a**/**9** ratio. The seven-membered imidate **9** was formed in considerable amounts when lower polarity solvents such as DCM or Et_2O were used (Table 1, entries 3−6). Notably, compound **9** was formed as the major product with $Fe(OTf)_3$

Received: March 9, 2015
Published: May 5, 2015

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

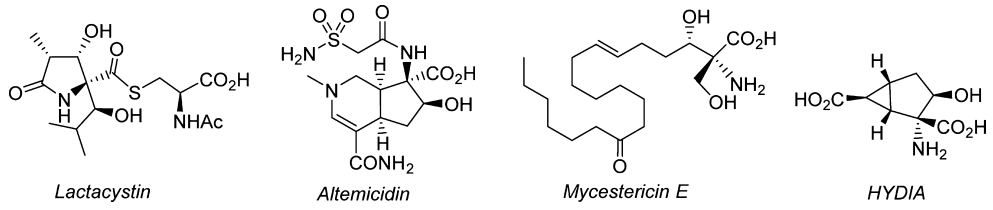
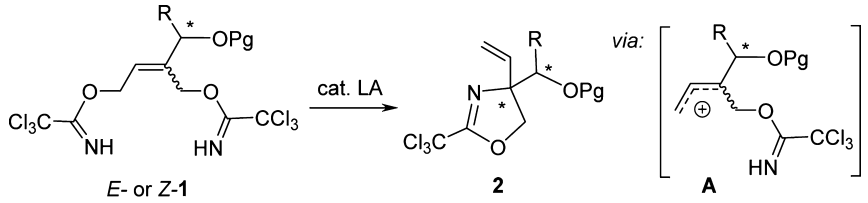
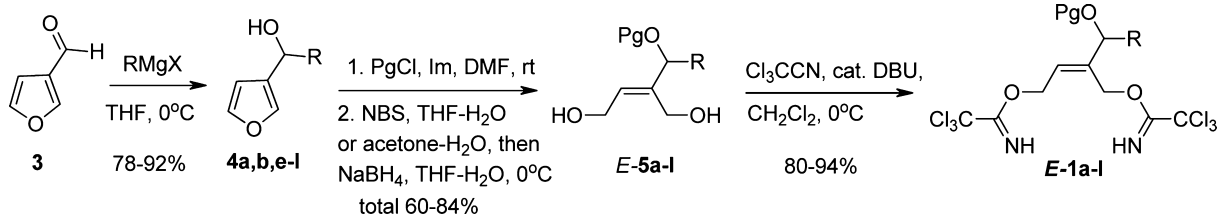


Figure 1. Natural products containing a C-quaternary threoninol moiety.

Scheme 1. 2-Vinyl Threoninol Derivatives via Cyclization of Allylic Bisimidates



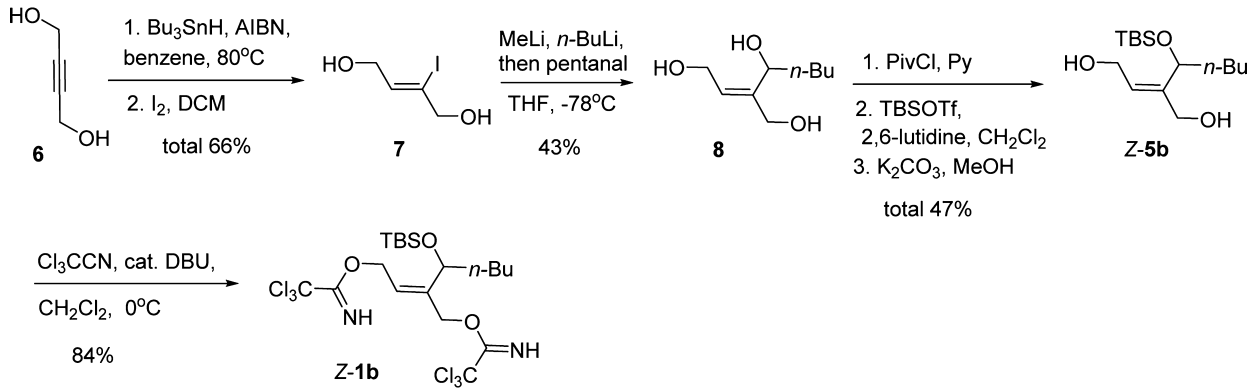
Scheme 2. Synthesis of Bisimidates (*E*)-1



a,b,e-l, Pg = TBS; **c**, Pg = TIPS, **d**, Pg = TBDPS

a,c,d, R = *i*-Pr; **b**, R = *n*-Bu; **e**, R = *t*-Bu; **f**, R = Ph; **g**, R = Bn; **h**, R = Me
i, R = allyl; R **j**, R = homoallyl; **k**, R = vinyl; **l**, R = propargyl

Scheme 3. Synthesis of Bisimidate (*Z*)-1b



as a catalyst in toluene (Table 1, entry 7). It was gratifying to find that the diastereoselectivity for oxazoline **2a** formation from (*E*)-**1a** was very high, favoring the *syn* isomer under optimal reaction conditions (Table 2, entries 1 and 2; see Supporting Information for proof of configuration by 2D NMR and X-ray).

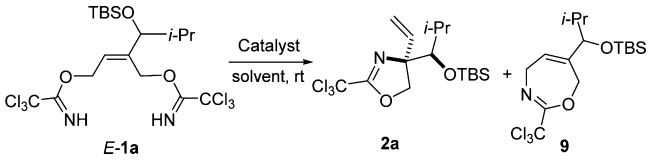
The double bond geometry in the bisimidate **1** had a significant impact on the diastereoselectivity, as observed in the cyclization of isomeric bisacetimidates (*E*)-**1b** and (*Z*)-**1b**. Cyclization of bisimidate (*E*)-**1b** was highly diastereoselective, favoring oxazoline *syn*-**2b** formation. In turn, isomeric bisimidate (*Z*)-**1b** gave a practically equal ratio of diastereomers *syn*-**2b** and *anti*-**2b** (Scheme 4).

Substrate scope was investigated in optimal conditions for bisimidate (*E*)-**1** cyclization (Scheme 5). Substrates (*E*)-**1c,d** bearing TIPS and TBDPS protecting groups could also be used to prepare the corresponding oxazolines *syn*-**2c,d**, although a slight decrease in diastereoselectivity was observed compared to that with the TBS analogue (*E*)-**1a**. Substrates containing branched substituents (**1a,e**) or a phenyl group (**1f**) at the stereogenic center gave a better diastereomeric ratio in favor of isomer *syn*-**2**. Notably, the selectivity was still good in the case of unbranched substrates (*E*)-**1b,g–j**. Loss of diastereoselectivity was observed in the case of the bisimidate **1k** bearing a vinyl group. The bisimidate **1l** containing a propargylic group gave a poor yield of oxazoline **2l** due to the formation of side products.

Enantioenriched alcohol (*S*)-**4a** was prepared by oxidation of racemic alcohol **4a** followed by CBS reduction[14] (see Experimental Section). Alcohol (*S*)-**4a** was transformed to

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934–5943

Table 1. Solvent Effect on the Regioselectivity in $HClO_4$/SiO_2 and $Fe(OTf)_3$-Catalyzed Cyclization of Bisimidate (*E*)-1a[a]



entry	Lewis acid	solvent	2a, yield[b] (dr)[c]	9, yield[b]
1	$HClO_4/SiO_2$	CH_3NO_2	89% (94:6)	8%
2	$Fe(OTf)_3$	CH_3NO_2	85% (94:6)	
3	$HClO_4/SiO_2$	CH_2Cl_2	49% (93:7)	40%
4	$Fe(OTf)_3$	CH_2Cl_2	35% (nd)	55%
5	$HClO_4/SiO_2$	Et_2O	*d*	56%
6	$Fe(OTf)_3$	Et_2O	35% (nd)	20%
7	$Fe(OTf)_3$	toluene	6% (nd)	74%

[a]Conditions: 0.2 mmol substrate, 20 mol % of catalyst, 2 mL of solvent. [b]^{1}H NMR yield using 1,4-(bistrichloromethyl)benzene as internal standard. [c]Diastereomeric ratio was determined by the ^{1}H NMR spectrum. [d]Formation of unidentified byproducts.

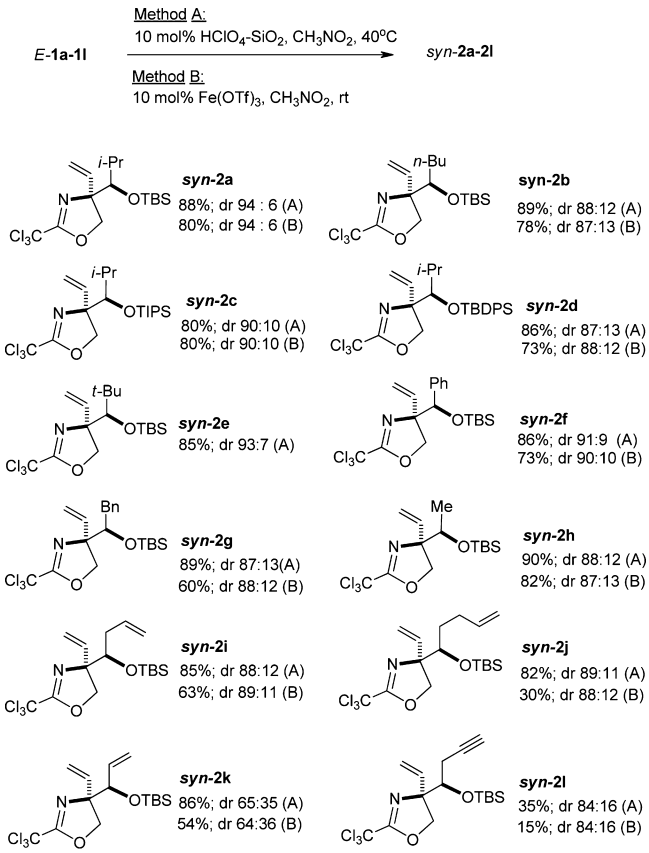
enantioenriched bisimidate (*S*,*E*)-**1a**, which was cyclized to oxazoline (*S*,*S*)-*syn*-**2a** (Scheme 6). The enantiomeric purity of its derivatization product (*S*,*S*)-**10** matched that of the starting material (*S*)-**4a**, indicating complete conservation of the stereochemistry through the whole sequence of transformations.

To verify the ionic mechanism for oxazoline **2** formation, diastereomeric bisimidates (*R**,*R**,*E*)-**1m** and (*S**,*R**,*E*)-**1m** bearing a methyl group in the allylic position were prepared starting from substituted furanaldehyde **11**[15] (Scheme 7). Both substrates (*R**,*R**,*E*)-**1m** and (*S**,*R**,*E*)-**1m** gave oxazoline *syn*-**2m** as the major isomer with the same diastereoselectivity when activated with $HClO_4$ adsorbed on silica gel. Notably, oxazoline *syn*-**2m** was formed exclusively as an *E*-configuration isomer. These results indicate that cyclization of both isomers (*R**,*R**,*E*)-**1m** and (*S**,*R**,*E*)-**1m** proceeds via the same intermediate, probably carbenium ion **A1**, according to the S_N1' mechanism.

In order to verify the kinetic/thermodynamic control for the cyclization of bisimidate **1** to oxazoline **2**, the minor isomer *anti*-**2a** was acquired and purified to 9:1 dr. It was subjected to the cyclization conditions (Method A, Scheme 2); however, the ratio of isomers remained unchanged. This indicated irreversible amination of the intermediate carbenium ion **A**.

After we confirmed the S_N1-type mechanism and the kinetic control in the cyclization of bisimidates **1**, the stereoinduction model for the formation of oxazolines *syn*-**2** was hypothesized. According to our recent investigations, the diastereoselectivity in allylic bisimidate systems can be explained by the formation

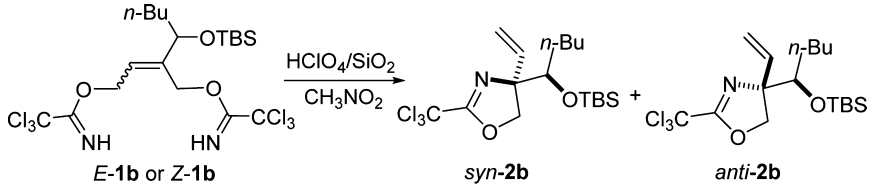
Scheme 5. Substrate Scope for Oxazoline *syn*-2 Formation from Bisimidates (*E*)-1



of the most stable carbenium ion conformer which undergoes cyclization via the energetically most favorable bond rotations.[9e] The most stable carbenium ion **A1** conformation is proposed in Figure 2. In this conformation, the R group is perpendicular to the plane of the carbenium ion to minimize the steric interactions. The position of the TBSO group can be explained by minimized dipole−dipole interaction with imidate and/or repulsive interaction of the C−O σ^* orbital with the carbenium ion. It could be assumed that, at the cyclization stage, imidate C−O bond rotation is energetically most favorable while C−C bond rotation is restricted by *E*,*E*-configuration of the carbenium ion (*E*,*E*)-**A1**. According to this model, the rotation around the C−C bond is facilitated in carbenium ion (*E*,*Z*)-**A1** generated from imidate (*Z*)-**1b** (Figure 2). This may explain the lack of selectivity in oxazoline **2b** formation from this substrate.

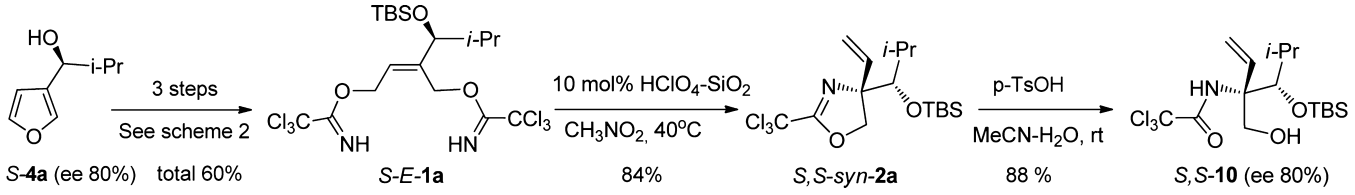
Synthetic utility of oxazolines **2** was demonstrated using cyclization product **2a** (Scheme 8). Hydrolysis of *syn*-**2a** gave 2-

Scheme 4. Diastereoselectivity for Oxazoline 2 Formation Depending on Bisimidate 1 Configuration

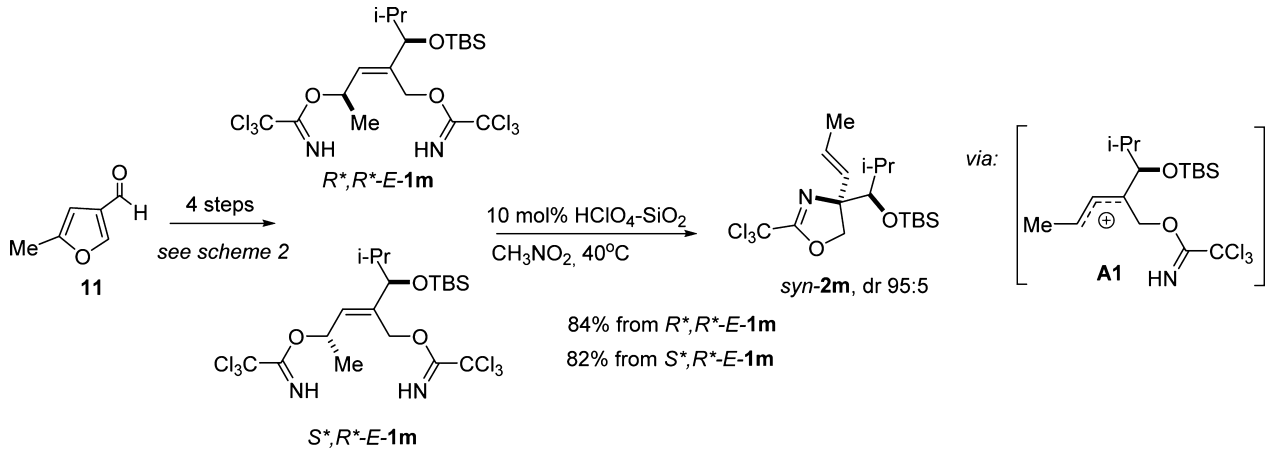


DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

Scheme 6. Retention of the Absolute Configuration in Bisimidate 1 Cyclization to Oxazoline 2



Scheme 7. Confirmation of the S_N1' Mechanism for Oxazoline 2 Formation in the Acid-Catalyzed Cyclization of Bisimidates 1



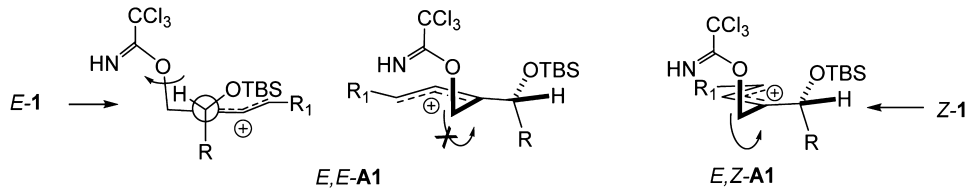
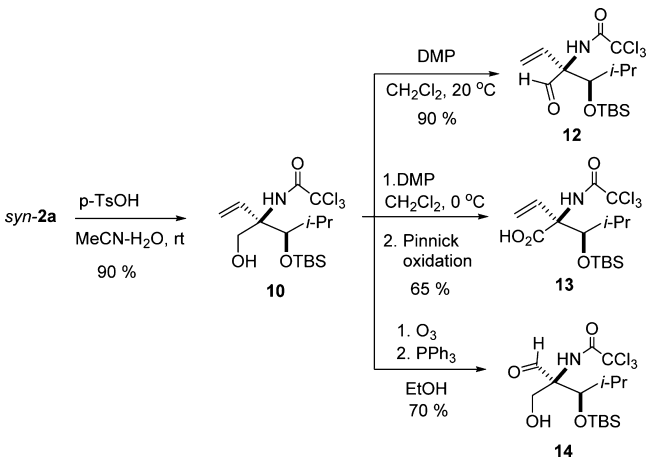


Figure 2. Stereoinduction model for the formation of oxazolines *syn*-**2**.

Scheme 8. Transformation of 4-Vinyl Oxazoline *syn*-2a to 2-Vinyl Threonine Derivatives



vinyl threoninol derivative **10**. Oxidation of primary alcohol in intermediate **10** to aldehyde gave 2-vinyl threoninal derivative **12**, while the oxidation to carboxylic acid gave 2-vinyl threonine derivative **13**. Ozonolysis of the double bond in **10** provided allothreoninal derivative **11**. These transformations demonstrate the derivatization potential of oxazolines **2** that will be used in future work for the natural product synthesis.

In summary, we have developed diastereoselective access to 2-vinyl threoninols from allylic bisimidates. The reaction likely proceeds via the allyl carbenium ion intermediate, where the stereochemistry of the C−N bond formation is controlled by the adjacent stereocenter containing an oxy group. The S_N1'/S_N1 selectivity can be adjusted by using $HClO_4$ adsorbed on silica gel or $Fe(OTf)_3$ as a catalyst and a strongly polar aprotic solvent such as nitromethane. High diastereoselectivity for *syn*-oxazoline formation was achieved starting with (*E*)-bisimidates. Such substrates can be readily prepared from furan-3-carbaldehyde in four steps. The products of bisimidate cyclization were transformed to C-quaternary threoninol, threoninal, and threonine derivatives, which can be further incorporated into complex natural compounds.

EXPERIMENTAL SECTION

General Information. Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. All reactions were performed under an inert atmosphere. Flash chromatography was carried out using silica gel (230−400 mesh). Thin layer chromatography (TLC) was performed on silica gel and was visualized by staining with $KMnO_4$. NMR spectra were recorded on 400 and 600 MHz spectrometers with chemical shift values (δ) in parts per million using the residual chloroform signal as the internal standard. Gas chromatographic (GC) analysis was performed on gas chromatographic system with mass selective detector. Exact molecular masses (HRMS) were determined on a hybrid quadrupole time-of-

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

flight mass spectrometer equipped with an electrospray ion source. Chiral high-performance liquid chromatography (HPLC) was performed on chiral stationary phase Lux cellulose 1 using 1% isopropyl alcohol/hexane as eluent.

Alcohols **4a,b,e−l** were prepared according to literature procedure.[16] These compounds have been previously described in the literature: 1-(furan-3-yl)-2-methylpropan-1-ol (**4a**),[16] 1-(furan-3-yl)-pentan-1-ol (**4b**),[17] 1-(furan-3-yl)-2,2-dimethylpropan-1-ol (**4e**),[18] furan-3-yl(phenyl)methanol (**4f**),[16,18] 1-(furan-3-yl)-2-phenylethanol (**4g**),[18] 1-(furan-3-yl)ethanol (**4h**),[19] 1-(furan-3-yl)but-3-en-1-ol (**4i**),[19] 1-(furan-3-yl)pent-4-en-1-ol (**11j**),[20] 1-(furan-3-yl)prop-2-en-1-ol (**11k**),[18,21] 1-(furan-3-yl)but-3-yn-1-ol (**11l**).[22]

(*S*)-1-(Furan-3-yl)-2-methylpropan-1-ol ((*S*)-4a). To a solution of racemic alcohol **4a** (2.7 g, 19.3 mmol) in dry DCM (100 mL) was added DMP (55 mL, 23.7 mmol), and the reaction mixture was stirred for 6 h at rt. Completion of the reaction was monitored by TLC. The reaction mixture was then diluted with DCM and neutralized with $NaHCO_3$ (2 × 10 mL). Organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude product. This was purified with column chromatography eluting with a mixture of EtOAc and petroleum ether (1:12) to give the corresponding ketone as yellow oil (2.1 g, 80%). The solution of ketone (0.5 g, 3.5 mmol) in 10 mL of THF was added to a solution of 1 M BH_3·THF complex (3.92 mL, 3.92 mmol) and CBS catalyst (0.2 g, 0.7 mmol) in dry THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at rt for 6 h. Completion of the reaction was monitored by TLC. The reaction mixture was then quenched with 5 mL of water and diluted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified with column chromatography eluting with a mixture of EtOAc and petroleum ether (1:10) to give alcohol (*S*)-**4a** (0.36 g, 72%). The spectral data matched that of racemic product **4a**:[16] $[\alpha]_{20}^{D}$ −10.78 (*c* = 1.0, CH_2Cl_2).

General Procedure for the Synthesis of Silyl-Protected (*E*)-Triols 5. To a solution of alcohol **4** (1 mmol) in DMF (2 mL) were added TBSCl (0.18 g, 1.1 mmol) and imidazole (0.1 g, 1.5 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 3 h, and the reaction was monitored by TLC. After the consumption of the starting material, the product was extracted into hexane (2 × 10 mL). The organic phase was washed with $NaHCO_3$ (5 mL) and then with brine (5 mL). The solution was concentrated, and the crude silyl-protected alcohol was used in the next step without purification. To a precooled solution of crude silyl-protected alcohol in a mixture of THF and H_2O (1:1, 30 mL) was slowly added NBS (0.19 g, 1.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min followed by very slow addition of $NaBH_4$ in small portions over a period of 20−30 min. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (100−200 mesh size) with EtOAc/petroleum ether (1:5) as the eluent to afford product **5**. For alcohols **5j**, **5k**, and **5l**, the oxidative cleavage of furan was performed in acetone−water (4:1) at −30 °C. Acetone was removed in vacuo, and the residue was dissolved in THF. To this mixture was added $NaBH_4$.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diol ((E)-**5a**).* Prepared according to the general procedure (0.23 g, 81%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (t, *J* = 6.7 Hz, 1H), 4.28−4.20 (m, 4H), 3.71 (d, *J* = 7.4 Hz, 1H), 1.90 (br s, OH), 1.89−1.77 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 3H), −0.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.3, 129.2, 83.6, 58.6, 58.4, 32.5, 25.8, 19.5, 18.7, 18.1, −4.2, −5.0; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{30}O_3SiNa$ 297.1856; found 297.1856.

*(S,E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diol ((S,E)-**5a**).* Prepared according to the general procedure (0.22 g, 79%): $[\alpha]_{20}^{D}$ −7.70 (*c* = 1.0, CH_2Cl_2), 80% ee.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)pentyl)but-2-ene-1,4-diol ((E)-**5b**).* Prepared according to the general procedure (0.23 g, 84%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 6.6 Hz, 1H), 4.26−4.10 (m, 5H), 2.69 (br s, OH), 1.63−1.56 (m, 2H), 1.32−1.24 (m, 4H), 0.89−0.83 (m, 12H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.4, 128.0, 78.1, 58.4, 57.9, 36.3, 27.9, 25.8, 22.5, 18.0, 14.0, −4.6, −4.9; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{32}O_3SiNa$ 311.2013; found 311.2009.

*(E)-2-(1-((Triisopropylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diol ((E)-**5c**).* Prepared according to the general procedure (0.25 g, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (t, *J* = 6.6 Hz, 1H), 4.25−4.22 (m, 4H), 3.95 (d, *J* = 7.0 Hz, 1H), 2.62 (br s, OH), 1.91−1.83 (m, 1H), 1.05 (s, 21H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.5, 129.4, 83.2, 58.6, 58.5, 33.4, 19.0, 18.8, 18.1, 12.6; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{36}O_3SiNa$ 339.2326; found 339.2332.

*(E)-2-(1-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diol ((E)-**5d**).* Prepared according to the general procedure (0.3 g, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 4H), 7.44−7.33 (m, 6H), 5.39 (t, *J* = 6.6 Hz, 1H), 4.05−3.90 (m, 5H), 1.90−1.83 (m, 1H), 1.08 (s, 9H), 0.93−0.77 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.4, 136.3, 136.2, 134.2, 133.7, 130.3, 129.7, 129.7, 127.5, 127.4, 83.7, 48.6, 58.4, 33.2, 27.2, 19.5, 19.1, 19.0; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{34}O_3SiNa$ 421.2169; found 421.2166.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2,2-dimethylpropyl)but-2-ene-1,4-diol ((E)-**5e**).* Prepared according to the general procedure (0.17 g, 60%): colorless solid; mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (t, *J* = 6.7 Hz, 1H), 4.27−4.14 (m, 4H), 3.75 (s, 1H), 3.35 (br s, OH), 0.89 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.8, 130.9, 77.0, 58.8, 58.7, 36.2, 26.5, 26.0, 25.8, 18.1, −4.2, −5.2. (C-OTBS overlapped with $CDCl_3$); HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$calcd for $C_{15}H_{32}O_3SiNa$ 311.2013; found 311.2019.

*(E)-2-(((tert-Butyldimethylsilyl)oxy)(phenyl)methyl)but-2-ene-1,4-diol ((E)-**5f**).* Prepared according to the general procedure (0.25 g, 82%): colorless solid; mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 5.94 (t, *J* = 6.8 Hz, 1H), 5.28 (s, 1H), 4.27−4.23 (m, 2H), 4.05 (d, *J* = 2.4 Hz, 2H), 0.92 (s, 9H), −0.08 (s, 3H), −0.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.8, 142.2, 128.9, 128.3, 127.4, 126.0, 79.0, 58.4, 58.0, 25.8, 23.5, 18.0, −4.8; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{28}O_3SiNa$ 331.1700; found 331.1700.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)but-2-ene-1,4-diol ((E)-**5g**).* Prepared according to the general procedure (0.26 g, 80%): colorless solid; mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.41 (m, 5H), 5.89 (t, *J* = 6.7 Hz, 1H), 4.61−4.44 (m, 5H), 3.13 (d, *J* = 6.6 Hz, 2H), 2.43 (br s, OH), 1.08 (s, 9H), 0.16 (s, 3H), 0.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.6, 138.4, 129.8, 128.1, 128.1, 126.3, 79.1, 58.4, 58.2, 44.0, 25.7, 18.0, −4.9, −5.5; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{30}O_3SiNa$ 345.1856; found 345.1853.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)ethyl)but-2-ene-1,4-diol ((E)-**5h**).* Prepared according to the general procedure (0.20 g, 82%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (t, *J* = 6.7 Hz, 1H), 4.39 (q, *J* = 6.3 Hz, 3H), 4.28−4.16 (m, 4H), 1.30 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.8, 126.5, 73.4, 58.4, 58.0, 25.8, 23.5, 18.0, −4.8; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{26}O_3SiNa$ 269.1543; found 269.1537.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)but-3-en-1-yl)but-2-ene-1,4-diol ((E)-**5i**).* Prepared according to the general procedure (0.17, 63%): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78−5.66 (m, 2H), 5.05 (d, *J* = 7.2 Hz, 1H), 5.01 (s, 1H), 4.23−4.15 (m, 5H), 2.71 (br s, OH), 2.35 (t, *J* = 7.1 Hz, 2H), 2.13 (s, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.3, 134.7, 128.4, 117.2, 77.4, 58.5, 58.0, 41.6, 25.7, 18.1, −4.7, −4.8; HRMS (ESI/TOF-Q) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{28}O_3SiNa$ 295.1700; found 295.1693.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)pent-4-en-1-yl)but-2-ene-1,4-diol ((E)-**5j**).* Prepared according to the general procedure (0.18 g, 65%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.70 (m, 2H), 5.03−4.94 (m, 2H), 4.14−4.29 (m, 5H), 2.11−1.97 (m, 2H),

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

1.77−1.64 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.4, 138.1, 128.2, 114.8, 77.2, 58.5, 58.0, 35.7, 29.8, 25.8, 18.0, −4.6, −4.9; HRMS (ESI/TOF-Q) m/z $[M + Na]^+$ calcd for $C_{15}H_{30}O_3SiNa$ 309.1856; found 309.1858.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)allyl)but-2-ene-1,4-diol ((E)-**5k**).* Prepared according to the general procedure (0.18 g, 71%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.76 (m, 2H), 5.30 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.6 Hz, 1H), 4.67 (d, J = 5.1 Hz, 1H), 4.24−4.15 (m, 4H), 2.52 (br s, OH), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.2, 139.3, 128.3, 115.0, 78.0, 58.5, 57.8, 25.8, 18.2, −4.7, −4.9; HRMS (ESI/TOF-Q) m/z $[M + Na]^+$ calcd for $C_{13}H_{26}O_3SiNa$ 281.1543; found 281.1544.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)but-3-yn-1-yl)but-2-ene-1,4-diol ((E)-**5l**).* Prepared according to the general procedure (0.2 g, 74%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (t, J = 6.6 Hz, 1H), 4.34−4.24 (m, 5H), 2.50 (dd, J = 6.6, 2.4 Hz, 2H), 1.99 (t, J = 2.4 Hz, 1H), 0.10 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.3, 129.4, 81.1, 75.6, 70.5, 58.4, 57.6, 27.5, 25.7, 18.1, −4.8, −4.9; HRMS (ESI/TOF-Q) m/z $[M + Na]^+$ calcd for $C_{14}H_{26}O_3SiNa$ 293.1543; found 293.1545.

General Procedure for the Synthesis of Bisimidates (*E*)-1. Molecular sieves (4 Å) were added to a solution of silyl-protected triol (*E*)-**5** (0.5 mmol) in DCM (15 mL). The reaction mixture was cooled to 0 °C, and then DBU (0.015 mL, 0.1 mmol, 20 mol %) was added. The solution was stirred at 0 °C for 30 min. Then trichloroacetonitrile (0.13 mL, 1.25 mmol) was added, and the reaction mixture was stirred until TLC showed complete conversion of starting material to the product (1 h). Solvent was removed, and the residue was purified by flash column chromatography using DCM as eluent to provide bisimidate **1**.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1a**).* Prepared according to the general procedure (0.25 g, 88%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (br s, 2H), 5.92 (t, J = 6.7 Hz, 1H), 5.0−4.92 (m, 3H), 4.81 (d, J = 12.5 Hz, 1H), 3.91 (d, J = 5.9 Hz, 1H), 1.83−1.73 (m, 1H), 0.89−0.86 (m, 15H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 140.5, 126.3, 91.4, 91.3, 80.2, 65.2, 64.3, 32.3, 25.9, 19.7, 18.2, 17.4, −4.4, −5.1; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{18}H_{31}Cl_6N_2O_3Si$ 561.0230; found 561.0225.

*(S,E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) (S,E-**1a**).* Prepared according to the general procedure (0.24 g, 85%): $[\alpha]_{20}^{D}$ −4.36 (c = 1.0, CH_2Cl_2).

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)pentyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1b**).* Prepared according to the general procedure (0.24 g, 85%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.31 (s, 1H), 5.96 (t, J = 6.8 Hz, 1H), 5.03−4.93 (m, 3H), 4.83 (d, J = 12.4 Hz, 1H), 4.23 (t, J = 6.1 Hz, 1H), 1.59−1.53 (m, 2H), 1.32−1.22 (m, 4H), 0.93−0.85 (m, 12H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 141.6, 124.9, 91.4, 91.3, 74.8, 65.2, 64.2, 36.4, 27.5, 25.8, 22.6, 18.2, 14.1, −4.6, −5.0; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{19}H_{33}Cl_6N_2O_3Si$ 575.0386; found 575.0388.

*(E)-2-(2-Methyl-1-((triisopropylsilyl)oxy)propyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) (E)-**1c**.* Prepared according to the general procedure (0.26 g, 88%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.30 (s, 1H), 5.93 (t, J = 6.6 Hz, 1H), 5.04−4.83 (m, 4H), 4.14 (d, J = 6.0 Hz, 1H), 1.87−1.78 (m, 1H), 1.05−0.89 (m, 27H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 140.0, 126.6, 91.4, 91.3, 80.6, 62.3, 64.6, 33.3, 18.8, 18.1, 12.6; unstable in conditions for HRMS determination.

*(E)-2-(1-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1d**).* Prepared according to the general procedure (0.29 g, 85%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.26 (s, 1H), 7.70−7.61 (m, 4H), 7.42−7.31 (m, 6H), 5.69 (t, J = 6.2 Hz, 1H), 4.83−4.70 (m, 4H), 4.02 (d, J = 6.2 Hz, 1H), 1.84−1.75 (m, 1H), 1.07 (s, 9H), 0.84 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 7.04 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 162.2, 138.6, 136.3, 136.1, 133.9, 133.6, 129.6, 127.4, 127.4, 127.6, 81.6, 65.4, 64.5, 33.0, 27.2, 19.6, 18.8, 18.4; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{28}H_{35}Cl_6N_2O_3Si$ 685.0543; found 685.0542.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2,2-dimethylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1e**).* Prepared according to the general procedure (0.24 g, 84%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.30 (s, 1H), 5.90 (t, J = 6.7 Hz, 1H), 5.05−4.80 (m, 4H), 3.89 (s, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), −0.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 162.3, 140.9, 125.9, 65.4, 36.4, 36.3, 26.2, 25.9, 18.1, −4.2, −5.3; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{19}H_{33}Cl_6N_2O_3Si$ 575.0386; found 575.0389.

*(E)-2-(((tert-Butyldimethylsilyl)oxy)(phenyl)methyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1f**).* Prepared according to the general procedure (0.26 g, 88%): light yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.27 (br s, 1H), 7.35−7.23 (m, 5H), 6.25 (t, J = 6.7 Hz, 1H), 5.36 (s, 1H), 5.03 (d, J = 6.7 Hz, 2H), 4.92 (d, J = 12.5 Hz, 1H), 4.52 (d, J = 12.5 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), −0.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3, 162.3, 144.8, 141.1, 128.2, 128.1, 127.5, 126.6, 124.4, 91.4, 91.2, 75.8, 65.3, 64.3, 25.8, 18.3, −4.9, −5.0; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{21}H_{29}Cl_6N_2O_3Si$ 595.0073; found 595.0041.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1g**).* Prepared according to the general procedure (0.28 g, 94%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.46 (br s, 1H), 7.43−7.32 (m, 5H), 6.10 (t, J = 6.8 Hz, 1H), 5.20 (d, J = 12.6 Hz, 1H), 5.13−5.06 (m, 3H), 4.55 (dd, J = 8.1, 4.2 Hz, 1H), 3.12−2.86 (m, 2H), 0.96 (s, 9H), 0.00 (s, 3H), −0.15 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 141.2, 138.4, 130.0, 128.0, 126., 125.4, 91.3, 91.3, 65.1, 64.5, 44.1, 25.8, 18.1, −5.1, −5.6; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{22}H_{31}Cl_6N_2O_3Si$ 609.0230; found 609.0230.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)ethyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1h**).* Prepared according to the general procedure (0.23 g, 86%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.30 (s, 1H), 6.02 (t, J = 6.7 Hz, 1H), 4.99−4.95 (m, 3H), 4.86 (d, J = 12.1 Hz, 1H), 4.43 (q, J = 6.3 Hz, 1H), 1.28 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 162.3, 142.6, 123.6, 91.4, 91.2, 70.1, 65.3, 64.3, 25.8, 23.51, 18.2. −4.9, −5.0; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{16}H_{27}Cl_6N_2O_3Si$ 532.9917; found 532.9912.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)but-3-en-1-yl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1i**).* Prepared according to the general procedure (0.23 g, 84%): light yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H). 8.31 (s, 1H), 5.99 (t, J = 6.8 Hz, 1H), 5.84−5.70 (m, 1H), 5.07−4.82 (m, 6H), 4.30 (t, J = 5.9 Hz, 1H), 2.40−2.25 (m, 2H), 0.88 (s, 9H), 0.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 141.0, 134.6, 125.2, 117.3, 91.3, 91.2, 74.4, 65.1, 64.3, 41.5, 25.8, 18.2, −4.7, −5.0; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{18}H_{29}Cl_6N_2O_3Si$ 559.0073; found 559.0071.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)pent-4-en-1-yl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1j**).* Prepared according to the general procedure (0.23 g, 80%): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.31 (s, 1H), 5.98 (t, J = 6.2 Hz, 1H), 5.84−5.74 (m, 1H), 5.03−4.82 (m, 6H), 4.26 (t, J = 6.2 Hz, 1H), 2.13−2.04 (m, 2H), 1.69−1.60 (m, 2H), 0.88 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 141.2, 138.4 125.8, 114.6, 91.3, 91.2, 74.2, 65.1, 64.1, 35.8 29.5, 25.8, 18.2, −4.96, −5.02; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{19}H_{31}Cl_6N_2O_3Si$ 573.0230; found 573.0229.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)allyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1k**).* Prepared according to the general procedure (0.24 g, 88%): light yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H). 8.32 (s, 1H), 6.09 (t, J = 6.6 Hz, 1H), 5.81−5.73 (m, 1H), 5.29 (d, J = 18.4 Hz, 1H), 5.12 (d, J = 10.6 Hz, 1H), 4.85−4.75 (m, 5H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 162.3, 139.9, 138.8, 124.7, 115.5, 91.3, 91.3, 75.2, 65.4, 64.2, 25.8, 18.3, −4.8, −4.9; unstable in conditions for HRMS determination.

*(E)-2-(1-((tert-Butyldimethylsilyl)oxy)but-3-yn-1-yl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((E)-**1l**).* Prepared according to the

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

general procedure (0.22 g, 82%): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.31 (s, 1H), 6.08 (t, J = 6.4 Hz, 1H), 5.02−4.82 (m, 4H), 4.44 (t, J = 6.4 Hz, 1H), 2.50−2.47 (m, 2H), 1.96 (t, J = 2.8 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 162.2, 140.0, 126.3, 81.1, 77.2, 73.3, 70.2, 65.05, 64.1, 27.8, 25.8, 18.2, −4.8, −5.0; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{18}H_{27}Cl_6N_2O_3Si$ 556.9917; found 556.9924.

*(Z)-2-Iodobut-2-ene-1,4-diol (**7**).* To a suspension of the butynediol **6** (0.5 g, 5.81 mmol) in benzene (30 mL) were added AIBN (0.76 g, 4.65 mmol) and (n-Bu)$_3$SnH (1.72 mL, 6.39 mmol). The solution was then heated for 2 h at 80 °C. The mixture was cooled to rt, and to this were added water and Et_2O. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a mixture of petroleum ether/EtOAc (2:1). (*Z*)-2-(Tributylstannyl)but-2-ene-1,4-diol derivative was isolated as an inseparable 15/1 mixture of *Z*/*E* isomers in 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (tt, J = 6.2, 1.5 Hz, 1H), 4.26 (d, J = 5.1 Hz, 2H), 4.15−4.11 (m, 3H), 1.53−1.45 (m, 6H), 1.36−1.26 (m, 7H), 0.99−0.95 (m, 6H), 0.89 (t, J = 7.0 Hz, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.5, 137.7, 69.5, 64.4, 29.1, 27.3, 13.6, 10.5; GC-MS (EI) m/z 361.0 [M − OH]$^+$. Iodine (0.48 g, 1.89 mmol) was added in a single portion to a solution of (*Z*)-2-(tributylstannyl)but-2-ene-1,4-diol (0.72 g, 1.89 mmol) in DCM (20 mL). The reaction mixture was stirred for 1 h at rt and quenched with 1 M aqueous KF solution (2 mL) and acetone (2 mL). After being stirred for 2 h, the solution was filtered through a pad of Celite. The aqueous layer was extracted with EtOAc. The organic phase was washed with saturated aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 1:1) to obtain iodide **7** (0.36 g, 87%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (tt, J = 5.5, 1.4 Hz, 1H), 5.52 (t, J = 6.1 Hz, 1H), 4.95 (t, J = 5.5 Hz, 1H), 4.05−3.98 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.8, 107.7, 69.5, 65.2; GC-MS (EI) m/z 213.9 [M]$^+$.

*(Z)-3-(Hydroxymethyl)oct-2-ene-1,4-diol (**8**).* To the solution of iodide **7** (1.05 g, 4.91 mmol) in dry THF (20 mL) was added MeLi (6.8 mL, 10.8 mmol, 1.6 M solution in diethyl ether) dropwise over 15 min at −40 °C. Stirring was continued for 5 min, and the mixture was cooled to −78 °C followed by dropwise addition of n-BuLi (6.1 mL, 7.4 mmol, 1.2 M solution in hexane). After 1.5 h, valeraldehyde (1.1 mL, 9.8 mL) was added, and the reaction mixture was warmed to 0 °C. The reaction was quenched with saturated aq NH_4Cl, and the aqueous phase was extracted with EtOAc. The organic phase was dried, filtered, and concentrated to afford an oil which was purified by flash column chromatography eluting with EtOAc to afford pure product **8** (0.38 g, 43%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, J = 7.4, 5.9 Hz, 1H), 4.56 (t, J = 7.4 Hz, 1H), 4.36−4.27 (m, 2H), 4.11−4.02 (m, 2H), 3.35 (br s, 1H), 1.90 (br s, 1H), 1.76−1.67 (m, 1H), 1.47−1.38 (m, 1H), 1.38−1.15 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.31, 126.69, 69.44, 62.97, 57.56, 35.12, 27.93, 22.53, 13.97; HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_9H_{18}O_3Na$ 197.1148; found 197.1153.

*(Z)-2-(1-((tert-Butyldimethylsilyl)oxy)pentyl)but-2-ene-1,4-diol ((Z)-**5b**).* To the solution of triol **8** (0.37 g, 2.13 mmol) in pyridine (5 mL) was added pivaloyl chloride (0.53 mL, 4.26 mmol) dropwise at 0 °C. The mixture was then stirred at 0 °C for 30 min. Solvent was evaporated, and the residue was purified by column chromatography on silica gel eluting with a mixture of petroleum ether and EtOAc (4:1) to yield bispivaloyl ester intermediate (0.45 g, 61%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (t, J=7.4 Hz, 1H) 4.8−4.57 (m, 5H), 2.32 (br s, 1H), 1.73−1.64 (m, 1H), 1.46−1.42 (m, 1H), 1.53−1.25 (m, 4H), 1.21 (s, 9H), 1.19 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.2, 141.4, 124.0, 69.4, 63.6, 178.5, 59.9, 38.8, 38.7, 35.2, 28.0, 27.2, 27.1, 22.6, 14.0; GC-MS (EI) m/z 241.1 [M − OCOtBu]$^+$. 2,6-Lutidine (0.26 mL, 2.25 mmol) was added to a solution of bispivaloyl ester intermediate (0.39 g, 1.12 mmol) in DCM (15 mL). Then *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.39 mL, 1.68 mmol) was slowly added, and the mixture was stirred for 30 min. The mixture was evaporated, and the residue was purified by flash chromatography on silica gel eluting with a mixture of petroleum ether and EtOAc (1:1) to obtain silyl-protected bispivaloyl ester intermediate (0.41 g, 80%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (dd, J = 7.8, 6.3 Hz, 1H), 4.77−4.55 (m, 4H), 4.47 (dd, J = 7.8, 5.5 Hz, 1H), 1.70−1.61 (m, 1H), 1.51−1.43 (m, 1H), 1.38−1.23 (m, 4H), 1.22 (s, 9H), 1.19 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.3,178.1, 141.9, 121.6, 70.2, 63.6, 60.0, 38.8, 38.7, 36.9, 28.0, 27.2, 27.2, 25.8, 22.6, 18.1, 14.1, −4.9, −5.1; GC-MS (EI) m/z 399.2 [M − C_4H_9]$^+$. To a stirred solution of silyl-protected bispivaloyl ester intermediate (0.41 g, 0.90 mmol) in MeOH (10 mL) was added K_2CO_3 (10 equiv) at rt, and the reaction mixture was stirred at 50 °C for 24 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel eluting with EtOAc to give the product (*Z*)-**5b** (0.25 g, 97%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (t, J = 7.0 Hz, 1H), 4.54 (t, J = 7.0 Hz, 1H), 4.33−4.26 (m, 2H), 4.19−4.07 (m, 2H), 2.33 (br s, 1H), 1.74−1.51 (m, 3H), 1.36−1.10 (m, 4H), 0.90 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.8, 126.06, 71.3, 64.9, 58.7, 36.9, 28.0, 22.6, 25.7, 18.0, 14.0, −4.8, −4.9; GC-MS (EI) m/z 231.1 [M − C_4H_9]$^+$; HRMS (ESI/TOF-Q) m/z calcd for $C_{15}H_{32}O_3Si$ Na 311.2013; found 311.2015 [M + Na]$^+$.

*(Z)-2-(1-((tert-Butyldimethylsilyl)oxy)pentyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) ((Z)-**1b**).* Prepared according to general procedure for the synthesis of bisimidates (*E*)-**1** (0.24 g, 84%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.32 (s, 1H), 5.86 (dd, J = 7.8, 5.9 Hz, 1H), 5.05−4.78 (m, 4H), 4.55 (dd, J = 5.5, 7.8 Hz, 1H), 1.75−1.66 (m, 1H), 1.61−1.55 (m, 1H), 1.42−1.20 (m, 4H), 0.90−0.87 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6. 162.5, 142.0, 121.9, 91.4, 91.3, 70.4, 68.9, 64.9, 36.9, 28.0, 25.8, 22.6, 18.1, 14.1, −4.8, −5.1; unstable in conditions for HRMS determination.

(R,R*,E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) (R*,R*-**1m**) and (S*,R*,E)-2-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)but-2-ene-1,4-diyl Bis(2,2,2-trichloroacetimidate) (S*,R*-**1m**).* *O*-TBS-protected triols were prepared in analogy to the synthesis of triols (*E*)-**5** starting with 5-methyl-3-furanaldehyde **11**. Isomeric *O*-TBS-protected triols were separated by flash chromatography and transformed to bisimidates (*R**,*R**)-**1m** and (*S**,*R**)-**1m** by a procedure analogous to the synthesis of imidates (*E*)-**1**.

*Bisimidate **1m**, Isomer **1**.* (Prepared according to the general procedure (0.12 g, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.27 (s, 1H), 5.78−5.75 (m, 1H), 5.65 (d, J = 9.0 Hz, 1H), 5.18 (d, J = 11.7 Hz, 1H), 4.74 (d, J = 11.7 Hz, 1H), 3.78 (d, J = 7.0 Hz, 1H), 1.79−1.70 (m, 1H), 1.46 (d, J = 6.2 Hz, 3H), 0.91−0.84 (m, 15H), 0.16 (s, 3H), −0.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.5, 161.5, 138.6, 132.6, 91.7, 91.3, 81.0, 70.0, 64.4, 32.4, 25.9, 20.3, 19.6, 18.1, 18.0, −4.7, −5.1; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{19}H_{33}Cl_6N_2O_3Si$ 575.0386; found 575.0384.

*Bisimidate **1m**, Isomer **2**.* Prepared according to the general procedure. (0.12 g, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.24 (s, 1H), 5.76−5.69 (m, 2H), 5.0 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 3.88 (d, J = 5.5 Hz, 1H), 1.78−1.67 (m, 1H), 1.47 (d, J = 5.9 Hz, 3H), 0.89−0.82 (m, 15H), 0.3 (s, 3H), −0.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6, 161.5, 138.2, 131.4, 91.7, 91.2, 79.8, 72.5, 65.4, 32.2, 25.9, 20.2, 19.7, 18.2, 16.8−4.1, −5.1; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{19}H_{33}Cl_6N_2O_3Si$ 575.0386; found 575.0420.

Procedure for the Preparation of Perchloric Acid Immobilized on Silica Gel ($HClO_4$−SiO_2). The catalyst system $HClO_4$−SiO_2 was prepared following the originally reported procedure.[13] To a suspension of silica gel (23.75 g, mesh no. 230−400) in Et_2O (50 mL) was added $HClO_4$ (1.25 g, 12.5 mmol, 1.78 mL of 70% aq solution of $HClO_4$), and the mixture was stirred magnetically for 30 min at rt. The Et_2O was removed evaporated, and the residue was heated at 100 °C for 72 h under vacuum to afford $HClO_4$−SiO_2 (0.5 mmol g^{-1}) as a free-flowing powder.

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

General Procedures for Cyclization of Imidates 1 to Oxazolines 2. Method A: To a solution of bisimidate **1** (0.25 mmol) in nitromethane (2 mL) was added $HClO_4$–SiO_2 (10 mol %) at 40 °C, and the reaction mixture was stirred for 30 min at 40 °C. After completion of the reaction (as monitored by TLC), the solvent was evaporated and the residue was diluted with hexane. The mixture was filtered to remove catalyst and trichloroacetamide. The filtrate was evaporated, and the residue was purified by column chromatography eluting with a mixture of Et_2O and petroleum ether (1:50). Method B: The procedure was analogous to Method A, except 10 mol % of $Fe(OTf)_3$ was used as a catalyst instead of $HClO_4$–SiO_2 and the reaction was performed at rt.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2a**).* Prepared according to the general procedure (Method A, 88 mg, 88%; Method B, 80 mg, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J = 17.0, 10.3 Hz, 1H), 5.25 (s, 1H), 5.21 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 8.6 Hz, 1H), 4.38 (d, J = 8.9 Hz, 1H), 3.71 (d, J = 2.2 Hz, 1H), 1.94–1.87 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.1, 138.9, 115.0, 81.0, 76.7, 30.6, 26.1, 22.3, 18.6, 16.8, −3.8, −3.9; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{16}H_{29}Cl_3NO_2Si$ 400.1028; found 400.1020.

*(S)-4-((S)-1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4-vinyl oxazoline (S,S-syn-**2a**).* Prepared according to the general procedure (Method A, 84 mg, 84%): $[\alpha]_{20}^{D}$ +17.16 (c = 1.0, CH_2Cl_2).

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)pentyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2b**).* Prepared according to the general procedure (Method A, 91 mg, 89%; Method B, 80 mg, 78%): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, J = 17.2, 10.2 Hz, 1H), 5.26–5.21 (m, 2H), 4.66 (d, J = 9.0 Hz, 1H), 4.37 (d, J = 8.6 Hz, 1H), 3.79 (q, J = 5.5 Hz, 1H), 1.49–1.25 (m, 6H), 0.90–0.86 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 139.3, 115.4, 76.9, 76.6, 33.1, 28.5, 26.0, 25.9, 22.9, 18.2, 13.9, −4.0, −4.2; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{17}H_{31}Cl_3NO_2Si$ 414.1184; found 414.1172.

(R)-4-((R*)-1-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2c**).* Prepared according to the general procedure (Method A, 88 mg, 80%; Method B, 80 mg, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, J = 16.7, 11.0 Hz, 1H), 5.24 (s, 1H), 5.20 (d, J = 7.0 Hz, 1H), 4.79 (d, J = 9.0 Hz, 1H), 4.41 (d, J = 9.0 Hz, 1H), 4.00 (d, J = 2.3 Hz, 1H), 1.94–1.87 (m, 1H), 1.16–0.93 (m, 27H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 140.2, 144.6, 80.9, 79.6, 76.7, 32.3, 18.4, 18.2, 18.2, 17.6, 13.4; HRMS (ESI/TOF-Q); unstable in conditions for HRMS determination.

(R)-4-((R*)-1-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2d**).* Prepared according to the general procedure (Method A, 112 mg, 86%; Method B, 95 mg, 73%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4H), 7.45–7.36 (m, 6H), 6.04 (dd, J = 17.6, 11.0 Hz, 1H), 5.11 (d, J = 13.0 Hz, 1H), 5.06 (d, J = 4.7 Hz, 1H), 4.86 (d, J = 8.6 Hz, 1H), 4.38 (d, J = 9.0 Hz, 1H), 3.79 (d, J = 1.6 Hz, 1H), 1.91–1.84 (m, 1H), 1.12 (s, 9H), 0.99 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.1, 144.3, 136.4, 136.4, 133.5, 133.4, 129.73, 129.67, 127.41, 127.36, 114.8, 81.1, 79.2, 77.1, 31.6 27.6, 27.4, 20.9, 19.9, 16.9; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{26}H_{33}Cl_3NO_2Si$ 524.1345; found 524.0768.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)pentyl)-2,2-dimethylpropyl)-4-vinyl oxazoline (syn-**2e**).* Prepared according to the general procedure (Method A, 87 mg, 85%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, J = 17.6, 10.8 Hz, 1H), 5.22 (d, J = 7.6 Hz, 1H), 5.18 (s, 1H), 4.70 (d, J = 8.6 Hz, 1H), 4.59 (d, J = 2.3 Hz, 1H), 3.62 (s, 1H), 0.97 (s, 9H), 0.93 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.8, 139.4, 113.9, 84.5, 79.9, 76.4, 36.9, 27.9, 26.6, 19.0, −2.3, −3.9; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{17}H_{31}Cl_3NO_2Si$ 414.1184; found 414.1172.

(R)-4-((R*)-4-(((tert-Butyldimethylsilyl)oxy)(phenyl)methyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2f**).* Prepared according to the general procedure (Method A, 93 mg, 86%; Method B, 79 mg, 73%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5H), 6.22 (dd, J = 17.6, 10.6 Hz, 1H), 5.32–5.28 (m, 2H), 4.95 (d, J = 9.0 Hz, 1H), 4.84 (s, 1H), 4.37 (d, J = 9.0 Hz, 1H), 0.90–0.86 (m, 12H), 0.93 (s, 12H), 0.07 (s, 3H), −0.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6, 138.3, 133.4, 128.2, 127.9, 127.6, 116.9, 93.3, 76.3, 67.5, 63.1, 25.8, 18.0, −4.5, −5.2; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{19}H_{27}Cl_3NO_2Si$ 434.0871; found 434.1209.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2g**).* Prepared according to the general procedure (Method A, 99 mg, 89%; Method B, 67 mg, 60%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 6.18 (dd, J = 17.6, 10.7 Hz, 1H), 5.43–5.31 (m, 3H), 4.73 (d, J = 8.9 Hz, 1H), 4.46 (d, J = 8.8 Hz, 1H), 2.96 (d, J = 14.0 Hz, 1H), 2.67 (dd, J = 14.0, 8.8 Hz, 1H), 0.02 (s, 3H), 0.84 (s, 9H), −0.55 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7, 138.9, 138.5, 130.1, 129.9, 128.4, 126.4, 86.7, 79.6, 78.3, 76.2, 39.5, 25.9, 18.1, −4.2, −5.1; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{20}H_{29}Cl_3NO_2Si$ 448.1028; found 448.1014.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)ethyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2h**).* Prepared according to the general procedure (Method A, 83 mg, 90%; Method B, 76 mg, 82%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, J = 18.0, 10.9 Hz, 1H), 5.27–5.22 (m, 2H), 4.77 (d, J = 8.6 Hz, 1H), 4.33 (d, J = 8.6 Hz, 1H), 4.00 (q, J = 6.3 Hz, 1H), 1.15 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.0, 139.4, 115.5, 79.4, 76.3, 72.4, 25.7, 18.2. 17.9, −4.1, −4.9; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{14}H_{25}Cl_3NO_2Si$ 372.0715; found 372.0713.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2i**).* Prepared according to the general procedure (Method A, 84 mg, 85%; Method B, 62 mg, 63%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, J = 17.1, 10.4 Hz, 1H), 5.98–5.79 (m, 1H), 5.22 (s, 1H), 5.28 (d, J = 6.1 Hz, 1H), 5.10–5.03 (m, 3H), 4.73 (d, J = 8.8 Hz, 1H), 4.36 (d, J = 8.8 Hz, 1H), 3.93 (t, J = 5.9 Hz, 1H), 2.39–2.24 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.8, 139.3, 134.9, 117.4, 115.5, 86.7, 79.4, 76.4, 76.3, 37.9, 25.9, 18.1, −3.7, −4.3; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{16}H_{27}Cl_3NO_2Si$ 398.0871; found 398.0818.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)pent-4-en-1-yl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2j**).* Prepared according to the general procedure (Method A, 84 mg, 82%; Method B, 30 mg, 30%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, J = 17.1, 10.4 Hz, 1H), 5.98–5.79 (m, 1H), 5.22 (s, 1H), 5.28 (d, J = 6.1 Hz, 1H), 5.10–5.03 (m, 3H), 4.73 (d, J = 8.8 Hz, 1H), 4.36 (d, J = 8.8 Hz, 1H), 3.93 (t, J = 5.9 Hz, 1H), 2.39–2.24 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6, 139.1, 138.2, 115.7, 114.8, 86.7, 79.6, 76.6, 32.6, 30.3, 26.0, 18.2, −3.9, −4.2; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{17}H_{29}Cl_3NO_2Si$ 412.1028; found 412.1005.

(R)-4-((R*)-1-((1-((tert-Butyldimethylsilyl)oxy)allyl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2k**).* Prepared according to the general procedure (Method A, 81 mg, 86%; Method B, 50 mg, 54%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (2:1 diastereomeric mixture) 6.16–5.66 (m, 1H), 5.33–5.18 (m, 4H), 4.46 (d, J = 8.6 Hz, 1H), 4.46 (d, J = 8.8 Hz, 1H), 4.46–4.20 (m, 2H), 0.89 (s, 9 H), 0.20–0.17 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 152.3, 138.9, 136.2, 135.9, 134.6, 118.4, 117.7, 117.2, 115.9, 81.5, 78.9, 76.1, 68.9, 45.3, 25.7, 18.1, −3.7, −4.1, −4.9, −5.1; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{15}H_{25}Cl_3NO_2Si$ 384.0715; found 384.0699.

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)but-3-yn-1-yl)-2-(trichloromethyl)-4-vinyl oxazoline (syn-**2l**).* Prepared according to the general procedure (Method A, 34 mg, 35%; Method B, 15 mg, 15%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dd, J = 17.6, 10.5 Hz, 1H), 4.93 (d, J = 8.6 Hz, 1H), 4.35 (d, J = 8.8 Hz, 1H), 4.00 (t, J = 5.5 Hz, 1H), 2.59–2.35 (m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 0.89 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 138.7, 116.1, 86.6, 81.3, 79.3, 75.0, 71.0, 25.9, 23.4, 18.1, −4.0, −4.7; HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{16}H_{25}Cl_3NO_2Si$ 396.0715; found 396.0707.

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934–5943

(R)-4-((R*)-1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4-((E)-prop-1-en-1-yl)-oxazoline (syn-**2m**).* Prepared according to the general procedure (Method A, 58 mg, 82%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72−5.59 (d, J = 15.7 Hz, 1H, H6), 5.64 (m, 1H, H7), 4.70 (d, J = 9.0 Hz, 1H, H4), 4.34 (d, J = 9.0 Hz, 1H, H4′), 3.68 (d, J = 2.4 Hz, 1H, H8), 1.87−1.94 (m, 1H, H9), 1.72 (dd, J = 6.2, 1.6 Hz, 3H, H12), 0.97−0.90 (m, 15H, $-C(CH_3)_2$, $-Si-C(CH_3)_3$), 0.10 (s, 6H, $-Si(CH_3)_2$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (C2), 133.6 (C6), 125.9 (C7), 81.3 (C8), 79.1 (C4), 77.1 (C5), 30.5 (C9), 26.1 (C22, C23,C24), 22.4 (C12), 18.6 (C11), 18.1 (C10), 16.9 (C19), −3.6 (C20), −4.0 (C21); HRMS (ESI/TOF-Q): unstable in HRMS conditions. See Supporting Information for 2D spectra.

*6-(1-((tert-Butyldimethylsilyl)oxy)-2-methylpropyl)-2-(trichloromethyl)-4,7-dihydro-1,3-oxazepine (**9**).* Isolated as a byproduct from the cyclization experiments of bisimidate **1a** in toluene using $Fe(OTf)_3$ as a catalyst (12 mg, 10 mol %): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (t, J = 5.1 Hz, 1H, H2), 4.97 (d, J = 13.7 Hz, 1H, H7), 4.81 (d, J = 13.7 Hz, 1H, H7′), 4.47 (dd, J = 18.8, 5.1 Hz, 1H, H3), 4.30 (dd, J = 18.8, 5.5 Hz, 1H, H3′), 3.70 (d, J = 7.4 Hz, 1H, H8), 1.74−1.65 (m, 1H, H9), 0.83−0.93 (m, 15H, $-C(CH_3)_2$, $-Si-C(CH_3)_3$), 0.04 (s, 3H, $-Si-CH_3$), −0.01 (s, 3H, $-Si-CH_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.4, 142.3, 128.7, 81.0, 67.3, 45.3, 33.2, 25.8, 19.1, 18.6, 18.1, −4.5, −5.1. See Supporting Information for 2D spectra.

N-((3R,4R*)-4-((tert-Butyldimethylsilyl)oxy)-3-(hydroxymethyl)-5-methylhex-1-en-3-yl)-2,2,2-trichloroacetamide (**10**).* To a solution of oxazoline *syn*-**2a** (0.2 g, 0.50 mmol) in mixture of MeCN and H_2O (5:1, 5 mL) was added *p*-TsOH (0.104 g, 0.55 mmol), and the reaction mixture was stirred for 1 h at rt. Completion of the reaction was monitored by TLC. The reaction mixture was then concentrated in vacuo and the residue diluted with Et_2O followed by neutralization with 5% aq $NaHCO_3$ (2 × 5 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude product. The crude residue was purified by column chromatography eluting with a mixture of EtOAc and petroleum ether (1:8) to yield the product **7** (0.188 g 90%) as colorless solid: mp 94−96 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.96 (dd, J = 17.6, 11.4 Hz, 1H), 5.37 (d, J = 11.5 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 4.08 (d, J = 11.4 Hz, 1H), 3.84 (d, J = 1.6 Hz, 1H), 3.78 (d, J = 11.4 Hz, 1H), 2.12−2.05 (m, 1H), 0.99−0.92 (m, 15H), 0.16 (s, 3H), 0.15 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 134.0, 116.1, 93.1, 78.4, 67.6, 66.7, 33.0, 26.2, 22.4, 18.6, −3.3, −4.0; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{16}H_{31}Cl_3NO_3Si$ 418.1133; found 418.1125.

*N-((3S,4S)-4-((tert-Butyldimethylsilyl)oxy)-3-(hydroxymethyl)-5-methylhex-1-en-3-yl)-2,2,2-trichloroacetamide (S,S-**10**).* Prepared in analogy to the racemate (0.18 g, 88%): $[\alpha]_{20}^{D}$ +6.98 (c = 1.0, CH_2Cl_2), 80% ee.

N-((3S,4R*)-4-((tert-Butyldimethylsilyl)oxy)-3-formyl-5-methylhex-1-en-3-yl)-2,2,2-trichloroacetamide (**12**).* To a solution of alcohol **10** (0.168 g, 0.40 mmol) in dry DCM (10 mL) was added DMP (1.4 mL, 0.48 mmol), and the reaction mixture was stirred for 6 h at rt. Completion of the reaction was monitored by TLC. The reaction mixture was then diluted with DCM and neutralized with $NaHCO_3$ (2 × 10 mL). Organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude product. The crude residue was purified with column chromatography eluting with a mixture of EtOAc and petroleum ether (1:16) to yield the product **8** (0.155g, 90%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.98 (s, 1H), 6.13 (dd, J = 17.6, 10.8 Hz, 1H), 5.40 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 17.6 Hz, 1H), 4.45 (d, J = 1.6 Hz, 1H), 0.98 (d, J = 7.0 Hz, 3H), 2.0 (m, 1H), 0.93 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.15 (s, 3H), 0.11 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 160.7, 132.0, 118.5, 92.5, 78.8, 77.0, 71.5, 29.8, 26.1, 21.6, 18.5, 15.8, −3.4, −4.1; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{16}H_{29}Cl_3NO_3Si$ 416.0977; found 416.0970.

(2S,3R*)-3-((tert-Butyldimethylsilyl)oxy)-4-methyl-2-(2,2,2-trichloroacetamido)-2-vinylpentanoic acid (**13**).* To a solution of aldehyde **12** (0.21 g, 0.50 mmol) and 2-methylbut-2-ene (0.35 mL, 6 mmol) in THF (3 mL) and *t*-BuOH (3 mL) was added a solution of $NaClO_2$ (0.23g, 2.5 mmol) and NaH_2PO_4 (0.30 g, 2.5 mmol) in H_2O at rt. After being stirred at room temperature for 1 h, the mixture was quenched with aq 1 N HCl (5 mL), and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude product. This was purified with column chromatography eluting with a mixture of EtOAc and petroleum ether (1:8) to yield the product **9** (0.15 g, 70%) as colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 6.27 (dd, J = 17.6, 11.0 Hz, 1H), 5.41 (d, J = 11.0 Hz, 1H), 5.38 (d, J = 17.6 Hz, 1H), 4.74 (s, 1H), 2.07−1.99 (m, 1H), 0.23 (s, 3H), 0.20 (s, 3H), 1.03−0.88 (m, 15H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 160.7, 133.4, 119.0, 92.4, 78.7, 29.8, 26.0, 21.4, 18.4, 16.1, −3.7, −3.9; HRMS (ESI/TOF-Q) m/z $[M + H]^+$ calcd for $C_{16}H_{29}Cl_3NO_4Si$ 432.0926; found 432.0926.

N-((2S,3R*)-3-((tert-Butyldimethylsilyl)oxy)-2-formyl-1-hydroxy-4-methylpentan-2-yl)-2,2,2-trichloroacetamide (**14**).* Ozone was introduced into a solution of alcohol **10** (0.2 g, 0.60 mmol) in EtOH (10 mL) for 15 min at −78 °C. After complete consumption of the starting material was confirmed (TLC analysis), excess ozone was removed with a stream of Ar gas. To the reaction mixture was added PPh_3 (0.78 g, 3 mmol) at −78 °C, and the mixture was stirred for 5 h at rt. The resulting mixture was diluted with 5% EtOAc in hexane and filtered to remove triphenylphosphine oxide. The solvent was evaporated, and the crude product was purified by column chromatography eluting with a mixture of EtOAc and petroleum ether (1:9) to yield the product **10** (176 mg, 70%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.57 (s, 1H), 5.92 (s, 1H), 4.37 (s, 1H), 4.23 (d, J = 11.4 Hz, 1H), 3.07 (br s, OH), 3.53 (s, 1H), 1.87−1.80 (m, 1H), 1.07−1.04 (m, 6H), 0.96 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.2, 164.4, 74.6, 68.5, 65.9, 61.7, 31.8, 26.1, 21.7, 18.6, 16.8, −4.3, −3.8; HRMS (ESI/TOF-Q): unstable in conditions for HRMS determination.

■ ASSOCIATED CONTENT

Supporting Information

ORTEP diagram for compound **10**. Complete set of results for the imidate **1** cyclization studies. Copies of ^{1}H NMR, ^{13}C NMR, and 2D spectra for compounds **1**−**14**. Copies of chiral HPLC chromatograms for compounds (*S*)-**4a** and *S*,*S*-**10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00529.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aigars@osi.lv.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The funding from European Social Fund (Project No. 1DP/1.1.1.2.0/13/APIA/VIAA/006) is acknowledged. We thank Prof. E. Liepins for assistance with 2D NMR spectra.

■ REFERENCES

(1) Reviews on C-quaternary amino acids: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569−623. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127−5143. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (d) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732. (e) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537−4558. (f) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1−63. (g) Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406−430.

(2) Recent stereoselective synthesis methods of C-quaternary amino acids: (a) Di Giacomo, M.; Vinci, V.; Serra, M.; Colombo, L. *Tetrahedron: Asymmetry* **2008**, *19*, 247−257. (b) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem.*

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943

Soc. **2008**, *130*, 12031−12037. (c) Zhang, X.; Cividino, P.; Poisson, J.-F.; Shpak-Kraievskyi, P.; Laurent, M. Y.; Martel, A.; Dujardin, G.; Py, S. *Org. Lett.* **2014**, *16*, 1936−1939. (d) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711−10718. (e) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530−5541. (f) Hata, S.; Koyama, H.; Shimizu, M. *J. Org. Chem.* **2011**, *76*, 9670−9677. (g) Iosub, V.; Haberl, A. R.; Leung, J.; Tang, M.; Vembaiyan, K.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2010**, *75*, 1612−1619. (h) Núñez-Villanueva, D.; Bonache, M. A.; Infantes, L.; García-López, M. T.; Martín-Martínez, M.; González-Muñiz, R. *J. Org. Chem.* **2011**, *76*, 6592−6603. (i) Berkowitz, D. B.; Wu, B.; Li, H. *Org. Lett.* **2006**, *8*, 971−974. (j) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611−2613.

(3) Woltering, T. J.; Adam, G.; Huguenin, P.; Wichmann, J.; Kolczewski, S.; Gatti, S.; Bourson, A.; Kew, J. N. C.; Richards, G.; Kemp, J. A.; Mutel, V.; Knoflach, F. *ChemMedChem* **2008**, *3*, 323−335.

(4) Fairhurst, N. W. G.; Mahon, M. F.; Munday, R. H.; Carbery, D. R. *Org. Lett.* **2012**, *14*, 756−759.

(5) Fairhurst, N. W. G.; Munday, R. H.; Carbery, D. R. *Synlett* **2013**, *24*, 496−498.

(6) Ariza, X.; Cornellà, J.; Font-Bardia, M.; Garcia, J.; Ortiz, J.; Sánchez, C.; Solans, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 4202−4205.

(7) (a) Martinková, M.; Gonda, J.; Uhríková, A.; Raschmanová, J. Š.; Kuchár, J. *Carbohydr. Res.* **2012**, *352*, 23−36. (b) Kaiya, Y.; Hasegawa, J.; Momose, T.; Sato, T.; Chida, N. *Chem.—Asian J.* **2011**, *6*, 209−219. (c) Momose, T.; Kaiya, Y.; Hasegawa, J.; Sato, T.; Chida, N. *Synthesis* **2009**, 2983−2991. (d) Sato, H.; Sato, K.; Iida, M.; Yamanaka, H.; Oishi, T.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1943−1947. (e) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151−154. (f) Oishi, T.; Ando, K.; Chida, N. *Chem. Commun.* **2001**, 1932−1933. (g) For Overman rearrangement see: Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456 and references cited therein.

(8) (a) Murga, J.; Portolés, R.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1807−1816. (b) Portolés, R.; Murga, J.; Falomir, E.; Carda, M.; Uriel, S.; Marco, J. A. *Synlett* **2007**, *2002*, 711−714.

(9) Our results in acyclic systems: (a) Grigorjeva, L.; Jirgensons, A. *Eur. J. Org. Chem.* **2011**, 2421−2425. (b) Grigorjeva, L.; Maleckis, A.; Klimovica, K.; Skvorcova, M.; Ivdra, N.; Leitis, G.; Jirgensons, A. *Chem. Heterocycl. Compd.* **2012**, *48*, 919−924. (c) Klimovica, K.; Grigorjeva, L.; Maleckis, A.; Popelis, J.; Jirgensons, A. *Synlett* **2011**, 2849−2851. (d) Jirgensons, A.; Grigorjeva, L.; Maleckis, A.; Klimovica, K. *Synlett* **2013**, 2345−2349. (e) Grigorjeva, L.; Kinens, A.; Jirgensons, A. *J. Org. Chem.* **2015**, *80*, 920−927.

(10) Seminal examples in cyclic systems: (a) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782−3783. (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552−553. (c) Ramstadius, C.; Hekmat, O.; Eriksson, L.; Stålbrand, H.; Cumpstey, I. *Tetrahedron: Asymmetry* **2009**, *20*, 795−807.

(11) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011−2018.

(12) The synthesis of a protected derivative has been reported: Commeiras, L.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* **2003**, *44*, 2311−2314.

(13) (a) Chakraborti, A. K.; Singh, B.; Chankeshwara, S. V.; Patel, A. R. *J. Org. Chem.* **2009**, *74*, 5967−5974. (b) Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896−1897. (c) Khatik, G. L.; Sharma, G.; Kumar, R.; Chakraborti, A. K. *Tetrahedron* **2007**, *63*, 1200−1210.

(14) Ghosh, A. K.; Chen, Z.-H. *Org. Lett.* **2013**, *15*, 5088−5091.

(15) Bai, H.; Bailey, S.; Bhumralkar, D. R.; Bi, F. C.; Guo, F.; He, M.; Humphries, P. S.; Ling, A. L.; Lou, J.; Nukui, S.; Zhou, R. U.S. Patent Appl. 20080280875 A1, November 13, 2008; *Chem. Abstr. 149*, 556429.

(16) Kelly, A. R.; Kerrigan, M. H.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 4097−4104.

(17) Kusababe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085−2091.

(18) Charbonnet, N.; Riguet, E.; Bochet, C. *Synlett* **2011**, 2231−2233.

(19) Gryparis, C.; Lykakis, I. N.; Efe, C.; Zaravinos, I.-P.; Vidali, T.; Kladou, E.; Stratakis, M. *Org. Biomol. Chem.* **2011**, *9*, 5655−5658.

(20) Lanfranchi, D. A.; Bour, C.; Boff, B.; Hanquet, G. *Eur. J. Org. Chem.* **2010**, 5232−5247.

(21) Shengule, S. R.; Willis, A. C.; Pyne, S. G. *Tetrahedron* **2013**, *69*, 8042−8050.

(22) Lee, A. S.; Chu, S.; Chang, Y.; Wang, S. *Tetrahedron Lett.* **2004**, *45*, 1551−1533.

DOI: 10.1021/acs.joc.5b00529
J. Org. Chem. 2015, 80, 5934−5943