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Intramolecular conjugate addition of γ- and δ-trichloroacetimidoyloxy-α,β-unsaturated esters in an acyclic system

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Abstract

An intramolecular conjugate addition of γ- and δ-trichloroacetimidoyloxy-α,β-unsaturated esters, a new way to construct 1,2-amino or 1,3-amino alcohol moieties in an acyclic system, is described. Very concise synthesis of D-vancosamine and 3-*epi*-D-vancosamine derivatives was also achieved utilizing this methodology.

Keywords: Intramolecular conjugate addition; Trichloroacetimidate; Vancosamine

1. Introduction

Amino sugars, especially deoxyamino sugars, are found in clinically important antibiotics such as antimicrobial macrolides and anthracycline antitumor antibiotics.[1] In most instances, the sugar parts of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not yet been evaluated.[2] We envisaged that a modification of the sugar moieties of these antibiotics may serve as a tool for investigating the significance of amino sugars and the structure–activity relationship, and elucidating the biosynthetic route of antibiotics.[3,4] For this purpose, a versatile and synthetic route for deoxyamino sugars is highly desirable. We were especially interested in developing a new synthetic route for deoxyamino sugars from non-sugar materials.[5,6]

1,2- and 1,3-amino alcohol moieties are often found in natural products and potent drugs, as seen in deoxyamino sugars, and they have also been used as synthetic intermediates. Thus, an effective method for the introduction of functionality to acyclic olefinic systems is required. While a variety of stereoselective synthetic methods especially for 1,2-amino alcohol moieties have been developed,[7] there are relatively few methods for 1,3-amino alcohols.[8] During our course of developing a simple synthetic strategy to deoxyamino sugars, an intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters was found.[6,9] We here disclose the details of the trichloroacetimidate-mediated functionalization useful for the introduction of a nitrogen functionality[10] on the β-carbon of γ- and δ-hydroxy-α,β-unsaturated esters, a new way to construct 1,2-amino or 1,3-amino alcohol moieties in an acyclic system.

2. Results and discussion

2.1. Intramolecular conjugate additions of γ-trichloroacetimidoyloxy-α,β-unsaturated esters

In order to estimate this intramolecular conjugate addition, we first investigated the cyclization reaction of several kinds of γ-trichloroacetimidoyloxy-α,β-unsaturated esters (Table 1), which were prepared from the corresponding allylic alcohols[11] by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trichloroacetonitrile in good to excellent yields.[12] When the substrate trichloroacetimidates **1a–d** were treated with

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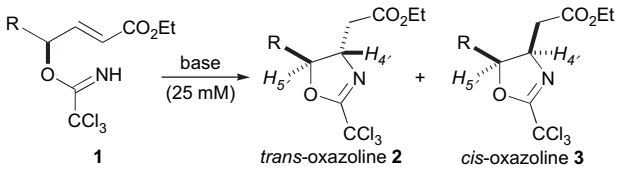
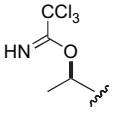
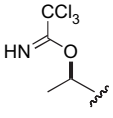
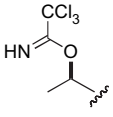
Table 1
Intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters **1**[a]



Entry	Substrate	R	Conditions	Product Ratio **2/3**	Yield[b] (%)
1	**1a**	Me	DBU (0.1 equiv), −10 °C	73:27[c]	93
2	**1a**	Me	*tert*-BuOK (1.0 equiv), 0 °C	66:34[c]	62
3	**1a**	Me	*tert*-BuOK (0.5 equiv), −78 °C	65:35[c]	85
4	**1a**	Me	NaH (1.4 equiv), −20 °C	68:32[c]	81
5	**1b**		DBU (0.3 equiv), 0 °C	78:22[d]	86
6	**1b**		*tert*-BuOK (1.0 equiv), 0 °C	49:51[d]	65
7	**1b**		*tert*-BuOK (0.1 equiv), −20 °C	47:53[d]	79
8	**1b**		*tert*-BuOK (0.1 equiv), −78 °C	28:72[d]	81
9[e]	**1c**		DBU (0.1 equiv), 0 °C	96:4[d]	97
10[e]	**1c**		*tert*-BuOK (0.1 equiv), −62 °C	40:60[f]	90
11	**1d**		DBU (1.6 equiv), −20 °C	86:14[c]	66
12	**1d**		*tert*-BuOK (0.6 equiv), −100 °C	50:50[c]	82
13	**1d**		NaH (2.2 equiv), −20 °C	67:33[c]	82

[a] All reactions were performed in CH_3CN (DBU) or THF (*tert*-BuOK, NaH).
[b] Combined yield.
[c] Inseparable products ratio determined by 270 MHz ^{1}H NMR spectroscopy.
[d] Products ratio calculated from their own isolated yield.
[e] Experimental results obtained when ***ent*-1c** was used.
[f] Separation of the isomers was not fully carried out and its ratio was determined by 270 MHz ^{1}H NMR spectroscopy.

a catalytic amount of DBU in CH_3CN, a facile cyclization occurred producing the oxazolines **2** (*trans*) and **3** (*cis*) (Table 1). The cis–trans stereochemistry of the oxazolines was determined according to the value of their proton coupling constants ($J_{H\text{-}4',H\text{-}5'}$),[13] and it was also confirmed by nuclear Overhauser enhancement (NOE) experiments.[6] In the case of substrate **1a**, the ratio of **2a/3a** was not affected by changing the conditions with maintained moderate trans-selectivity (entries 1–4). In the series with more sterically bulky R groups, when DBU was used as a base, higher trans-selectivity was observed (entry 5, 9, 11). Cyclization was also performed with stoichiometric amount of sodium hydride (NaH) in THF (entry 4, 13), showing little difference in the stereoselectivity. The trans-selectivity observed in the cyclization can be anticipated using the transition state (TS) models shown in Figure 1. The cyclization is thought to proceed through trans-TS model to give the *trans*-oxazolines, since cis-TS model is unfavorable than the trans-TS model due to its steric hindrance between the side chain R and the alkenyl group. With the exception of the compound **1c**, trans-selectivity was not so high like the case of the carbamate-mediated intramolecular conjugate additions.[14]

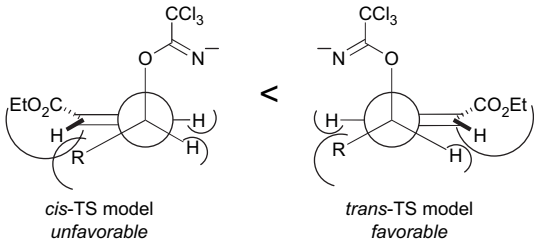


Figure 1. Proposed transition state models for cyclization.

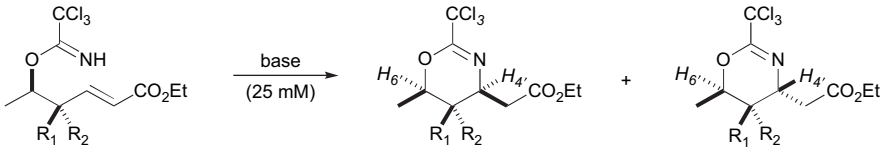
Interestingly, reversal of diastereofacial selectivity was found (entry 6 and 10). In fact, upon treatment with potassium *tert*-butoxide (*tert*-BuOK) in THF, *cis*-oxazoline was dominantly produced. A notable temperature effect; namely, the ratio of *cis*-oxazoline increased with decreasing the reaction temperature, was also found (entries 6–8). These results indicated that *trans*-oxazoline was the thermodynamically controlled product as compared with the result of DBU. The reversal of diastereofacial selectivity was realized only at very low temperature as not reported in the carbamate-mediated intramolecular conjugate additions. It might be anticipated that the energy difference between trans-TS model and cis-TS model was somewhat smaller than those of the carbamate derivatives.

It is interesting to note that bis-trichloroacetimidate **1d** showed a marked tendency to cyclize five-membered oxazoline ring in the competitive cyclization between allylic and homoallylic trichloroacetimidates (entries 11–13). In this case, moderate trans-selectivity was observed by the treatment of DBU or NaH, while reversal of the selectivity was not fully realized with *tert*-BuOK even at −100 °C.

2.2. Intramolecular conjugate additions of δ-trichloroacetimidoyloxy-α,β-unsaturated esters

Next, we investigated the intramolecular conjugate additions of δ-trichloroacetimidoyloxy-α,β-unsaturated esters **4** (Table 2), which were prepared from the corresponding homoallylic alcohols.[15] They were smoothly cyclized to six-membered cyclic compounds; namely, dihydrooxazines **5** (*cis*) and **6** (*trans*) by the treatment with *tert*-BuOK or NaH.

Table 2
Intramolecular conjugate addition of δ-trichloroacetimidoyloxy-α,β-unsaturated esters **4**[a]



4 *cis*-dihydrooxazine **5** *trans*-dihydrooxazine **6**

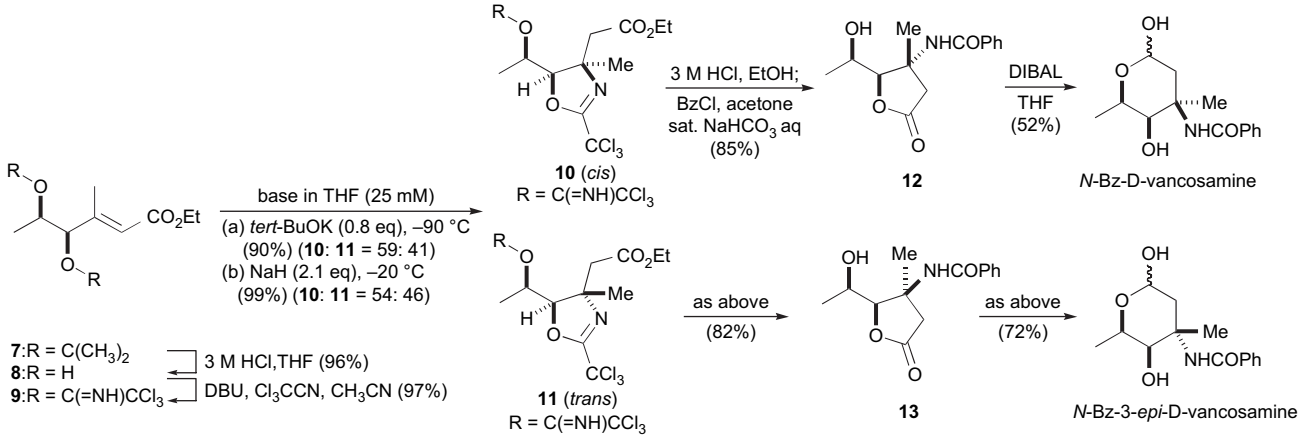
Entry	Substrate			Conditions	Product	
		R_1	R_2		Ratio **5/6**	Yield[b] (%)
1	**4a**	H	H	*tert*-BuOK (0.4 equiv), 0 °C	88:12[c]	86
2	**4a**	H	H	NaH (1.1 equiv), 0 °C	87:13[c]	86
3	**4a**	H	H	DBU (0.4 equiv), rt	—	—[d]
4	**4b**[e]	H	OMe	*tert*-BuOK (0.34 equiv), −20 °C	Exclusively cis	79
5	**4b**[e]	H	OMe	NaH (1.2 equiv), −20 °C	Exclusively cis	88
6	**4b**[e]	H	OMe	DBU (0.4 equiv), rt	—	—[d]
7	**4c**	OPMP	H	*tert*-BuOK (0.4 equiv), −20 °C	28:72[f]	79
8	**4c**	OPMP	H	NaH (1.1 equiv), 0 °C	24:76[f]	89
9	**4d**	OTBS	H	*tert*-BuOK (0.4 equiv), 0 °C	41:59[f]	76
10	**4d**	OTBS	H	NaH (1.1 equiv), 0 °C	28:72[f]	79
11	**4d**	OTBS	H	DBU (2.3 equiv), rt	—	—[g]

[a] All reactions were performed in CH_3CN (DBU) or THF (*tert*-BuOK, NaH).
[b] Combined yield.
[c] Inseparable products ratio determined by 270 MHz ^1H NMR spectroscopy.
[d] Removal of *O*-trichloroacetimino group was mainly observed.
[e] Racemic material was used.
[f] Products ratio calculated from their own isolated yield.
[g] Removal of *O*-trichloroacetimino group and subsequent TBS group migration was observed.

It should be noted that in the δ-trichloroacetimidoyloxy series the cyclization was not realized with DBU even at rt, and gradual removal of *O*-trichloroacetimino group was mainly observed instead (entry 3, 6, 11). The stereochemistry of the obtained dihydrooxazines was determined by NOE experiments, and it was also confirmed according to the value of their proton coupling constants.[16] In the case of substrate **4a**, cyclization was observed with moderate cis-selectivity (entry 1, 2). The γ-substituents played an important role for switching the diastereofacial selectivity. Actually, when a methoxy group was introduced at R_2 position, the cyclization proceeded with complete cis-selectivity (entry 4, 5), while when R_1 group was substituted by *p*-methoxyphenyloxy (PMPO) group or *tert*-butyldimethylsilyloxy (TBSO) group, the reaction was found to be carried out with moderate trans-selectivity (entries 7–10). Similar reversal of selectivity was also observed in the case of the carbamate-mediated intramolecular conjugate addition, and it was explained as cooperation of the steric and stereoelectronic effects.[14]

2.3. Concise synthesis of D-vancosamine and its 3-epimer

We planned to utilize the oxazoline ring formation for the synthesis of C-branched deoxyamino sugars, especially for vancosamine,[17] the deoxyamino sugar constituent of vancomycin, and other antibiotics (Scheme 1). For the introduction



Scheme 1. Concise synthesis of D-vancosamine and 3-*epi*-D-vancosamine derivatives.

of the C(3) methyl-branched amino group of the vancosamine, we envisioned the methyl-branched bis-trichloroacetimidate **9** as a substrate for the intramolecular conjugate addition. The bis-imidate **9** was synthesized from the chiral diol **8**, which was prepared from the known acetonide **7**,[18] in 97% yield. Bis-trichloroacetimidate **9** underwent a smooth conjugate addition constructing the oxazolines **10** (*cis*) and **11** (*trans*) by the treatment of *tert*-BuOK (**10/11**=59:41; 90% yield) or NaH (**10/11**=54:46; 99% yield) in THF. When DBU was used as a base, effective cyclization was not realized, since unknown by-products formation was observed while the starting imidate **9** still remained. The cis–trans stereochemistry of the oxazolines was confirmed by nuclear Overhauser enhancement (NOE) experiments,[19] and it was ultimately determined by conversion to the vancosamine derivatives. Introduction of the methyl group on the double bond was expected to reduce the energy difference between trans-TS model and cis-TS model in Figure 1, but the effect was not so strong as expected. Then high cis-selectivity was not fully realized, however, the obtained oxazolines in high yield were fortunately separable, different from the case of **2d** and **3d**. Next, the hydrolysis of oxazoline ring and spontaneous γ-lactone formation and N-benzoylation were, respectively, carried out to give the γ-lactone **12** and **13** in good yields (85% for **12**; 82% for **13**). Final half reduction was successfully effected by diisopropylaluminum hydride (DIBAL) to produce *N*-Bz-D-vancosamine (52%) and *N*-Bz-3-*epi*-D-vancosamine (72%), respectively. The ratios of α- and β-anomers after ca. 1 month in DMSO-d_6 (α/β=ca. 1:3 for *N*-Bz-D-vancosamine; ca. 1:1 for *N*-Bz-3-*epi*-D-vancosamine) together with the detection of a small amount of the furanose forms were well accorded with that reported in the literature.[20] Additionally, their absolute values of specific optical rotation were also in good agreement with the enantiomers.[20]

3. Conclusion

In conclusion, we have succeeded in developing a trichloroacetimidate-mediated method for the introduction of a nitrogen functionality on the β-carbon of γ- and δ-hydroxy-α,β-unsaturated esters, a novel way for constructing 1,2-amino or 1,3-amino alcohol moieties in an acyclic system. Very concise synthesis of D-vancosamine derivatives and its 3-epimer was also achieved utilizing this methodology. Further investigations concerning the scope of this methodology are in progress.

4. Experimental section

4.1. General

All melting points are uncorrected. NMR spectra were recorded on a JEOL GSX-270 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in δ values based on internal tetramethylsilane (δ_H=0) or solvent signal ($CDCl_3$ δ_C=77.0; DMSO-d_6 δ_C=39.5; C_6D_6 δ_H=7.15) as reference. IR spectra were recorded on a HORIBA FT-720 Fourier-transform infrared spectrometer. Optical rotations were measured on a Rudolph Research Analytical AUTOPOL V polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured on a Applied Biosystems QSTAR XL hybrid Q-TOF or a JEOL JMS-SX102A (FAB and EI) mass spectrometer. Flash silica gel column chromatography was carried out on KANTO CHEMICAL CO., INC. Silica Gel 60 N (spherical, neutral, 40–50 μm) or Merck Kieselgel 60 (230–400 mesh), Art. Nr. 9385.

4.2. General procedure for the trichloroacetimidates

To a cooled (bath temp below −20 °C) solution of corresponding alcohol and trichloroacetonitrile (10 equiv) in acetonitrile was added dropwise DBU (ca. 1.1–1.2 equiv), and the mixture was stirred for ca. 30 min under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into cold saturated aq NH_4Cl and extracted with EtOAc. The extract was washed successively with saturated aq NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography to give the trichloroacetimidate.

4.3. Data of the trichloroacetimidates

4.3.1. Ethyl (2E,4S)-4-trichloroacetimidoyloxypent-2-enoate (*1a*)

Yield: 77%; colorless oil; $[\alpha]_D^{27.1}$ −0.637 (*c* 1.57, $CHCl_3$); ν_{max} (neat) 3344, 2983, 1722, 1664, 1308, 1282, 1182, 1076, 1043, 976, 796, 648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 6.96 (dd, *J*=4.5, 15.8 Hz, 1H), 6.09 (dd, *J*=1.7, 15.6 Hz, 1H), 5.65 (ddq, *J*=1.7, 4.7, 6.6 Hz, 1H), 4.21 (q, *J*=7.1 Hz, 2H), 1.49 (d, *J*=6.6 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.1, 161.5, 145.5, 121.1, 91.3, 73.6, 60.6, 19.0, 14.2. Anal. Calcd for $C_9H_{12}Cl_3NO_3$: C, 37.46; H, 4.19; N, 4.85. Found: C, 37.02; H, 3.89; N, 4.66%.

4.3.2. Ethyl (2E,4R,5R)-5-tert-butyldimethylsilyloxy-4-trichloroacetimidoyloxyhex-2-enoate (*1b*)

Yield: 99%; colorless oil; $[\alpha]_D^{24.5}$ +40.0 (*c* 1.17, $CHCl_3$); ν_{max} (neat) 3348, 2956, 2931, 2858, 1724, 1670, 1660, 1311, 1259, 1180, 1099, 1078, 1049, 835, 798, 777, 648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.05 (dd, *J*=4.0, 15.9 Hz, 1H), 6.14 (dd, *J*=1.8, 15.9 Hz, 1H), 5.52 (ddd, *J*=1.9, 4.6, 4.6 Hz, 1H), 4.23–4.10 (m, 1H), 4.21 (q, *J*=7.0 Hz, 2H), 1.30 (t, *J*=7.0 Hz, 3H), 1.15 (d, *J*=6.2 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.9, 161.9, 141.8, 122.6, 91.2, 79.5, 67.5, 60.5, 25.7, 18.5, 17.9, 14.2, −4.9. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.47; H, 6.23; N, 3.15%.

4.3.3. Ethyl (2E,4S,5R)-5-tert-butyldimethylsilyloxy-4-trichloroacetimidoyloxyhex-2-enoate (*ent-1c*)

Yield: 94%; colorless oil; $[\alpha]_D^{23.7}$ −7.60 (*c* 2.31, $CHCl_3$); ν_{max} (neat) 3348, 2956, 2931, 2858, 1724, 1670, 1377, 1311, 1259, 1180, 1117, 1080, 1047, 984, 831, 796, 777, 648 cm^{-1}; ^{1}H

NMR (270 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 7.01 (dd, J=5.1, 16.0 Hz, 1H), 6.07 (dd, J=1.5, 15.8 Hz, 1H), 5.39 (ddd, J=1.5, 5.1, 5.1 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 4.06 (dq, J=5.3, 6.3 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H), 1.25 (d, J=6.4 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.8, 161.7, 142.3, 122.9, 91.3, 81.0, 69.8, 60.5, 25.7, 20.1, 17.9, 14.2, −4.5, −5.0. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.70; H, 6.31; N, 3.12%.

*4.3.4. Ethyl (2E,4R,5R)-4,5-bis(trichloroacetimidoyloxy)-hex-2-enoate (**1d**)*

Yield: 96%; colorless oil; $[\alpha]_D^{28.1}$ +26.1 (c 0.980, $CHCl_3$); ν_{max} (neat) 3344, 2985, 1724, 1664, 1300, 1282, 1184, 1074, 831, 796, 648, 490 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 8.44 (br s, 1H), 6.98 (dd, J=4.7, 15.8 Hz, 1H), 6.21 (dd, J=1.7, 15.8 Hz, 1H), 5.86 (ddd, J=1.7, 4.9, 4.9 Hz, 1H), 5.41 (dq, J=5.3, 6.4 Hz, 1H), 4.21 (dq, J=7.2, 11.0 Hz, 1H), 4.20 (dq, J=7.1, 10.9 Hz, 1H), 1.42 (d, J=6.4 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.5, 161.6, 161.3, 140.0, 124.2, 91.2, 90.9, 76.7, 74.1, 60.7, 14.5, 14.2. Anal. Calcd for $C_{12}H_{14}Cl_6N_2O_4$: C, 31.13; H, 3.05; N, 6.05. Found: C, 31.12; H, 3.08; N, 5.89%.

*4.3.5. Ethyl (2E,5R)-5-(trichloroacetimidoyloxy)hex-2-enoate (**4a**)*

Yield: 85%; colorless oil; $[\alpha]_D^{29.4}$ +6.12 (c 1.05, $CHCl_3$); ν_{max} (neat) 3344, 2981, 1720, 1662, 1321, 1306, 1292, 1273, 1180, 1080, 1057, 1045, 980, 796, 648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 6.95 (ddd, J=7.4, 7.4, 15.6 Hz, 1H), 5.91 (ddd, J=1.4, 1.4, 15.7 Hz, 1H), 5.16 (ddq, J=6.2, 6.2, 6.2 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 2.63 (dddd, J=1.4, 6.5, 7.4, 14.7 Hz, 1H), 2.59 (dddd, J=1.6, 5.6, 7.4, 14.7 Hz, 1H), 1.82 (d, J=6.2 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.1, 161.9, 143.2, 124.4, 91.6, 74.2, 60.3, 37.9, 18.8, 14.2. Anal. Calcd for $C_{10}H_{14}Cl_3NO_3$: C, 39.69; H, 4.66; N, 4.63. Found: C, 39.64; H, 4.38; N, 4.54%.

4.3.6. Ethyl (2E,4S,5R*)-5-(trichloroacetimidoyloxy)-4-methoxyhex-2-enoate (**4b**)*

Yield: 96%; colorless oil; ν_{max} (neat) 3344, 2985, 1722, 1664, 1300, 1176, 1078, 796, 648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 6.85 (dd, J=5.9, 15.7 Hz, 1H), 6.11 (dd, J=1.5, 15.8 Hz, 1H), 5.10 (dq, J=4.3, 6.4 Hz, 1H), 4.21 (q, J=7.1 Hz, 2H), 4.03 (ddd, J=1.5, 4.3, 5.9 Hz, 1H), 3.42 (s, 3H), 1.35 (d, J=6.6 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.8, 161.8, 143.8, 124.1, 91.5, 81.8, 76.6, 60.5, 58.3, 14.2, 14.1. Anal. Calcd for $C_{11}H_{16}Cl_3NO_4$: C, 39.72; H, 4.85; N, 4.21. Found: C, 39.41; H, 4.79; N, 3.99%.

*4.3.7. Ethyl (2E,4R,5R)-5-(trichloroacetimidoyloxy)-4-(4-methoxyphenoxy)hex-2-enoate (**4c**)*

Yield: 94%; colorless oil; $[\alpha]_D^{25.1}$ +17.1 (c 0.575, $CHCl_3$); ν_{max} (neat) 3340, 2985, 1720, 1664, 1508, 1304, 1227, 1180, 1059, 796, 648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.03 (dd, J=4.6, 15.7 Hz, 1H), 6.95−6.87 (m, 2H), 6.85−6.77 (m, 2H), 6.19 (dd, J=1.6, 15.7 Hz, 1H), 5.36 (dq, J=5.3, 6.4 Hz, 1H), 4.99 (ddd, J=1.6, 5.0, 5.0 Hz, 1H), 4.20 (dq, J=7.1, 11.2 Hz, 1H), 4.19 (dq, J=7.1, 11.4 Hz, 1H), 3.76 (s, 3H), 1.40 (d, J=6.4 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.8, 161.9, 154.5, 151.7, 142.4, 124.3, 117.1, 114.6, 91.3, 77.9, 75.2, 60.6, 55.6, 14.3, 14.2. Anal. Calcd for $C_{17}H_{20}Cl_3NO_5$: C, 48.08; H, 4.75; N, 3.30. Found: C, 47.99; H, 4.63; N, 3.18%.

*4.3.8. Ethyl (2E,4R,5R)-4-tert-butyldimethylsilyloxy-5-(trichloroacetimidoyloxy)hex-2-enoate (**4d**)*

Yield: 96%; colorless oil; $[\alpha]_D^{25.9}$ +55.7 (c 0.620, $CHCl_3$); ν_{max} (neat) 3348, 2956, 2931, 1724, 1664, 1298, 1288, 1261, 1084, 1063, 835, 798, 650 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 7.02 (dd, J=4.1, 15.6 Hz, 1H), 6.11 (dd, J=1.9, 15.6 Hz, 1H), 5.07 (dq, J=5.0, 6.4 Hz, 1H), 4.65 (ddd, J=1.8, 4.1, 4.8 Hz, 1H), 4.21 (dd, J=7.1, 10.9 Hz, 1H), 4.20 (dq, J=7.1, 10.9 Hz, 1H), 1.30 (t, J=7.2 Hz, 3H), 1.25 (d, J=6.4 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.3, 161.9, 146.1, 122.6, 91.5, 76.9, 70.8, 60.4, 25.7, 18.1, 14.2, 13.3, −4.9, −5.0. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.56; H, 6.48; N, 3.11%.

*4.4. Typical procedure of the conjugate additions using DBU: ethyl 2-((4R,5S)-2-(trichloromethyl)-4,5-dihydro-5-((1R)-tert-butyldimethylsilyloxyethyl)oxazol-4-yl)acetate (**ent-2c**) and ethyl 2-((4S,5S)-2-(trichloromethyl)-4,5-dihydro-5-((1R)-tert-butyldimethylsilyloxyethyl)oxazol-4-yl)acetate (**ent-3c**)*

To an ice-cooled solution of the trichloroacetimidate ***ent*-1c** (58.2 mg, 0.134 mmol) in acetonitrile (5.5 mL) was added dropwise DBU (2.0 μL, 0.013 mmol), and the mixture was stirred for ca. 16 h under Ar atmosphere. The reaction mixture was poured into cold saturated aq NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=5:1) to give *trans*-oxazoline ***ent*-2c** (colorless oil, less polar, 53.4 mg, 92%) and *cis*-oxazoline ***ent*-3c** (colorless oil, more polar, 2.0 mg, 3.4%).

*4.4.1. trans-Oxazoline **ent-2c***

$[\alpha]_D^{27.4}$ +40.8 (c 0.495, $CHCl_3$); ν_{max} (neat) 2956, 2931, 2858, 1736, 1664, 1375, 1257, 1182, 1159, 1115, 1078, 1032, 991, 837, 795, 777 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.57 (ddd, J=5.6, 5.8, 6.6 Hz, 1H), 4.51 (dd, J=4.5, 6.6 Hz, 1H), 4.165 (dq, J=7.2, 10.8 Hz, 1H), 4.164 (dq, J=7.1, 10.8 Hz, 1H), 4.02 (dq, J=4.4, 6.3 Hz, 1H), 2.72 (dd, J=5.8, 15.6 Hz, 1H), 2.66 (dd, J=5.6, 15.8 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H), 1.20 (d, J=6.4 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.1, 162.4, 91.0, 86.5, 68.6, 64.6, 60.8, 39.3, 25.8, 19.3, 17.9, 14.2, −4.1, −4.8. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.67; H, 6.37; N, 3.08%.

*4.4.2. cis-Oxazoline **ent-3c***

$[\alpha]_D^{27.5}$ −40.1 (c 0.635, $CHCl_3$); ν_{max} (neat) 2956, 2931, 2858, 1736, 1662, 1379, 1257, 1180, 1107, 1036, 993, 835, 793, 777, 669 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.83

(ddd, J=5.8, 8.1, 9.6 Hz, 1H), 4.68 (dd, J=5.3, 9.6 Hz, 1H), 4.194 (dq, J=7.2, 10.9 Hz, 1H), 4.190 (dq, J=5.6, 6.4 Hz, 1H), 4.18 (dq, J=7.1, 10.8 Hz, 1H), 3.00 (dd, J=5.9, 16.3 Hz, 1H), 2.65 (dd, J=8.0, 16.3 Hz, 1H), 1.30 (d, J=6.4 Hz, 3H), 1.21 (t, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.108 (s, 3H), 0.105 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.1, 162.3, 91.0, 88.7, 67.1, 64.5, 60.8, 35.1, 25.8, 20.5, 17.9, 14.2, −3.8, −4.7. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.63; H, 6.55; N, 3.09%.

*4.5. Typical procedure of the conjugate additions using tert-BuOK: ethyl 2-((4S,5R)-2-(trichloromethyl)-4,5-dihydro-5-((1R)-tert-butyldimethylsilyloxyethyl)oxazol-4-yl)acetate (**2b**) and ethyl 2-((4R,5R)-2-(trichloromethyl)-4,5-dihydro-5-((1R)-tert-butyldimethylsilyloxyethyl)oxazol-4-yl)acetate (**3b**)*

To a solution of the trichloroacetimidate **1b** (56.0 mg, 0.129 mmol) in THF (5.5 mL) was added *tert*-BuOK (1.7 mg, 0.015 mmol) in one portion under Ar atmosphere at −78 °C, and the mixture was stirred for ca. 2 h. The reaction mixture was poured into cold saturated aq NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=11:1) to give *trans*-oxazoline **2b** (colorless solid, less polar, 12.9 mg, 23%) and *cis*-oxazoline **3b** (colorless oil, more polar, 32.7 mg, 58%). Analytical sample (colorless powder) of **2b** was obtained by recrystallization from MeOH (−15 °C).

*4.5.1. trans-Oxazoline **2b***

Mp 52.0−52.5 °C; $[\alpha]_D^{27.6}$ −78 (c 0.18, $CHCl_3$); ν_{max} (KBr) 2958, 2931, 2858, 1728, 1664, 1375, 1244, 1186, 1149, 1063, 1038, 941, 920, 839, 798, 777, 663 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.51 (dd, J=2.6, 6.0 Hz, 1H), 4.48 (ddd, J=4.3, 6.0, 8.1 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 4.05 (dq, J=2.4, 6.4 Hz, 1H), 2.84 (dd, J=4.3, 16.7 Hz, 1H), 2.60 (dd, J=8.4, 16.6 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H), 1.26 (d, J=6.4 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.5, 162.5, 91.3, 86.6, 68.8, 64.8, 60.8, 39.0, 25.6, 19.0, 17.9, 14.2, −4.2, −5.0. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.47; H, 6.31; N, 3.18%.

*4.5.2. cis-Oxazoline **3b***

$[\alpha]_D^{27.3}$ −41.7 (c 0.620, $CHCl_3$); ν_{max} (neat) 2958, 2931, 2858, 1732, 1664, 1329, 1255, 1184, 1093, 1030, 1001, 926, 837, 793, 777, 671 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.80 (dd, J=2.1, 9.6 Hz, 1H), 4.72 (ddd, J=5.3, 9.2, 9.6 Hz, 1H), 4.20 (dq, J=7.2, 10.7 Hz, 1H), 4.17 (dq, J=7.2, 10.7 Hz, 1H), 4.01 (dq, J=2.1, 6.4 Hz, 1H), 3.13 (dd, J=9.2, 17.3 Hz, 1H), 3.03 (dd, J=5.3, 17.3 Hz, 1H), 1.31 (d, J=6.4 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.7, 162.4, 88.9, 86.8, 67.6, 64.8, 60.9, 34.3, 26.0, 20.6, 18.0, 14.2, −3.1, −4.9. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.77; H, 6.33; N, 2.99%.

4.6. Data of the oxazolines

*4.6.1. Ethyl 2-((4S,5S)-2-(trichloromethyl)-4,5-dihydro-5-methyloxazol-4-yl)acetate (**2a**) and ethyl 2-((4R,5S)-2-(trichloromethyl)-4,5-dihydro-5-methyloxazol-4-yl)-acetate (**3a**)*

Colorless oil; $[\alpha]_D^{28.6}$ −35.6 (c 1.00, $CHCl_3$, sample cyclized with DBU); ν_{max} (neat) 2983, 1734, 1658, 1375, 1238, 1184, 1024, 893, 829, 795, 665 cm^{-1}; ^{1}H NMR (270 MHz, C_6D_6) δ major (trans) 4.26 (dq, J=6.3, 6.3 Hz, 1H), 3.94 (ddd, J=5.0, 6.3, 9.1 Hz, 1H), 3.81 (q, J=7.3 Hz, 2H), 2.46 (dd, J=4.9, 16.7 Hz, 1H), 2.03 (dd, J=9.1, 16.6 Hz, 1H), 1.04 (d, J=6.2 Hz, 3H), 0.863 (t, J=7.1 Hz, 3H); minor (cis) 4.55 (dq, J=6.4, 9.2 Hz, 1H), 4.43 (ddd, J=6.3, 8.7, 9.2 Hz, 1H), 3.88−3.73 (overlapping m, 2H), 2.50 (dd, J=6.3, 16.8 Hz, 1H), 2.14 (dd, J=8.5, 16.7 Hz, 1H), 0.865 (t, J=7.2 Hz, 3H), 0.77 (d, J=6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ major (trans) 170.4, 162.2, 86.6, 85.6, 69.5, 60.9, 38.7, 20.4, 14.14; minor (cis) 170.9, 162.3, 86.7, 82.9, 65.0, 61.0, 34.5, 14.5, 14.11. Anal. Calcd for $C_9H_{12}Cl_3NO_3$: C, 37.46; H, 4.19; N, 4.85. Found: C, 37.38; H, 4.23; N, 4.58%.

*4.6.2. Ethyl 2-((4S,5R)-5-(R)-1-(trichloroacetimidoyl-oxy)ethyl)-2-(trichloromethyl)-4,5-dihydro-oxazol-4-yl)acetate (**2d**) and ethyl 2-((4R,5R)-5-(R)-1-(trichloro-acetimidoyloxy)ethyl)-2-(trichloromethyl)-4,5-dihydro-oxazol-4-yl)acetate (**3d**)*

Colorless oil; $[\alpha]_D^{28.2}$ −53 (c 0.42, $CHCl_3$, sample cyclized with *tert*-BuOK at −100 °C); ν_{max} (neat) 3344, 2983, 1732, 1668, 1375, 1348, 1300, 1284, 1236, 1186, 1080, 1032, 987, 930, 839, 795, 650 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ major (trans) 8.43 (s, 1H), 5.35 (dq, J=2.2, 6.5 Hz, 1H), 4.78 (dd, J=2.2, 5.7 Hz, 1H), 4.50 (ddd, J=4.1, 5.8, 9.8 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 2.92 (dd, J=4.0, 17.0 Hz, 1H), 2.62 (dd, J=9.8, 16.9 Hz, 1H), 1.50 (d, J=6.4 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); minor (cis) 8.49 (s, 1H), 5.18 (br q, J=6.6 Hz, 1H), 5.12 (dd, J=1.0, 9.9 Hz, 1H), 4.82 (ddd, J=4.9, 9.9, 10.7 Hz, 1H), 4.11−4.28 (overlapping, 2H), 3.11 (dd, J=5.0, 17.8 Hz, 1H), 2.71 (dd, J=10.7, 18.0 Hz, 1H), 1.46 (d, J=6.4 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ major (trans) 170.4, 162.3, 160.8, 91.1, 89.2, 86.3, 75.2, 65.3, 61.0, 38.5, 14.7, 14.1; minor (cis) 171.5, 162.0, 161.8, 90.9, 86.7, 86.4, 73.1, 64.9, 61.1, 34.2, 15.2, 14.1; HRMS (ESI-TOF) calcd for $C_{12}H_{15}Cl_6N_2O_4$ $[M+H]^+$: 460.9157, found: 460.9157.

4.7. Data of the dihydrooxazines

*4.7.1. Ethyl 2-((4R,6R)-2-(trichloromethyl)-5,6-dihydro-6-methyl-4H-1,3-oxazin-4-yl)acetate (**5a**) and ethyl 2-((4S,6R)-2-(trichloromethyl)-5,6-dihydro-6-methyl-4H-1,3-oxazin-4-yl)acetate (**6a**)*

Colorless oil; $[\alpha]_D^{29.3}$ +26.0 (c 1.11, $CHCl_3$, sample cyclized with *tert*-BuOK); ν_{max} (neat) 2981, 1734, 1676, 1446, 1375, 1340, 1240, 1203, 1180, 1122, 1026, 958, 791, 667 cm^{-1}; ^{1}H NMR (270 MHz, C_6D_6) δ major (cis) 3.96 (q, J=7.1 Hz, 2H), 3.72 (dddd, J=4.6, 6.5, 7.9, 11.1 Hz, 1H), 3.57 (ddq, J=2.6,

6.3, 11.4 Hz, 1H), 2.56 (dd, *J*=6.3, 15.7 Hz, 1H), 2.13 (dd, *J*=7.8, 15.7 Hz, 1H), 1.36 (ddd, *J*=2.6, 4.5, 13.5 Hz, 1H), 0.96 (t, *J*=7.2 Hz, 3H), 0.84 (d, *J*=6.2 Hz, 3H), 0.73 (ddd, *J*=11.3, 11.3, 13.6 Hz, 1H); minor (trans) 4.02–3.80 (overlapping m, 4H), 2.52 (dd, *J*=6.2, 15.4 Hz, 1H), 2.06 (dd, *J*=8.3, 15.4 Hz, 1H), 1.17 (ddd, *J*=4.6, 6.5, 14.0 Hz, 1H), 1.15 (ddd, *J*=5.7, 5.7, 14.0 Hz, 1H), 0.94 (t, *J*=7.2 Hz, 3H), 0.80 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ major (cis) 171.3, 154.1, 92.3, 74.3, 60.56, 51.1, 41.4, 34.4, 20.8, 14.2; minor (trans) 171.0, 153.8, 92.5, 71.2, 60.65, 47.6, 40.8, 31.4, 20.2, 14.2. Anal. Calcd for $C_{10}H_{14}Cl_3NO_3$: C, 39.69; H, 4.66; N, 4.63. Found: C, 40.02; H, 4.59; N, 4.48%.

4.7.2. Ethyl 2-((4S,5S*,6R*)-2-(trichloromethyl)-5,6-dihydro-5-methoxy-6-methyl-4H-1,3-oxazin-4-yl)-acetate (**5b**)*

Colorless oil; ν_{max} (neat) 2983, 1736, 1684, 1215, 1124, 1099, 818, 793, 665 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.18 (q, *J*=7.1 Hz, 2H), 4.14 (dq, *J*=6.3, 9.2 Hz, 1H), 3.82 (ddd, *J*=5.8, 6.5, 8.9 Hz, 1H), 3.55 (s, 3H), 3.11 (dd, *J*=9.0, 9.0 Hz, 1H), 2.79 (dd, *J*=5.8, 14.7 Hz, 1H), 2.64 (dd, *J*=6.5, 14.9 Hz, 1H), 1.53 (d, *J*=6.2 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.0, 152.7, 91.6, 79.4, 76.5, 60.6, 60.5, 56.6, 38.1, 17.8, 14.2. Anal. Calcd for $C_{11}H_{16}Cl_3NO_4$: C, 39.72; H, 4.85; N, 4.21. Found: C, 39.85; H, 4.85; N, 4.13%.

*4.7.3. Ethyl 2-((4S,5R,6R)-2-(trichloromethyl)-5,6-dihydro-5-(4-methoxyphenoxy)-6-methyl-4H-1,3-oxazin-4-yl)-acetate (**5c**)*

Colorless oil; $[\alpha]_D^{27.6}$ +5.0 (*c* 0.10, $CHCl_3$); ν_{max} (neat) 2933, 1728, 1682, 1506, 1225, 1180, 1039, 793 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.89–6.76 (m, 4H), 4.70 (dd, *J*=1.3, 3.2 Hz, 1H), 4.60 (ddq, *J*=1.3, 1.3, 6.6 Hz, 1H), 4.21 (dddd, *J*=1.3, 3.0, 5.3, 9.8 Hz, 1H), 4.05 (dq, *J*=7.2, 10.7 Hz, 1H), 4.02 (dq, *J*=7.1, 10.7 Hz, 1H), 3.76 (s, 3H), 2.83 (dd, *J*=5.3, 17.1 Hz, 1H), 2.74 (dd, *J*=9.8, 17.3 Hz, 1H), 1.42 (d, *J*=6.4 Hz, 3H), 1.14 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.8, 154.3, 153.6, 153.3, 116.5, 114.7, 91.9, 76.3, 71.0, 60.6, 55.7, 55.2, 36.5, 17.1, 14.1; HRMS (EI) calcd for $C_{17}H_{20}Cl_3NO_5$ $[M]^+$: 423.04071, found: 423.0405.

*4.7.4. Ethyl 2-((4R,5R,6R)-2-(trichloromethyl)-5,6-dihydro-5-(4-methoxyphenoxy)-6-methyl-4H-1,3-oxazin-4-yl)-acetate (**6c**)*

Colorless oil; $[\alpha]_D^{27.2}$ +36.7 (*c* 0.570, $CHCl_3$); ν_{max} (neat) 2983, 1732, 1682, 1506, 1223, 1184, 1036, 823, 793, 671 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.98–6.90 (m, 2H), 6. 87–6.80 (m, 2H), 4.63 (dq, *J*=3.1, 6.5 Hz, 1H), 4.39 (dd, *J*=3.1, 4.8 Hz, 1H), 4.22 (ddd, *J*=4.8, 5.5, 8.3 Hz, 1H), 4.17 (dq, *J*=7.2, 10.8 Hz, 1H), 4.16 (dq, *J*=7.1, 10.8 Hz, 1H), 3.77 (s, 3H), 2.78 (dd, *J*=5.6, 15.6 Hz, 1H), 2.57 (dd, *J*=8.3, 15.6 Hz, 1H), 1.48 (d, *J*=6.4 Hz, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.5, 154.8, 153.2, 150.7, 117.6, 114.8, 91.9, 72.7, 71.6, 60.9, 55.7, 52.1, 38.4, 15.1, 14.2; HRMS (EI) calcd for $C_{17}H_{20}Cl_3NO_5$ $[M]^+$: 423.04071, found: 423.0407.

*4.7.5. Ethyl 2-((4S,5R,6R)-5-tert-butyldimethylsilyloxy-2-(trichloromethyl)-5,6-dihydro-6-methyl-4H-1,3-oxazin-4-yl)acetate (**5d**)*

Colorless oil; $[\alpha]_D^{26.6}$ −0.198 (*c* 0.505, $CHCl_3$); ν_{max} (neat) 2931, 1732, 1684, 1375, 1255, 1228, 1180, 1165, 1057, 839, 795 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.44 (ddq, *J*=1.2, 1.2, 6.6 Hz, 1H), 4.17 (q, *J*=7.1 Hz, 2H), 4.04 (dd, *J*=1.1, 2.4 Hz, 1H), 4.01 (dddd, *J*=1.3, 2.5, 5.8, 8.6 Hz, 1H), 2.74 (dd, *J*=5.8, 17.5 Hz, 1H), 2.70 (dd, *J*=8.7, 17.2 Hz, 1H), 1.39 (d, *J*=6.4 Hz, 3H), 1.28 (t, *J*=7.2 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 172.0, 153.2, 92.0, 77.04, 65.6, 60.5, 56.1, 36.8, 25.8, 18.3, 17.4, 14.2, −3.9, −4.2; HRMS (FAB) calcd for $C_{16}H_{29}Cl_3NO_4Si$ $[M+H]^+$: 432.09314, found: 432.0931.

*4.7.6. Ethyl 2-((4R,5R,6R)-5-tert-butyldimethylsilyloxy-2-(trichloromethyl)-5,6-dihydro-6-methyl-4H-1,3-oxazin-4-yl)acetate (**6d**)*

Colorless oil; $[\alpha]_D^{25.5}$ +54.1 (*c* 0.765, $CHCl_3$); ν_{max} (neat) 2956, 2931, 1736, 1682, 1261, 1223, 1128, 839, 795, 667 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.38 (dq, *J*=2.9, 6.5 Hz, 1H), 4.182 (dq, *J*=7.2, 10.8 Hz, 1H), 4.178 (dq, *J*=7.0, 11.3 Hz, 1H), 3.95 (ddd, *J*=4.6, 5.6, 8.2 Hz, 1H), 3.83 (dd, *J*=2.9, 4.6 Hz, 1H), 2.68 (dd, *J*=5.8, 15.6 Hz, 1H), 2.48 (dd, *J*=8.2, 15.7 Hz, 1H), 1.37 (d, *J*=6.4 Hz, 3H), 1.28 (t, *J*=7.2 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.6, 153.0, 92.1, 73.1, 66.8, 60.8, 55.4, 38.3, 25.6, 17.9, 15.2, 14.2, −4.7, −4.8. Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C, 44.40; H, 6.52; N, 3.24. Found: C, 44.70; H, 6.58; N, 3.09%.

4.8. Syntheses of N-Bz-3-D-vancosamine and N-Bz-3-epi-D-vancosamine

*4.8.1. Ethyl (2E,4R,5R)-4,5-dihydroxy-3-methylhex-2-enoate (**8**)*

To a solution of the known acetonide **7** (1.35 g, 5.91 mmol) in THF (32 mL) was added dropwise 3 M HCl (32 mL), and the mixture was stirred for 2.5 h. Then excess amount of $NaHCO_3$ powder was carefully added portionwise to the reaction mixture. The aqueous mixture was saturated with NaCl, and extracted with EtOAc and CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=1:2) to give diol **8** (1.07 g, 96%) as a colorless solid. Analytical sample (colorless powder) was obtained by recrystallization from EtOAc/hexane (0 °C); mp 40.0–43.5 °C; $[\alpha]_D^{29.4}$ −0.995 (*c* 1.01, $CHCl_3$); ν_{max} (KBr) 3446, 3396, 2981, 1709, 1647, 1223, 1153, 1038, 860 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.95–5.91 (m, 1H), 4.17 (q, *J*=7.1 Hz, 2H), 3.91–3.79 (m, 2H), 2.81 (br d, 1H), 2.43 (br s, 1H), 2.13 (d, *J*=1.5 Hz, 3H), 1.29 (t, *J*=7.1 Hz, 3H), 1.20 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.5, 156.9 117.6, 81.0, 68.4, 60.0, 19.4, 15.1, 14.2. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.46; H, 8.61%.

*4.8.2. Ethyl (2E,4R,5R)-4,5-bis(trichloroacetimidoyloxy)-3-methylhex-2-enoate (**9**)*

To a cooled (bath temp below −20 °C) solution of the diol **8** (122.2 mg, 0.649 mmol) and trichloroacetonitrile (1.30 mL, 13.0 mmol) in acetonitrile (3.5 mL) was added dropwise DBU (213.5 μL, 1.43 mmol), and the mixture was stirred for ca. 30 min under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into cold saturated aq NH_4Cl and extracted with EtOAc. The extract was washed successively with saturated aq NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=5.5:1) to give bis-trichloroacetimidate **9** (301.7 mg, 97%) as a colorless solid. Analytical sample (colorless needles) was obtained by recrystallization from hexane; mp 71.5–74.5 °C; $[\alpha]_D^{26.1}$ +1.07 (*c* 0.655, $CHCl_3$); ν_{max} (KBr) 3336, 2989, 1718, 1658, 1313, 1227, 1167, 1076, 1059, 1009, 872, 800, 650, 571 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 8.37 (br s, 1H), 6.09–6.05 (m, 1H), 5.51–5.40 (m, 2H), 4.17 (dd, *J*=7.2, 10.9 Hz, 1H), 4.14 (dd, *J*=7.1, 10.9 Hz, 1H), 2.27 (d, *J*=1.5 Hz, 3H), 1.41 (d, *J*=6.2 Hz, 3H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.0, 161.8, 161.3, 150.9, 119.3, 91.3, 91.0, 82.7, 74.2, 60.0, 16.0, 15.2, 14.2. Anal. Calcd for $C_{13}H_{16}Cl_6N_2O_4$: C, 32.73; H, 3.38; N, 5.87. Found: C, 32.74; H, 3.41; N, 5.82%.

*4.8.3. Ethyl 2-((4R,5R)-5-((R)-1-(trichloroacetimidoyloxy)ethyl)-2-(trichloromethyl)-4,5-dihydro-4-methyloxazol-4-yl)acetate (**10**) and ethyl 2-((4S,5R)-5-((R)-1-(trichloroacetimidoyloxy)ethyl)-2-(trichloromethyl)-4,5-dihydro-4-methyloxazol-4-yl)acetate (**11**)*

To a solution of the trichloroacetimidate **9** (517.9 mg, 1.09 mmol) in THF (44 mL) was added *tert*-BuOK (99.8 mg, 0.889 mmol) in one portion under N_2 atmosphere at below −90 °C, and the mixture was stirred for ca. 2 h. The reaction mixture was poured into cold saturated aq NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=5:1) to give *cis*-oxazoline **10** (less polar, 277.1 mg, 54%) and *trans*-oxazoline **11** (more polar, 189.9 mg, 37%). Analytical sample of **10** and **11** were obtained by recrystallization from EtOAc/hexane.

*4.8.3.1. cis-Oxazoline **10**.* Colorless needles; mp 95.3–97.5 °C; $[\alpha]_D^{27.4}$ −104 (*c* 0.575, $CHCl_3$); ν_{max} (KBr) 3338, 2989, 1718, 1660, 1338, 1306, 1228, 1201, 1119, 1080, 796, 687, 652 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 5.45 (dq, *J*=0.9, 6.4 Hz, 1H), 4.75 (d, *J*=0.9 Hz, 1H), 4.19 (dd, *J*=7.2, 10.8 Hz, 1H), 4.17 (dd, *J*=7.1, 10.9 Hz, 1H), 2.98 (d, *J*=17.7 Hz, 1H), 2.85 (d, *J*=18.2 Hz, 1H), 1.46 (d, *J*=6.4 Hz, 3H), 1.44 (d, *J*=0.6 Hz, 3H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.4, 161.1, 160.8, 92.0, 91.0, 86.7, 73.9, 70.4, 61.0, 39.8, 26.5, 15.3, 14.1. Anal. Calcd for $C_{13}H_{16}Cl_6N_2O_4$: C, 32.73; H, 3.38; N, 5.87. Found: C, 33.02; H, 3.38; N, 5.81%.

*4.8.3.2. trans-Oxazoline **11**.* Colorless needles; mp 69.5–70.3 °C; $[\alpha]_D^{27.9}$ −66.5 (*c* 0.580, $CHCl_3$); ν_{max} (KBr) 3327, 2991, 1718, 1668, 1331, 1284, 1248, 1109, 1072, 1028, 796, 677, 650 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 5.34 (dq, *J*=1.1, 6.4 Hz, 1H), 5.07 (d, *J*=1.1 Hz, 1H), 4.17 (q, *J*=7.1 Hz, 2H), 2.69 (d, *J*=15.6 Hz, 1H), 2.59 (d, *J*=15.6 Hz, 1H), 1.502 (s, 3H), 1.497 (d, *J*=6.4 Hz, 3H), 1.28 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.1, 161.4, 160.9, 91.1, 90.0, 86.5, 73.1, 71.0, 60.9, 45.5, 19.8, 15.8, 14.2. Anal. Calcd for $C_{13}H_{16}Cl_6N_2O_4$: C, 32.73; H, 3.38; N, 5.87. Found: C, 32.95; H, 3.37; N, 5.87%.

*4.8.4. (3R,4R,5R)-3-Benzamido-5-hydroxy-3-methyl-4-hexanolide (**12**)*

To a solution of the *cis*-oxazoline **10** (586.1 mg, 1.23 mmol) in EtOH (21 mL) was added 3 M HCl (21 mL) and the mixture was refluxed for ca. 19 h. The reaction mixture was concentrated in vacuo and added acetone (9 mL) and saturated aq $NaHCO_3$ (22 mL). To the mixture was added dropwise benzoyl chloride (428 μL, 3.68 mmol), and the mixture was stirred for ca. 1 h at rt. The mixture was concentrated in vacuo and the residue was diluted with brine and the whole mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=1:2.5) to give lactone **12** (275.0 mg, 85%). Analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; mp 173.0–174.5 °C; $[\alpha]_D^{26.6}$ +46.3 (*c* 0.580, EtOH); ν_{max} (KBr) 3452, 3346, 3309, 2987, 1780, 1759, 1666, 1635, 1541, 1522, 1315, 1292, 1194, 1142, 989, 725, 694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.77–7.68 (m, 2H), 7.57–7.40 (m, 3H), 6.14 (br s, 1H), 4.84 (d, *J*=1.9 Hz, 1H), 4.22 (ddq, *J*=1.9, 6.4, 6.4 Hz, 1H), 2.94 (d, *J*=17.5 Hz, 1H), 2.88 (d, *J*=17.5 Hz, 1H), 1.78 (s, 3H), 1.54 (d, *J*=6.2 Hz, 3H), 1.38 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.2, 167.5, 134.1, 132.0, 128.7, 126.8, 87.7, 66.3, 59.7, 42.5, 20.7, 20.3. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.74; H, 6.51; N, 5.27%.

*4.8.5. (3S,4R,5R)-3-Benzamido-5-hydroxy-3-methyl-4-hexanolide (**13**)*

To a solution of the *trans*-oxazoline **11** (111.7 mg, 0.234 mmol) in EtOH (5 mL) was added 3 M HCl (5 mL) and the mixture was refluxed for ca. 15 h. The reaction mixture was concentrated in vacuo and added acetone (1.65 mL) and saturated aq $NaHCO_3$ (4.2 mL). To the mixture was added dropwise benzoyl chloride (81.5 μL, 0.702 mmmol), and the mixture was stirred for ca. 1 h at rt. The mixture was concentrated in vacuo and the residue was diluted with brine and the whole mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=1:2.5) to give lactone **13** (50.8 mg, 82%). Analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; mp 124.5–126.0 °C; $[\alpha]_D^{27.0}$ −37.7 (*c* 0.560, EtOH); ν_{max} (KBr) 3321, 2976, 1782, 1645, 1541, 1300, 1159, 1138, 985, 729 cm^{-1}; ^1H NMR (270 MHz,

$CDCl_3$) δ 8.59 (br s, 1H), 7.80–7.72 (m, 2H), 7.54–7.37 (m, 3H), 4.31 (dq, J=6.7, 9.5 Hz, 1H), 4.09 (s, 1H), 3.59 (d, J=17.5 Hz, 1H), 2.62 (d, J=17.5 Hz, 1H), 2.24 (d, J=9.8 Hz, 1H), 1.74 (s, 3H), 1.51 (d, J=6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.6, 167.3, 134.2, 131.8, 128.6, 126.9, 87.4, 65.1, 59.9, 41.8, 22.3 (2). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.52; N, 5.27%.

4.8.6. 3-Benzamido-2,3,6-trideoxy-3-C-methyl-D-lyxo-hexopyranose (N-Bz-D-vancosamine)

To a solution of the lactone **12** (75.6 mg, 0.287 mmol) in dry THF (4.2 mL) was added dropwise DIBAL (1.46 mL, 0.98 M in hexane, 1.43 mmol) under Ar atmosphere at −60 °C, and the reaction mixture was stirred for 1.5 h at −60° to −50 °C. The reaction was quenched by the dropwise addition of acetone/MeOH (1:1, 3 mL) and the mixture was allowed to warm gradually to rt with stirring for ca. 4 h. The mixture was filtered through a pad of Celite. The filter cake was washed with acetone/MeOH (1:1) and then the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc) to give *N*-Bz-D-vancosamine (39.9 mg, 52%) along with over-reduced triol (11.8 mg, 15%). Analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; mp 152.0–154.0 °C (lit.[20] 155 °C); $[\alpha]_D^{29.1}$ +81.9 (after 10 min), +34.7 (after 1 day, constant) (*c* 0.525, MeOH) (lit.[20] L-form $[\alpha]_D^{20}$ −86.6 (*c* 0.5, MeOH)); ν_{max} (KBr) 3332, 2931, 1645, 1581, 1533, 1491, 1284, 1097, 1016, 710 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6, after 1 month) data were in agreement with the reported in lit. 20; ^{13}C NMR (67.8 MHz, DMSO-d_6) δ α-isomer 165.6, 135.7, 130.9, 128.1, 126.9, 90.1, 71.2, 62.6, 54.3, 35.2, 23.2, 17.47; β-isomer 165.7, 135.6, 130.8, 128.0, 127.0, 92.0, 70.0, 68.2, 56.1, 38.7, 21.4, 17.52. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.21; H, 7.20; N, 5.24%.

4.8.7. 3-Benzamido-2,3,6-trideoxy-3-C-methyl-D-xylo-hexopyranose (N-Bz-3-epi-D-vancosamine)

To a solution of the lactone **13** (33.1 mg, 0.126 mmol) in dry THF (1.9 mL) was added dropwise DIBAL (641 μL, 0.98 M in hexane, 0.628 mmol) under Ar atmosphere at −60 °C, and the reaction mixture was stirred for 1 h at −60° to −55 °C. The reaction was quenched by the dropwise addition of acetone/MeOH (1:1, 2 mL) and the mixture was allowed to warm gradually to rt with stirring for ca. 4 h. The mixture was filtered through a pad of Celite. The filter cake was washed with acetone/MeOH (1:1), and then the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc) to give *N*-Bz-3-*epi*-D-vancosamine (24.1 mg, 72%). Analytical sample (colorless solid) was obtained by recrystallization from EtOAc/hexane; mp 222.0–224.0 °C (lit.[20] 230–233 °C); $[\alpha]_D^{28.0}$ +69.6 (after 10 min), $[\alpha]_D^{29.7}$ +45.7 (after 1 day, constant) (*c* 0.505, MeOH) (lit.[20] L-form $[\alpha]_D^{20}$ −61.3 (*c* 0.5, MeOH)); ν_{max} (KBr) 3361, 3239, 2979, 1643, 1549, 1362, 1327, 1261, 1113, 1099, 1016, 964, 868, 802, 723, 694, 631 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6, after 1 month) data were in agreement with the reported in lit. 20; ^{13}C NMR (67.8 MHz, DMSO-d_6) δ α-isomer 164.9, 135.4, 131.1, 128.5, 126.3, 90.5, 67.6, 62.5, 54.7, 35.4, 22.8, 17.34; β-isomer 166.7, 135.8, 130.8, 127.9, 127.3, 92.1, 68.4, 67.9, 57.1, 37.0, 23.3, 17.31. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.18; H, 7.23; N, 5.23%.

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