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Synthesis of a common key intermediate for (−)-tetrodotoxin and its analogs

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Abstract—A key intermediate for tetrodotoxin and its analogs such as (−)-5,11-dideoxytetrodotoxin was stereoselectively synthesized from a chiral starting material, levoglucosenone, via Diels–Alder reaction and the Overman rearrangement as key steps. The Overman rearrangement of the precursor bearing hydroxy group of C-8 was also described.

1. Introduction

Tetrodotoxin (**1**) is one of the most famous marine natural products because of its frequent involvement in fatal poisoning and the unique chemical structure.[1] The structure was elucidated in 1964 by three groups including Hirata–Goto, Tsuda and Woodward.[2] As the specific inhibition of sodium ion influx through voltage dependent channel proteins, tetrodotoxin has been served as an important biochemical tool in neurophysiological area.[3] Tetrodotoxin and its analogs (Fig. 1)[4] have been isolated not only from puffer fish, but also from other animals such as frog, newt, octopus;[5] farm-raised puffer fish lacked the toxin, but accumulated it when fed the toxic puffer fish livers.[6] In 1986, tetrodotoxin producing bacteria were reported.[7] These studies strongly suggested the food chain for accumulation of the toxin into puffer fish from microorganisms. Biologically interesting issues have been reported such as biosynthesis of tetrodotoxin,[8] detoxication, molecular mechanism for accumulation of tetrodotoxin in puffer fish,[9] actual biological function,[10] etc. In order to answer these questions, labeled tetrodotoxin derivatives have been highly desirable;[11] however, derivatization of naturally occurring tetrodotoxin was so difficult due to the unusual chemical properties. In spite of many synthetic efforts,[12] only one total synthesis of the racemate was reported by Kishi–Goto and co-workers in 1972.[13] The novel structure including contiguous asymmetric centers, polyhydroxylated cyclohexane ring, a novel zwitter ion structure between cyclic guanidine and *ortho* ester still present a challenge for total synthesis. Recently, we achieved stereocontrolled synthesis of (−)-5,11-dideoxytetrodotoxin (**5**).[14] In this paper, we describe a practical synthesis of a versatile intermediate for tetrodotoxin and its analogs as shown in Fig. 1.

2. Results and discussion

2.1. Synthetic plan

Our synthetic plan for the tetrodotoxins is illustrated in Scheme 1. Tetrodotoxin and its analogs **A** could be

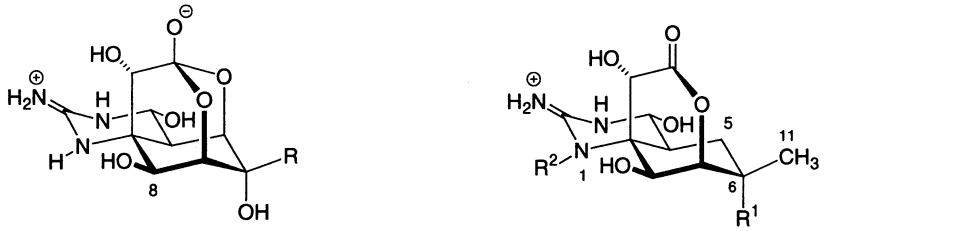

Figure 1. Structures of tetrodotoxin and its analogs.

Keywords: tetrodotoxin; Diels–Alder reaction; Overman rearrangement; levoglucosenone; A-strain.

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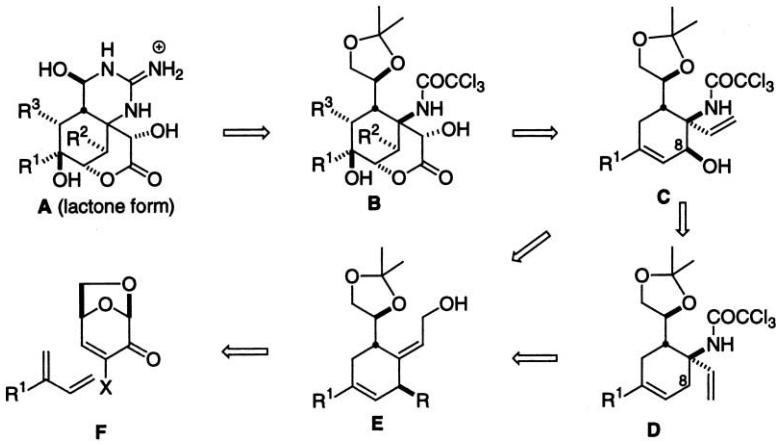
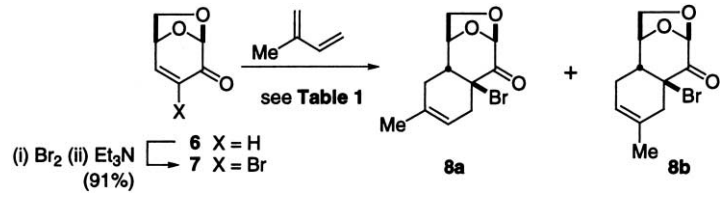


Scheme 1. Retrosynthetic plan for tetrodotoxin and its analogs.

synthesized from the corresponding lactone intermediate **B** having all the requisite functionalities of a cyclohexane ring for a tetrodotoxin molecule. The lactone **B** was retrosynthesized into **C**, in which a hydroxy group at C-8 is a common functionality found in all the naturally occurring tetrodotoxins. For introduction of the hydroxy group, two routes were explored. The first route is oxygenation at C-8 of **D** (**D**→**C**), which could be synthesized from the Overman rearrangement[15] of **E**. The second one is to introduce a hydroxy group into the precursor **E** followed by the Overman rearrangement (**E**→**C**). The former route was ultimately adopted in our synthesis of (−)-5,11-dideoxytetrodotoxin (**5**) through a novel neighboring group participation of the trichloroacetamide because of the total efficiency.[14] The latter approach will also be disclosed in this paper. The nitrogen functionality of **D** or **C** would be introduced by the so-called Overman rearrangement from *exo*-allylic alcohol **E** (R=H or OR) via allylic trichloroacetimidate[15] in which an allylic strain[16] could be operative with high stereoselectivity. The precursor **E** could arise from the Diels–Alder reaction between halo-levoglucosenone **F** as a chiral starting material and butadiene derivative. This paper deals with: (i) the details of the practical synthesis of versatile key intermediate **D** and (ii) an attempt to introduce a requisite hydroxy group of the C-8 position before the Overman rearrangement.[17]

2.2. Diels–Alder reaction

Levoglucosenone **6** has been selected as a chiral starting material for our tetrodotoxin synthesis (Scheme 2).[18] Bromination of levoglucosenone was followed by elimination of hydrogen bromide with Et_3N to give bromolevoglucosenone **7**[19] in 91% yield. According to our initial study using butadiene as the simplest diene for the Diels–Alder cycloaddition[20] to synthesize **D** (R^1=H),[21] bromolevoglucosenone **7** was heated with isoprene in a sealed tube at 120°C to give an inseparable mixture (7:3) of **8a** and **b**. The resulting mixture could not be separated even in the later stages, which prompted us to examine conditions promoted by Lewis acid in order to improve the selectivity. Representative results are shown in Table 1. In the presence



Scheme 2. Diels–Alder reaction between **7** and isoprene.

Table 1. Diels–Alder reaction between **7** and isoprene

Entry	Conditions			Products	
	Lewis acid (equiv.)	Solvent	Temperature	Yield (%)	Ratio (**8a/8b**)[a]
1	–	CH_2Cl_2	120°C[b]	80	**7:3**
2	$BF_3{\cdot}OEt_2$ (0.2)	CH_2Cl_2	0°C–rt	–[c]	**10:1**
3	$LiClO_4$ (5 M)	Et_2O	rt	82	**8:1**
4	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	rt	50	**10:1**
5	$BF_3{\cdot}OEt_2$ (1)	CH_3CN	0°C–rt	76	**15:1**
6	$SnCl_4$ (1)	CH_3CN	0°C–rt	64	**10:1**

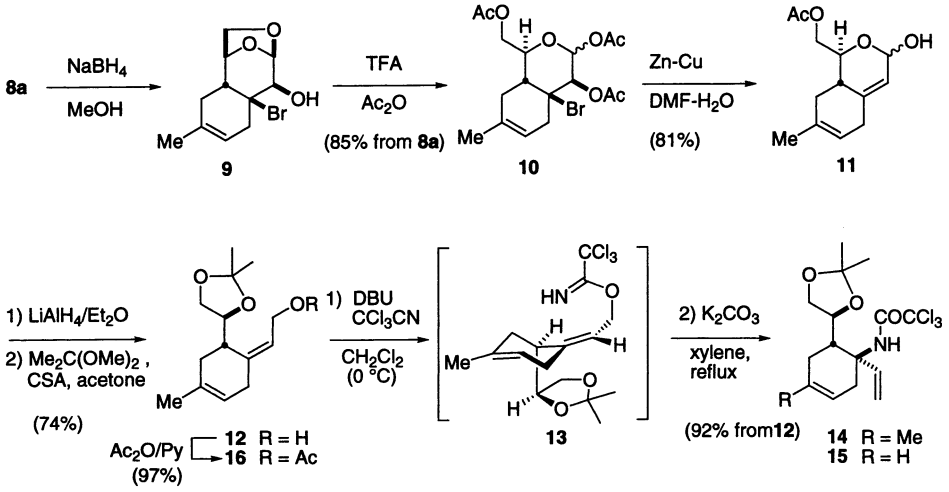
[a] The ratios were determined by the integration values of ^{1}H NMR.
[b] The reaction was conducted in a sealed tube.
[c] The yield could not be determined because of inseparable polymer.

of cat. Lewis acid such as $BF_3{\cdot}OEt_2$, $SnCl_4$, in CH_2Cl_2, the product was obtained along with a considerable amount of polymer, which was difficult to remove (entry 2). The Diels–Alder reaction in $LiClO_4$–ether solution[22] gave a better result (entry 3). Scandium triflate catalyzed reaction[23] gave the desired product in moderate yield with better regioselectivity (entry 4). Further examinations led us to find that the conditions with Lewis acid such as $BF_3{\cdot}OEt_2$, $SnCl_4$, in acetonitrile were superior in respect to the yield and the regioselectivity (entries 5 and 6). In particular, a stoichiometric amount of $BF_3{\cdot}OEt_2$ in acetonitrile[24] was the best condition to give the desired adduct **8a** in good yield with the highest regioselectivity (entry 5). Acetonitrile as a solvent prevented polymerization to result in good yield, probably because the solvent attenuated the acidity of the Lewis acid.

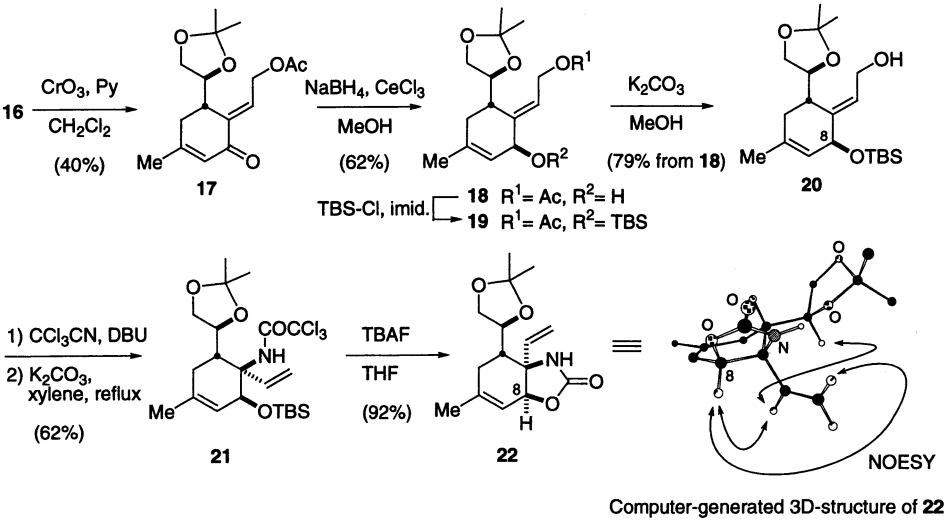
2.3. Synthesis of the precursor for the Overman rearrangement

The ketone **8a** was reduced with $NaBH_4$ in methanol to give the β-alcohol **9**, which was treated with trifluoroacetic acid (TFA) in Ac_2O[25] to afford triacetate **10** in good overall yield. To introduce an *exo*-double bond whose *Z* olefin geometry was indispensable for the next stereoselective Overman rearrangement, the bromoacetate was reduced with Zn–Cu couple[26] to give **11**. The pyranose ring of **11** was cleaved with $LiAlH_4$ to give a triol, in which 1,2-glycol was protected as acetonide to afford an allylic alcohol **12** as a precursor for the Overman rearrangement.

The trichloroacetimidate **13** was prepared from the allylic alcohol **12** with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and trichloroacetonitrile in CH_2Cl_2 at 0°C. In a large-scale preparation of imidate from **12** (over 10 g), a lower temperature around −20°C was recommended. The preferred conformation of this intermediate **13** is shown in Scheme 3. That is, the acetonide side chain occupies the pseudo-axial position because of A-strain[16] between the *exo*-allyl trichloroacetimidate and the acetonide side chain. Consequently, we predicted that nitrogen group should be introduced from the upper face as shown in **13**. In fact, the rearrangement proceeded at a xylene-reflux temperature in the presence of K_2CO_3 to give the product **14** as a single



Scheme 3. Synthesis of key intermediate **14**.



Scheme 4. Hydroxylation of C-8 and the Overman rearrangement.

stereoisomer in over 90% yield from **12** on a 20 g scale. Addition of K_2CO_3 was indispensable to keep the high yield with high reproducibility.[27] The stereochemistry was confirmed by comparison to the model compound **15**, whose structure was unambiguously determined by X-ray crystallographic analysis.[21]

2.4. Overman rearrangement of hydroxylated allylic imidate

In order to synthesize naturally occurring tetrodotoxin analogs (Fig. 1), a hydroxy group must be introduced into the C-8 position. We describe another approach to introduce the hydroxy group at the C-8 position prior to the rearrangement, while the hydroxy group was introduced by neighboring group participation of **14** in the synthesis of (−)-5,11-dideoxytetrodotoxin.[14] The precursor **20** bearing the hydroxyl group at the C-8 position was synthesized from **16** as shown in Scheme 4. Allylic oxidation of the C-8 position in **16** was best accomplished with CrO_3–pyridine[28] in CH_2Cl_2 to give **17** in moderate yield. The ketone was then reduced with $NaBH_4$ and $CeCl_3$[29] to give an alcohol **18** as a single isomer. The configuration of C-8 could not be determined at this stage (vide infra). Protection of the alcohol **18** as *t*-butyldimethylsilyl (TBS) ether was followed by deacetylation to afford the allylic alcohol **20** as a precursor of the Overman rearrangement. The corresponding imidate underwent the Overman rearrangement under our modified conditions (at xylene-reflux temperature in the presence of K_2CO_3) to afford the desired product **21** in about 60% yield. We found that K_2CO_3 prevented the imidate from aromatization under the conditions.[27] The reaction proceeded slower than the Overman rearrangement of **13**. Desilylation of the product **21** with tetra-*n*-butylammonium fluoride (TBAF) in THF gave a cyclic carbamate **22**. The structure including stereochemistry of the C-8 position was established by analysis of the NOESY spectra of **22** as depicted in Scheme 4. Unfortunately, the configuration was opposite to that of naturally occurring tetrodotoxins.

3. Conclusion

We established a highly efficient and stereocontrolled synthesis of a key intermediate for tetrodotoxin. The synthesis described here is capable of preparing the key intermediate **14** on 50 g scale with high reproducibility. The compound **14** was eventually transformed into (−)-5,11-dideoxytetrodotoxin (**5**).[14] This study also indicated that the alcohol such as **20** could be served as a precursor for the Overman rearrangement to afford more functionalized nitrogen containing cyclohexane product. The syntheses of other tetrodotoxin analogs as shown in Fig. 1 from the common intermediate **14** are currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Infrared spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Brucker ARX-400 (400 MHz) and Varian Gemini-2000 (300 MHz) spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Brucker ARX-400 (100 MHz) and Varian Gemini-2000 (75 MHz) spectrometers. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Low resolution mass spectra were recorded on a JEOL JMS-D 100 (EI), JEOL DX-705L (FAB) and JEOL Mstation (FAB) spectrometers. High resolution mass spectra (HRMS) were recorded on JEOL DX-705L and JEOL Mstation spectrometers, and reported in *m*/*z*. Elemental analyses were performed by the Analytical Laboratory at the School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel coated glass plates 60F-254 (Merck, Art 5715) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heated as developing agents. Cica-Merck silica gel (60, particle size 0.063–0.2 mm A STM) was used for open-column chromatography. Preparative thin-layer chromatography separations were carried out on 0.5 mm silica gel plates 60F-254 (Merck, Art 5774) or prepared silica gel 60 FP-254 (Merck, Art 7747), layer thickness 2.0 mm. Non-aqueous reactions were carried out under nitrogen or argon atmosphere unless otherwise stated. Anhydrous ethyl ether was purchased from Kanto Chemical Co., Inc. in a bottle as ethyl ether anhydrous. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. Pyridine and triethylamine were dried over anhydrous KOH. $BF_3{\cdot}OEt_2$ was distilled from CaH_2. All other commercially available reagents were used as received.

4.1.1. Bromolevoglucosenone 7.[19] Levoglucosenone (**6**) (60.5 g, 0.479 mol) was dissolved in CH_2Cl_2 (1.20 L). To the cooled (at 0°C) solution was added bromine (ca. 24 mL. 0.48 mmol) dropwise until the color of the mixture turned brown. Et_3N (134 mL, 0.958 mmol) was added at the same temperature. After stirring for 30 min, the mixture was filtered through the pad of Super-Cel, the filtrate was diluted with CH_2Cl_2 (1.20 L) and water (600 mL) and partitioned. The aqueous layer (1.5 L) was extracted with CH_2Cl_2 (×6). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 650 g, Et_2O/hexane=1:4→1:2→1:1→2:1) to afford **7** (98.0 g, 91%).

4.1.2. Bromoketone 8a. To an ice-cold solution of bromolevoglucosenone **7** (70.1 g, 0.342 mol) in CH_3CN (1.00 L) was added $BF_3{\cdot}OEt_2$ (46.0 mL, 0.359 mol) dropwise over 20 min. After stirring at 0°C for 20 min, isoprene (171 mL, 1.71 mol) was added dropwise over 25 min. After stirring at 0°C for 10 min and at rt for additional 1.5 h, the reaction mixture was cooled to 0°C, and quenched with sat. $NaHCO_3$ solution (1 L). The mixture was extracted with AcOEt (1 L×1, 0.5 L×2), and the combined organic extract was washed with water (1 L×2) and brine (1 L×1). The solution was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 1300 g, ether/hexane=1:10→1:5) to give a bromoketone **8a** (75.4 g,

76%). Mp 90–91°C (as colorless prisms from Et_2O–hexane). $[\alpha]_D^{23}=-1.06$ (*c* 15.3, $CHCl_3$). IR (KBr) ν_{max} 2967, 2921, 2853, 1735, 1625, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (3H, s, C*H*$_3$–C═CH), 2.16 (1H, dd, *J*=16, 5.5 Hz, C*H*$_A$H$_B$–CMe═CH), 2.47 (1H, dd, *J*=16, 8 Hz, CH$_A$*H*$_B$–CMe═CH), 2.59 (1H, brd, *J*=16 Hz, MeC═CH–C*H*$_A$H$_B$), 2.88 (1H, brdd, *J*=8, 5.5 Hz, –C*H*–), 2.99 (1H, dd, *J*=16, 5.5 Hz, MeC═CH–CH$_A$*H*$_B$), 3.88 (1H, dd, *J*=7.5, 5.5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.48 (1H, brd, *J*=5.5 Hz, O–CH$_2$–C*H*–O), 4.56 (1H, d, *J*=7.5 Hz, O–CH$_A$*H*$_B$–CH–O), 5.27 (1H, s, O–C*H*–O), 5.47 (1H, m, MeC═C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 34.4, 36.9, 48.2, 56.0, 67.1, 79.2, 100.1, 119.2, 137.4, 195.3. EI-MS *m*/*z* 274 (M^+), 272 (M^+). HRMS (EI) calcd for $C_{11}H_{13}O_3{}^{79}Br$ (M^+) 272.0048, found 272.0029. Anal. calcd for $C_{11}H_{13}O_3Br$: C, 48.53; H, 4.82. Found: C, 48.53; H, 4.98.

4.1.3. Bromohydrin 9. To an ice-cold solution of bromoketone **8a** (22.1 g, 81.1 mmol) in MeOH (300 mL) was added $NaBH_4$ (1.53 g, 40.5 mmol) portionwise over 30 min. After stirring at 0°C for 10 min, the reaction mixture was carefully quenched with small amount of AcOH, and concentrated. The residue was dissolved in CH_2Cl_2 and water, and partitioned. The aqueous layer was further extracted with CH_2Cl_2 (×2). The combined organic extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude alcohol **9** (21.9 g) as a dark brown foam. This material was used for the next reaction without purification. A portion of this material was purified by column chromatography (ether/hexane=1:3) to afford the analytically pure sample. $[\alpha]_D^{25}=-68.3$ (*c* 0.98, $CHCl_3$). IR (KBr) ν_{max} 3442, 2963, 2898, 1475, 1439, 1389, 1325, 1239, 1078 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (3H, brs, C*H*$_3$–C═CH), 2.31–2.38 (2H, m, C*H*$_2$–CMe═CH), 2.48 (1H, d, *J*=12.5 Hz, O*H*), 2.73 (1H, d quintet, *J*=17, 2.5 Hz, MeC═CH–C*H*$_A$H$_B$), 2.92–3.02 (2H, m, MeC═CH–CH$_A$*H*$_B$ and –C*H*–), 3.20 (1H, dd, *J*=12.5, 2 Hz, HO–C*H*), 3.74 (1H, dd, *J*=7.5, 5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.27 (1H, dd, *J*=5, 1.5 Hz, O–CH$_2$–C*H*–O), 4.71 (1H, d, *J*=7.5 Hz, O–CH$_A$*H*$_B$–CH–O), 5.23 (1H, m, MeC═C*H*), 5.36 (1H, d, *J*=2 Hz, O–C*H*–O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 33.8, 40.6, 44.6, 67.0, 70.3, 74.0, 78.3, 101.8, 118.0, 133.4. MS (EI) *m*/*z* 274 (M^+), 272 (M^+). HRMS (EI) calcd for $C_{11}H_{15}O_3Br$ (M^+) 274.0205, found 274.0201. Anal. calcd for $C_{11}H_{15}O_3Br$: C, 48.02; H, 5.50. Found: C, 47.93; H, 5.76.

4.1.4. Triacetate 10. To an ice-cold solution of the crude bromohydrin **9** (21.9 g) in Ac_2O (220 mL) was added TFA (22 mL) dropwise over 5 min. After stirring at 0°C for 30 min, the reaction mixture was evaporated to remove TFA. The solution was diluted with toluene (250 mL) and concentrated in vacuo. The residue was purified by column chromatography (silica gel 450 g, ether/hexane=1:2→2:1) to give a triacetate **10** (29.4 g, 85% in 2 steps from **8a**) as a diastereo mixture (**10a**,**b**=9:1 by ^1H NMR). Further purification by careful column chromatography (ether/hexane=1:2) afforded **10a** as a white amorphous solid and **10b** as colorless crystals (from ether–hexane).

10a: $[\alpha]_D^{26}=+47.8$ (*c* 1.63, $CHCl_3$). IR (KBr) ν_{max} 2969, 2932, 2857, 1748, 1439, 1371, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (3H, brs, C*H*$_3$–C═CH), 1.93 (1H, brd, *J*=17 Hz, C*H*$_A$H$_B$–CMe═CH), 2.11 (3H, s, O*Ac*), 2.12 (3H, s, O*Ac*), 2.20 (3H, s, O*Ac*), 2.54–2.76 (3H, m, CH$_A$*H*$_B$–CMe═CH, MeC═CH–C*H*$_A$H$_B$ and –C*H*–), 3.57 (1H, brd, *J*=20 Hz, MeC═CH–CH$_A$*H*$_B$), 3.96 (1H, ddd, *J*=10, 4, 3 Hz, O–CH$_2$–C*H*–O), 4.20 (1H, dd, *J*=12, 3 Hz, O–C*H*$_A$H$_B$–CH–O), 4.26 (1H, dd, *J*=12, 4 Hz, O–CH$_A$*H*$_B$–CH–O), 5.07 (1H, brs, AcO–C*H*), 5.36 (1H, m, MeC═C*H*), 6.04 (1H, d, *J*=1 Hz, AcO–C*H*–O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 21.0, 23.2, 28.8, 34.4, 39.1, 64.6, 65.3, 70.0, 71.7, 92.0, 116.5, 130.5, 168.1, 169.4, 170.8. MS (FAB) *m*/*z* 359 (M−OAc). HRMS (FAB) calcd for $C_{15}H_{20}O_5Br$ (M−OAc) 359.0494, found 359.0472.

10b: Mp 164–165°C (as colorless crystals from Et_2O–hexane). $[\alpha]_D^{26}=+25.6$ (*c* 1.53, $CHCl_3$). IR (KBr) ν_{max} 2978, 2932, 2889, 1771, 1751, 1736, 1442, 1374, 1229, 1074, 1031 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (3H, s, C*H*$_3$–C═CH), 1.94 (1H, br d, *J*=18 Hz, C*H*$_A$H$_B$–CMe═CH), 2.08 (3H, s, O*Ac*), 2.11 (3H, s, O*Ac*), 2.24 (3H, s, O*Ac*), 2.51–2.65 (2H, m, –C*H*– and CH$_A$*H*$_B$–CMe═CH), 2.81 (1H, brd, *J*=20 Hz, MeC═CH–C*H*$_A$H$_B$), 3.03 (1H, brd, *J*=20 Hz, MeC═CH–CH$_A$*H*$_B$), 3.73 (1H, ddd, *J*=10.5, 5, 2.5 Hz, O–CH$_2$–C*H*–O), 4.23 (1H, dd, *J*=12.5, 5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.29 (1H, dd, *J*=12.5, 2.5 Hz, O–CH$_A$*H*$_B$–CH–O), 5.27 (1H, brs, AcO–C*H*), 5.33 (1H, brs, MeC═C*H*), 6.09 (1H, d, *J*=1.5 Hz, AcO–C*H*–O). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 23.4, 28.3, 34.6, 38.7, 64.6, 64.7, 72.0, 3.4, 89.5, 114.8, 131.2, 168.6, 169.9, 170.7. MS (FAB) *m*/*z* 359 (M−OAc). Anal. calcd for $C_{17}H_{23}O_7Br$: C, 48.70; H, 5.53. Found: C, 48.69; H, 5.57.

4.1.5. Hemiacetal 11. A solution of **10a**,**b** (29.4 g, 68.6 mmol) in DMF (500 mL) was mixed with H_2O (100 mL) at 0°C and then allowed to warm to rt. An activated zinc–copper couple (30 g) was added to the reaction mixture and the reaction vessel was immersed in an oil bath (at 55°C). After vigorous stirring for 1 h, the mixture was cooled to an ice bath temperature. Prolonged reaction time over 2 h at ca. 60°C provided considerably reduced yields because of product decomposition. The mixture was then filtered through a pad of Super-Cel, and the precipitate was washed with AcOEt. The combined filtrate was extracted with AcOEt (×3). The combined organic extract was washed with water (×2) and brine (×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 350 g, ether/hexane=1:2→1:1) to give a hemiacetal **11** (13.2 g, 81%) as a light yellow amorphous solid.

Major isomer: IR (KBr) ν_{max} 3432, 2963, 2908, 1741, 1437, 1368, 1236 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (3H, brs, C*H*$_3$–C═CH), 1.70–1.85 (1H, m, C*H*$_A$H$_B$–CMe═CH), 2.12 (3H, s, O*Ac*), 2.12–2.21 (1H, m, CH$_A$*H*$_B$–CMe═CH), 2.42 (1H, m, –C*H*–), 2.68–2.98 (2H, m, MeC═CH–C*H*$_2$), 3.97 (1H, ddd, *J*=10, 6, 2 Hz, O–CH$_2$–C*H*–O), 4.22 (1H, dd, *J*=12, 6 Hz, O–C*H*$_A$H$_B$–CH–O), 4.35 (1H, dd, *J*=12, 2 Hz, O–CH$_A$*H*$_B$–CH–O), 5.36 (1H, m, MeC═C*H*), 5.44 (1H, brs, O–C*H*–OH), 5.65 (1H, m, HO–CH–C*H*═C). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 23.3, 31.4, 32.8, 33.3, 64.5, 70.7, 89.1, 119.0, 119.1, 131.1, 138.7, 171.3. MS (EI) *m*/*z* 238 (M^+).

HRMS (EI) calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205, found 238.1187.

4.1.6. Allylic alcohol 12. $LiAlH_4$ (6.40 g, 0.169 mol) was placed in a 1 L three-necked round-bottomed flask equipped with a magnetic stirrer, a dropping funnel and nitrogen inlet, and anhydrous Et_2O (400 mL) was added. After cooling to 0°C, the hemiacetal **11** (16.0 g, 67.6 mmol) in ether (40 mL) was added by use of dropping funnel over 30 min. The suspension was refluxed for 5 h, and then cooled to −78°C. The reaction was carefully quenched with water and aqueous potassium sodium tartrate. The resulting mixture was stirred for 2 h and then extracted with AcOEt (×10). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude triol (14.4 g) as a colorless oil. To a solution of the crude triol in acetone (325 mL) and 2,2-dimethoxypropane (16.3 mL, 0.133 mol) was added DL-camphorsulfonic acid (CSA) (3.13 g, 13.5 mmol). After stirring at rt for 15 min, the reaction mixture was quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (×3). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 300 g, ether/hexane=1:3→1:2→1:1→2:1) to give an allylic alcohol **12** (11.8 g, 74%, 2 steps from **11**) as a colorless oil. $[\alpha]_D^{26}$=+8.78 (*c* 1.11, $CHCl_3$). IR (KBr) ν_{max} 3440, 2984, 2912, 1436, 1380, 1212, 1069 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s, C*H*$_3$ of acetonide), 1.43 (3H, s, C*H*$_3$ of acetonide), 1.63–1.72 (1H, m, C*H*$_A$H$_B$–CMe=CH), 1.64 (3H, brs, C*H*$_3$–C=CH), 2.26–2.38 (1H, m, CH$_A$*H*$_B$–CMe=CH), 2.33 (1H, dd, *J*=9, 2 Hz, CH$_2$O*H*), 2.67 (1H, brd, *J*=20 Hz, MeC=CH–C*H*$_A$H$_B$), 2.92–3.08 (2H, m, MeC=CH–CH$_A$*H*$_B$ and –C*H*–), 3.66 (1H, t, *J*=7.5 Hz, O–C*H*$_A$H$_B$–CH–O), 3.91 (1H, ddd, *J*=11.5, 9, 7.5 Hz, HO–C*H*$_A$H$_B$), 4.13 (1H, dd, *J*=7.5, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.16–4.24 (1H, m, O–CH$_2$–C*H*–O), 4.26 (1H, brdd, *J*=11.5, 7.5 Hz, HO–CH$_A$*H*$_B$), 5.39 (1H, brs, MeC=C*H*), 5.85 (1H, td, *J*=7.5, 2 Hz, HO–CH$_2$–C*H*=C). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.3, 26.4, 31.6, 32.7, 39.0, 56.8, 69.0, 75.2, 109.2, 120.1, 124.4, 130.7, 139.9. MS (EI) *m/z* 238 (M^+), 223 [$(M-CH_3)^+$], 178 [$(M-60)^+$]. HRMS (EI) calcd for $C_{14}H_{22}O_3$ (M^+) 238.1569, found 238.1558. Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.42; H, 9.56.

4.1.7. Trichloroacetimidate 13. To a solution of allylic alcohol **12** (18.5 g, 77.7 mmol) in dry CH_2Cl_2 (370 mL) cooled at −35°C was added DBU (13.9 mL, 93.2 mmol). To this solution was added CCl_3CN (9.35 mL, 93.2 mmol) dropwise over 10 min. After stirring at −35°C for 1 h, the reaction mixture was quenched with sat. NH_4Cl solution (300 mL) and extracted with CH_2Cl_2 (300 mL×2, 200 mL×1). The combined organic extract was washed with sat. NH_4Cl solution (1 L×1), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in Et_2O and passed through a short column packed with anhydrous Na_2SO_4 and silica gel (to remove polymeric products). The eluent was evaporated to give the crude trichloroacetimidate **13** as a light yellow oil. This material was used for the subsequent step without any purifications. IR (KBr) ν_{max} 3345, 2983, 2931, 1661, 1455, 1370, 1289, 1072 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s, C*H*$_3$ of acetonide), 1.41 (3H, s, C*H*$_3$ of acetonide), 1.64 (3H, brs, C*H*$_3$–C=CH), 1.72 (1H, brd, *J*=18 Hz, C*H*$_A$H$_B$–CMe=CH), 2.33 (1H, brd, *J*=18 Hz, CH$_A$*H*$_B$–CMe=CH), 2.67 (1H, brd, *J*=19 Hz, MeC=CH–C*H*$_A$H$_B$), 2.94–3.10 (2H, m, MeC=CH–CH$_A$*H*$_B$ and –C*H*–), 3.71 (1H, dd, *J*=8, 6.5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.10 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.23 (1H, dt, *J*=10, 6.5 Hz, O–CH$_2$–C*H*–O), 4.77 (1H, ddd, *J*=12, 6, 2 Hz, O–C*H*$_A$H$_B$–CH=C), 5.00 (1H, ddd, *J*=12, 8, 1 Hz, O–CH$_A$*H*$_B$–CH=C), 5.38 (1H, brs, MeC=C*H*), 5.71 (1H, ddd, *J*=8, 6, 2 Hz, O–CH$_2$–C*H*=C), 8.25 (1H, brs, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 25.3, 26.7, 32.3, 33.3, 39.8, 65.3, 68.6, 75.7, 91.5, 109.0, 118.2, 120.2, 131.1, 142.5, 162.7. MS (FAB) *m/z* 382 (M+H), 384 (M+H), 386 (M+H). HRMS (FAB) calcd for $C_{16}H_{23}NO_3Cl_3$ (M+H), calcd 382.0743, found 382.0749.

4.1.8. Trichloroacetamide 14. The crude imidate **13** was dissolved in *p*-xylene (600 mL) and powdered anhydrous K_2CO_3 (1.2 g) was added. The mixture was heated at reflux temperature for 20 h with vigorous stirring. After cooling to rt, the mixture was filtered through a pad of Super-Cel, and the precipitate was washed with toluene. The combined filtrate was evaporated in vacuo. The residue was purified by column chromatography (silica gel 550 g, ether/hexane=1:10→1:5) to give a trichloroacetamide **14** (27.4 g, 92% from **12**). Mp 100–102°C (as white crystals from hexane). $[\alpha]_D^{27}$=+70.2 (*c* 0.97, $CHCl_3$). IR (KBr) ν_{max} 3313, 2987, 2924, 1727, 1542, 1261, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, s, C*H*$_3$ of acetonide), 1.42 (3H, s, C*H*$_3$ of acetonide), 1.64–1.71 (5H, m, C*H*$_2$–C*Me*=CH), 2.08 (1H, td, *J*=9, 7.5 Hz, –C*H*–), 2.27 (1H, d quintet, *J*=17.5, 2.5 Hz, MeC=CH–C*H*$_A$H$_B$), 3.37 (1H, ddq, *J*=17.5, 6, 1.5 Hz, MeC=CH–CH$_A$*H*$_B$), 3.63 (1H, dd, *J*=9, 7.5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.03 (1H, td, *J*=9, 5.5 Hz, O–CH$_2$–C*H*–O), 4.10 (1H, dd, *J*=7.5, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 5.30 (1H, dd, *J*=17, 1 Hz, CH=C*H*$_A$H$_B$), 5.32 (1H, dd, *J*=11, 1 Hz, CH=CH$_A$*H*$_B$), 5.39 (1H, m, MeC=C*H*), 5.82 (1H, dd, *J*=17, 11 Hz, C*H*=CH$_2$), 9.21 (1H, brs, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 26.2, 26.5, 30.0, 35.8, 44.3, 59.9, 68.8, 76.3, 93.8, 109.9, 116.0, 119.0, 130.8, 133.7, 160.4. MS (FAB) *m/z* 382 (M+H), 384 (M+H), 386 (M+H). HRMS (FAB) calcd for $C_{16}H_{23}NO_3Cl_3$ (M+H), calcd 382.0743, found 382.0721. Anal. calcd for $C_{16}H_{22}O_3NCl_3$: C, 50.08; H, 6.04; N, 3.65. Found: C, 50.25; H, 5.97; N, 3.59.

4.1.9. Allyl acetate 16. A solution of the allylic alcohol **12** (2.37 g, 9.95 mmol) in pyridine (10 mL) and Ac_2O (10 mL) was stirred at rt for 1 h. The reaction mixture was diluted with toluene (20 mL), and concentrated in vacuo. The residue was purified by column chromatography (silica gel 100 g, ether/hexane=1:1→2:1→3:1) to give the acetate **16** (2.69 g, 97%) as a colorless oil. $[\alpha]_D^{27}$=+79.1 (*c* 0.98, $CHCl_3$). IR (KBr) ν_{max} 2987, 1735, 1438, 1370, 1231, 1157, 1073 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s, C*H*$_3$ of acetonide), 1.39 (3H, s, C*H*$_3$ of acetonide), 1.62 (3H, s, C*H*$_3$–C=CH), 1.70 (1H, brd, *J*=19 Hz, C*H*$_A$H$_B$–CMe=CH), 2.04 (3H, s, O*Ac*), 2.30 (1H, brd, *J*=19 Hz, CH$_A$*H*$_B$–CMe=CH), 2.62 (1H, brd, *J*=21 Hz, MeC=CH–C*H*$_A$H$_B$), 2.93 (1H, dd, *J*=10, 6.5 Hz, –C*H*–), 3.20 (1H, brd, *J*=21 Hz, MeC=CH–CH$_A$*H*$_B$), 3.70 (1H, dd, *J*=8.5, 6.5 Hz, O–C*H*$_A$H$_B$–CH–O), 4.10 (1H, dd, *J*=8.5,

6.5 Hz, O–CH$_A$H$_B$–CH–O), 4.20 (1H, dt, J=10, 6.5 Hz, O–CH$_2$–CH–O), 4.74 (1H, ddd, J=12.5, 6.5, 2 Hz, AcO–CH$_A$H$_B$), 4.77 (1H, dd, J=12.5, 8.5 Hz, AcO–CH$_A$H$_B$), 5.37 (1H, brs, MeC=CH), 5.58 (1H, ddd, J=8.5, 6.5, 2 Hz, AcO–CH$_2$–CH=C). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.0, 23.2, 25.3, 26.7, 32.4, 33.4, 39.7, 60.3, 68.7, 75.7, 109.1, 118.9, 120.3, 131.2, 141.6, 171.1. EI-MS m/z 265 (M−15). Anal. calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.54; H, 8.69.

4.1.10. Dienone 17. CrO_3 (4.82 g, 48.2 mmol, dried over P_2O_5 prior to use) was suspended in dry CH_2Cl_2 (4 mL) and pyridine (7.8 mL, 96.4 mmol) was added at 0°C. After stirring at 0°C for 5 min, the acetate **16** (900 mg, 3.24 mmol) in dry CH_2Cl_2 (2 mL) was added and the mixture was stirred for 5 h 30 min. Et_2O and Super-Cel were then added, the mixture was filtered through a pad of Super-Cel. The precipitate was washed with Et_2O, and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O and the solution was passed through a column packed with anhydrous Na_2SO_4 and silica gel (to remove chromium residue). The eluent was evaporated and the residue was purified by column chromatography (silica gel 25 g, ether/hexane=1:1→2:1→3:1) to give dienone **17** (381 mg, 40%) as a colorless oil. $[\alpha]_D^{26}$=+51.7 (c 1.19, CHCl$_3$). IR (KBr) ν_{max} 2986, 1740, 1675, 1373, 1229, 1064 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.28 (3H, s, CH$_3$ of acetonide), 1.38 (3H, s, CH$_3$ of acetonide), 1.98 (3H, t, J=1 Hz, CH$_3$–C=CH), 2.08 (3H, s, OAc), 2.10 (1H, brd, J=19 Hz, CH$_A$H$_B$–CMe=CH), 2.69 (1H, m, CH$_A$H$_B$–CMe=CH), 3.24 (1H, brt, J=7 Hz, –CH–), 3.61 (1H, ddd, J=10, 7, 3.5 Hz, O–CH$_2$–CH–O), 3.99–4.09 (2H, m, O–CH$_2$–CH–O), 4.69 (1H, dd, J=14.5, 5 Hz, AcO–CH$_A$H$_B$), 4.95 (1H, dd, J=14.5, 8.5 Hz, AcO–CH$_A$H$_B$), 6.05 (1H, dq, J=2.5, 1 Hz, MeC=CH), 6.80 (1H, dd, J=8.5, 5 Hz, AcO–CH$_2$–CH=C). ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.8, 24.6, 25.2, 26.3, 32.2, 39.7, 61.0, 68.1, 76.8, 109.4, 127.2, 133.8, 135.7, 159.0, 170.9, 186.3. EI-MS m/z 294 (M$^+$), 279 (M−15). Anal. calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.30; H, 7.73.

4.1.11. Allyl alcohol 18. The dienone **17** (242 mg, 0.823 mmol) and $CeCl_3{\cdot}(H_2O)_7$ (307 mg, 0.823 mmol) were dissolved in MeOH (7.5 mL) and the solution was cooled to 0°C. To this solution was added $NaBH_4$ (31 mg, 0.82 mmol) portionwise. After stirring at 0°C, sat. NH_4Cl solution and sat. potassium sodium tartrate solution were added, and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 12 g, ether/hexane=2:1) to give the allyl alcohol **18** (151 mg, 62%) as a colorless oil. $[\alpha]_D^{26}$=+92.6 (c 0.59, CHCl$_3$). IR (KBr) ν_{max} 3445, 2933, 1736, 1372, 1237, 1070, 1029 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.31 (3H, s, CH$_3$ of acetonide), 1.39 (3H, s, CH$_3$ of acetonide), 1.67 (3H, brs, CH$_3$–C=CH), 1.67–1.73 (1H, m, CH$_A$H$_B$–CMe=CH–), 2.05 (3H, s, OAc), 2.32 (1H, m, CH$_A$H$_B$–CMe=CH), 3.04 (1H, dd, J=8.5, 6.5 Hz, –CH–), 3.65 (1H, ddd, J=13, 6, 5 Hz, O–CH$_A$H$_B$–CH–O), 4.05–4.16 (2H, m, O–CH$_A$H$_B$–CH–O), 4.62 (1H, ddd, J=13, 6.5, 2 Hz, AcO–CH$_A$H$_B$), 4.79–4.86 (2H, m, AcO–CH$_A$H$_B$ and HO–CH), 5.45 (1H, brs, MeC=CH), 5.91 (1H, ddd, J=8.5, 6.5, 2 Hz, AcO–CH$_2$–CH=C). ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.9, 22.8, 25.3, 26.7, 33.6, 40.3, 60.4, 67.1, 68.9, 76.0, 109.3, 117.3, 125.3, 135.2, 143.5, 171.1. EI-MS m/z 296 (M$^+$), 281 (M−15). Anal. calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16. Found: C, 64.86; H, 8.31.

4.1.12. TBS ether 19. To a solution of the allyl alcohol **18** (151 mg, 0.509 mmol) in DMF (4.5 mL) were added imidazole (177 mg, 4.07 mmol) and TBSCl (153 mg, 1.02 mmol). After stirring at rt for 1 h, the reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic extract was washed with H_2O (×2) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product **19** (232 mg) as a colorless oil. This material was used for next reaction without purification. A portion of this material was purified by column chromatography (ether/hexane=1:3→1:2→1:1) to afford the analytically pure sample. $[\alpha]_D^{25}$=+82.9 (c 1.28, CHCl$_3$). IR (KBr) ν_{max} 2930, 1741, 1379, 1232, 1082 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.11 (3H, s, CH$_3$–Si), 0.12 (3H, s, CH$_3$–Si), 0.95 (9H, s, t-Bu–Si), 1.29 (3H, s, CH$_3$ of acetonide), 1.35 (3H, s, CH$_3$ of acetonide), 1.65 (3H, brs, CH$_3$–C=CH), 1.69 (1H, brd, J=19 Hz, CH$_A$H$_B$–CMe=CH), 2.02 (3H, s, –OAc), 2.26–2.38 (1H, m, CH$_A$H$_B$–CMe=CH), 3.06 (1H, brdd, J=9, 6.5 Hz, –CH–), 3.62 (1H, dd, J=7.5, 6 Hz, O–CH$_A$H$_B$–CH–O), 4.40 (1H, dd, J=7.5, 6 Hz, O–CH$_A$H$_B$–CH–O), 4.12 (1H, dt, J=9, 6 Hz, O–CH$_2$–CH–O), 4.58 (1H, ddd, J=12.5, 6.5, 2 Hz, AcO–CH$_A$H$_B$), 4.79 (1H, dd, J=12.5, 8.5 Hz, AcO–CH$_A$H$_B$), 4.86 (1H, brs, TBSO–CH), 5.34 (1H, brs, MeC=CH), 5.82 (1H, ddd, J=8.5, 6.5, 2 Hz, AcO–CH$_2$–CH=C). ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.1, −5.0, 18.4, 21.0, 22.8, 25.4, 25.9, 26.7, 34.0, 39.6, 60.2, 67.9, 68.9, 76.3, 109.0, 116.4, 126.2, 134.4, 143.1, 171.1. EI-MS m/z 410 (M$^+$) 395 (M−15), 350 (M−60). Anal. calcd for $C_{22}H_{38}O_5Si$: C, 64.35; H, 9.33. Found: C, 64.29; H, 9.60.

4.1.13. Allyl alcohol 20. To a solution of the crude acetate **19** (232 mg) in MeOH (6 mL) was added anhydrous K_2CO_3 (300 mg). After vigorous stirring at rt for 15 min, sat. NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 6 g, ether/hexane=1:1) to give the allyl alcohol **20** (147 mg, 79%, 2 steps from **18**) as a colorless oil. $[\alpha]_D^{27}$=+68.3 (c 2.75, CHCl$_3$). IR (KBr) ν_{max} 3457, 2931, 2858, 1256, 1159, 1075 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.12 (3H, s, CH$_3$–Si), 0.14 (3H, s, CH$_3$–Si), 0.95 (9H, s, t-Bu–Si), 1.31 (3H, s, CH$_3$ of acetonide), 1.40 (3H, s, CH$_3$ of acetonide), 1.56–1.69 (1H, m, CH$_A$H$_B$–CMe=CH), 1.66 (3H, brs, CH$_3$–C=CH), 2.02 (1H, m, OH), 2.34 (1H, m, CH$_A$H$_B$–CMe=CH), 3.08 (1H, brt, J=7.5 Hz, –CH–), 3.60 (1H, m, O–CH$_A$H$_B$–CH–O), 3.94–4.15 (3H, m, O–CH$_A$H$_B$–CH–O and HO–CH$_A$H$_B$), 4.25 (1H, dd, J=12, 8 Hz, HO–CH$_A$H$_B$), 4.84 (1H, brs, TBSO–CH), 5.37 (1H, brs, MeC=CH), 6.11 (1H, td, J=8, 2 Hz, HO–CH$_2$–CH=C). ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.0, −4.9, 18.4, 22.8, 25.4, 25.9, 26.5, 33.3, 39.4, 57.2, 67.5, 69.3, 76.0, 109.3, 122.2, 126.2, 133.9, 141.9. MS (FAB) m/z 369 (M+H). HRMS (FAB) calcd for $C_{20}H_{37}O_4Si$ (M+H),

369.2461, found 369.2440. Anal. calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.84; Found: C, 65.18; H, 9.87; N.

4.1.14. Trichloroacetamide 21. To an ice-cold solution of allylic alcohol **20** (76 mg, 0.21 mmol) in dry CH_2Cl_2 (5 mL) were added DBU (49 μL, 0.32 mmol) and CCl_3–CN (39 μL, 0.39 mmol) successively. The mixture was stirred at 0°C for 45 min. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. NH_4Cl solution (×2), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure.

*Trichloroacetimidate of **20***. IR (KBr) ν_{max} 2932, 1664, 1380, 1287, 1256, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (3H, s, C*H*$_3$–Si), 0.13 (3H, s, C*H*$_3$–Si), 0.95 (9H, s, *t*-Bu–Si), 1.29 (3H, s, C*H*$_3$ of acetonide), 1.37 (3H, s, C*H*$_3$ of acetonide), 1.66 (3H, brs, C*H*$_3$–C═CH), 1.72 (1H, br d, *J*=18 Hz, C*H*$_A$H$_B$–CMe═CH–), 2.34 (1H, brd, *J*=18 Hz, CH$_A$*H*$_B$–CMe═CH), 3.08 (1H, m, –C*H*–), 3.62 (1H, dd, *J*=8, 6 Hz, O–C*H*$_A$H$_B$–CH–O), 4.05 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.14 (1H, dt, *J*=9, 6 Hz, O–CH$_2$–C*H*–O), 4.86 (1H, m, O–C*H*$_A$H$_B$–CH═C), 4.88 (1H, d, *J*=6 Hz, TBSO–C*H*) 4.95 (1H, ddd, *J*=13, 7, 1.5 Hz, O–CH$_A$*H*$_B$–CH═C) 5.36 (1H, brs, MeC═C*H*), 5.95 (1H, td, *J*=7, 2 Hz, O–CH$_2$–C*H*═C), 8.25 (1H, brs, N*H*). MS (FAB) *m/z* 512 (M+H). The crude imidate was dissolved in xylene (10 mL) and powder of K_2CO_3 (20 mg) was added. The mixture was heated at a reflux temperature for 36 h. After cooling to rt, the mixture was filtered through a pad of Super-Cel, washed with toluene. The combined filtrate was evaporated in vacuo. The residue was purified by column chromatography to give the trichloroacetamide **21** (65 mg, 62%) and unreacted imidate (11 mg, 10%).

*Trichloroacetamide **21***. Mp 130–132°C. (as white prisms from Et_2O–hexane) $[\alpha]_D^{27}$=+133 (*c* 0.40, $CHCl_3$). IR (KBr) ν_{max} 3327, 2930, 1727, 1533, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s, (C*H*$_3$)$_2$–Si), 0.85 (9H, s, *t*-Bu–Si), 1.39 (3H, s, C*H*$_3$ of acetonide), 1.41 (3H, s, C*H*$_3$ of acetonide), 1.51–1.62 (1H, m, C*H*$_A$H$_B$–CMe═CH), 1.69 (3H, brs, C*H*$_3$–C═CH), 1.75 (1H, dd, *J*=18.5, 6 Hz, CH$_A$*H*$_B$–CMe═CH), 2.48 (1H, ddd, *J*=11.5, 9.5, 6 Hz, –C*H*–), 3.68 (1H, m, O–C*H*$_A$H$_B$–CH–O), 4.01–4.11 (2H, m, O–CH$_A$*H*$_B$–C*H*–O), 4.87 (1H, d, *J*=6 Hz, TBSO–C*H*), 5.33 (1H, dd, *J*=11, 1 Hz, CH═C*H*$_A$H$_B$), 5.38 (1H, dd, *J*=17.5, 1 Hz, CH═CH$_A$*H*$_B$), 5.56 (1H, brd, *J*=6 Hz, MeC═C*H*), 5.68 (1H, dd, *J*=17.5, 11 Hz, C*H*═CH$_2$), 8.91 (1H, brs, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −3.7, 18.1, 22.7, 25.9, 26.3, 26.5, 30.6, 38.6, 64.4, 66.2, 68.7, 75.6, 94.0, 109.9, 116.0, 123.1, 132.4, 135.4, 159.3. HRMS (FAB) calcd for $C_{22}H_{37}O_4NCl_3Si$ (M+H), 512.1557, found 512.1540. Anal. calcd for $C_{22}H_{36}O_4NCl_3Si$: C, 51.51; H, 7.07; N, 2.73. Found: C, 51.47; H, 7.07; N, 2.62.

4.1.15. Carbamate 22. To a solution of the trichloroacetamide **21** (14.5 mg, 23.8 μmol) in THF (0.5 mL) was added *n*-Bu_4NF (1M in THF, 12 μL, 12 μmol). After stirring at rt for 1 h, the mixture was quenched with sat. NH_4Cl solution and extracted with AcOEt (×3). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel TLC (ether/hexane=3:1) to give the carbamate **22** (7.6 mg, 92%). Mp 106–108°C (as colorless needles from Et_2O–hexane). $[\alpha]_D^{26}$=+44.2 (*c* 0.21, $CHCl_3$). IR (KBr) ν_{max} 3406, 2916, 1760, 1372, 1067 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s, C*H*$_3$ of acetonide), 1.42 (3H, s, C*H*$_3$ of acetonide), 1.62–1.83 (2H, m, C*H*$_2$–CMe═CH), 1.82 (3H, s, C*H*$_3$–C═CH) 1.98 (1H, td, *J*=10, 8 Hz, –C*H*–), 3.60 (1H, t, *J*=8 Hz, O–C*H*$_A$H$_B$–CH–O), 3.95 (1H, ddd, *J*=10, 8, 6 Hz, O–CH$_2$–C*H*–O), 4.08 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.48 (1H, brd, *J*=4.5 Hz, Me–C═CH–C*H*–O), 5.34 (1H, dd, *J*=11, 1 Hz, CH═C*H*$_A$H$_B$), 5.40 (1H, dd, *J*=17.5, 1 Hz, CH═CH$_A$*H*$_B$), 5.66 (1H, m, MeC═C*H*), 5.84 (1H, dd, *J*=17.5, 11 Hz, C*H*═CH$_2$), 5.98 (1H, brs, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 25.7, 26.6, 29.4, 43.4, 62.8, 68.9, 76.9, 78.5, 109.9, 116.6, 117.3, 133.3, 140.8, 158.5. MS (FAB) *m/z* 280 (M+H). HRMS (FAB) calcd for $C_{15}H_{22}O_4N$ (M+H), 280.1549, found 280.1535. Anal. calcd for $C_{15}H_{21}O_4N$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.48; H, 7.55; N, 4.84.

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