Scalable Synthesis of a New Dihydroxylated Intermediate for Tetrodotoxin and Its Analogues

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Received 26 January 2010; revised 8 March 2010

Abstract: The synthesis of a novel intermediate for tetrodotoxin and its analogues, possessing two hydroxy groups at C-8 and C-11, is described. The procedure involves a Diels–Alder reaction between bromolevoglucosenone and a *tert*-butyldiphenylsilyl-protected isoprenol during which the C-11 group hydroxy is installed. Subsequent transformations, including an Overman rearrangement, affords a cyclohexene intermediate containing a trichloroacetamide moiety as a requisite amino functionality for installation of the guanidine unit present in tetrodotoxin. Hydroxylation at C-8 is carried out via neighboring group participation of the trichloroacetamide to furnish the desired diol intermediate.

Key words: tetrodotoxin, Diels–Alder reaction, hydroxylation, neighboring group participation, Overman rearrangement

Our research has led to the synthesis of tetrodotoxin (**1**),[1] a well-known natural product, and several of its analogues including 11-deoxytetrodotoxin (**2**),[2] 8,11-dideoxytetrodotoxin (**3**),[3] and 5,11-dideoxytetrodotoxin (**4**),[4] from common intermediate **5**[5] (Figure 1). Since compound **5** has no hydroxy groups on the cyclohexene ring, its regioselective and stereoselective hydroxylation was a major issue in the above synthetic studies. Hydroxylation at C-8 has been established via neighboring group participation of a trichloroacetamide;[4] however, introduction of the hydroxy group at C-11 still remains problematic, despite the fact that we were able to hydroxylate at C-11 by allylic oxidation with selenium dioxide during our total synthesis of tetrodotoxin.[1] Hence, a general route to prepare tetrodotoxin analogues hydroxylated at C-11 is still required, as these are necessary for biochemical research associated with tetrodotoxin. Recently, we reported the synthesis of compound **6**, a newly designed intermediate possessing hydroxy groups at C-11 and C-8, starting from the common intermediate **5**.[6] Herein, we report a new and scalable synthesis of the dihydroxylated intermediate **7**.[7]

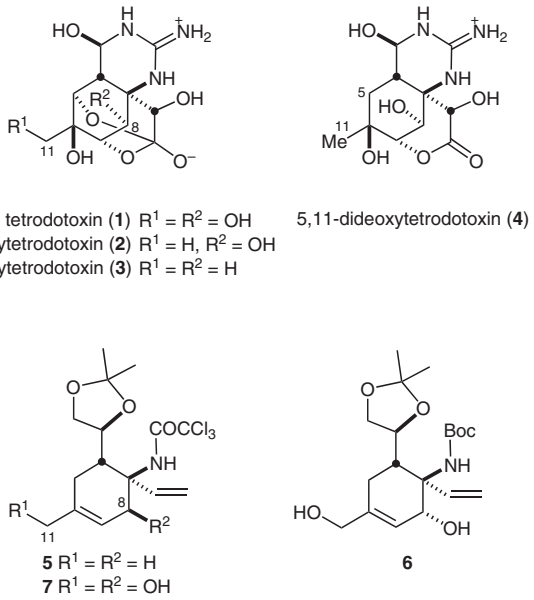
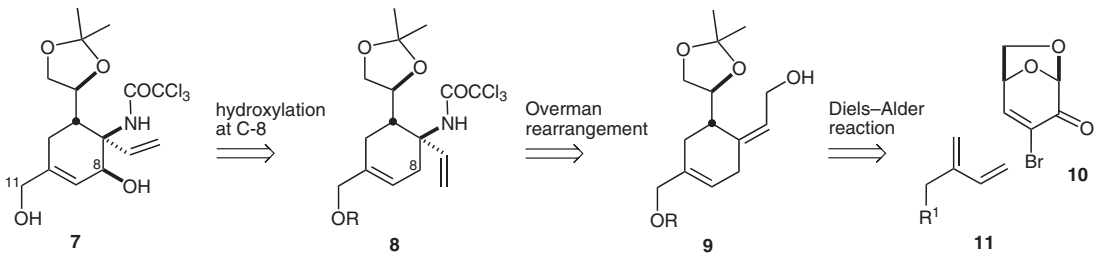


Figure 1 Structures of tetrodotoxin, its analogues and synthetic intermediates

Since common intermediate **5** had been prepared via a Diels–Alder reaction between bromolevoglucosenone (**10**) and isoprene **11** (R^1 = H),[5] we planned to synthesize new intermediate **7** starting with the Diels–Alder reaction between **10** and isoprenol **11** (R^1 = OH) as the diene (Scheme 1). The resulting cycloadduct could be transformed into cyclohexene **8** via Overman rearrangement of allylic alcohol **9**, and finally into the new intermediate **7**

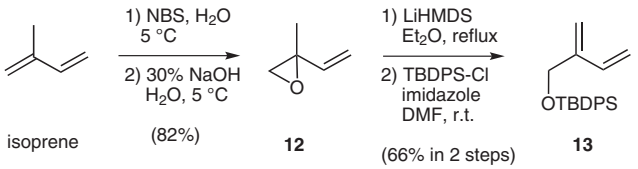


Scheme 1 Synthetic plan for intermediate **7**

SYNTHESIS 2010, No. 12, pp 1992–1998
Advanced online publication: 19.04.2010
DOI: 10.1055/s-0029-1218747; Art ID: F02010SS

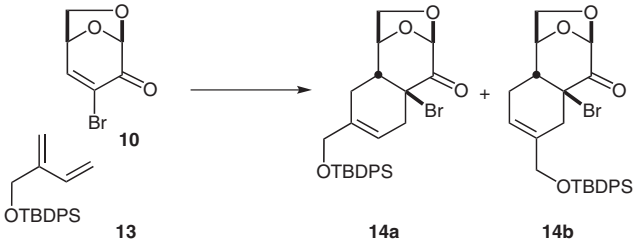
according to the method developed previously in our laboratory.[4]

Our preliminary studies on the Diels–Alder reaction of compound **10** with isoprenol and its derivatives **11** (R^1 = OH or R^1 = OR) indicated that isoprenol was unstable under Lewis acid conditions, and so we instead employed *tert*-butyldiphenylsilyl-protected isoprenol **13** as the diene. It was anticipated that the *tert*-butyldiphenylsilyl group of isoprenol **13** would be compatible with the reaction conditions throughout the synthesis of intermediate **7**. Of the several syntheses of isoprenol **11** (R^1 = OH) reported to date,[8] we chose the method of Silverstein,[9] beginning from isoprene, because of its simple procedure and the low cost of the starting material and reagents (Scheme 2). Thus, isoprene was treated with *N*-bromosuccinimide in water to give an intermediate bromohydrin which was exposed to aqueous sodium hydroxide to afford isoprene monoxide **12** in good yield. When base-promoted isomerization of **12** was carried out with lithium diisopropylamide in accord with the literature,[9] a low yield (ca. 30%) of product **13** was obtained after silylation with *tert*-butyldiphenylsilyl chloride and imidazole in *N*,*N*-dimethylformamide. Extensive examination of the reaction conditions revealed that the use of lithium hexamethyldisilazide, at reflux in diethyl ether, improved the yield giving 66% of **13** after protection with *tert*-butyldiphenylsilyl chloride. This modified method is practical for the synthesis of isoprenol derivatives, and made it possible to prepare over 100 grams of **13** with good reproducibility.



Scheme 2 Synthesis of *tert*-butyldiphenylsilyl-protected isoprenol **13**

With a sufficient amount of diene **13** in hand, the Diels–Alder reaction with bromolevoglucosenone (**10**) was examined (Equation 1 and Table 1). In our synthesis of compound **5**, the Diels–Alder reaction between **10** and isoprene was best carried out using boron trifluoride–diethyl ether complex in acetonitrile as the solvent, to give the desired product in high yield and with excellent regioselectivity (76% yield, 15:1).[5] To our surprise, the Diels–Alder reaction between **10** and protected isoprenol **13**, under identical conditions, gave a complex mixture of products (Table 1, entry 1). We therefore investigated the conditions for this Diels–Alder reaction further. Heating the reaction in toluene at reflux temperature without a Lewis acid gave a 2:1 mixture of the products **14a** and **14b** (Table 1, entry 2),[10] while the same reaction without solvent, proceeded at room temperature to give the same products, but with improved regioselectivity (ca. 4:1) (Table 1, entry 3). The use of lithium perchlorate–diethyl ether complex ($LiClO_4$·OEt_2)[11] did not improve the regioselectivity (Table 1, entry 4). The reaction in the presence of the Lewis acids, ytterbium(III) triflate [$Yb(OTf)_3$] and scandium(III) triflate [$Sc(OTf)_3$][12] gave similar results (Table 1, entries 5 and 6). In the event, the use of boron trifluoride–diethyl ether complex in dichloromethane as solvent, at 0 °C, proved to be the optimum conditions for this Diels–Alder reaction, providing an 89% yield of the products with high regioselectivity (**14a**:**14b**, >20:1) (Table 1, entry 7).



Equation 1

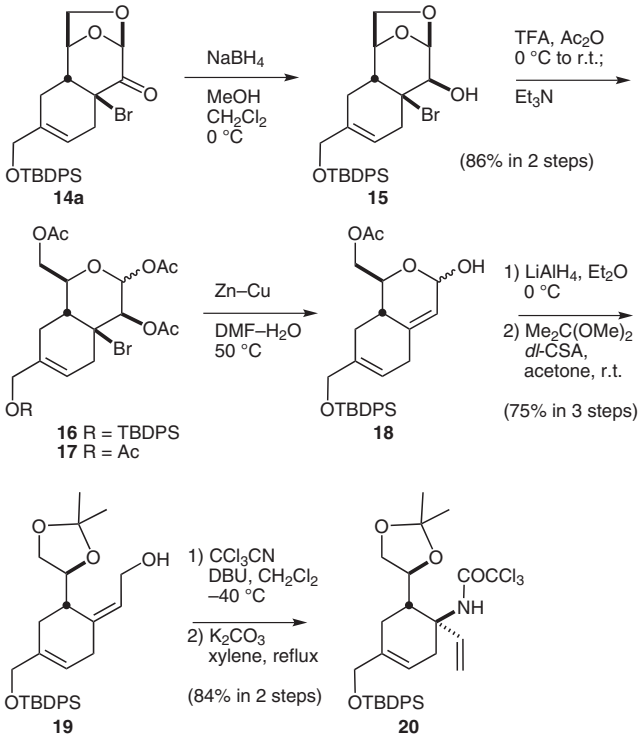
Table 1 Diels–Alder Reaction between Bromolevoglucosenone (**10**) and Diene **13**

Entry	Lewis acid and/or solvent	Temp	Time	Yield (%)	**14a/14b**[a]
1	BF_3·OEt_2 (1 equiv), MeCN	0 °C	5 h	complex mixture	
2	toluene	110 °C	21 h	48	2:1
3	neat	r.t.	5 d	63	4:1
4	5 M $LiClO_4$·Et_2O	r.t.	18 h	46	4:1
5	$Yb(OTf)_3$ (0.1 equiv), CH_2Cl_2	r.t.	9 d	70	4:1
6	$Sc(OTf)_3$ (0.1 equiv), CH_2Cl_2	r.t.	8 d	82	4:1
7	BF_3·OEt_2 (2 equiv), CH_2Cl_2	0 °C	15 h	89	>20:1

[a] The ratio was determined by ^{1}H NMR spectroscopy.

The product **14a** was transformed into trichloroacetamide **20** according to the reported procedure for the synthesis of **5**.[5] Although all the reactions shown in Scheme 3 proceeded smoothly to give the desired products in good yields, two comments are worthwhile. We did not encounter any difficulties in preparing bicyclic compound **16** from bromohydrin **15** on a 65 gram scale. However, when ca. 150 grams of **15** was used for the same reaction, the desired product **16** was obtained in 60% yield along with a significant amount of by-product **17** (36% yield). This was due to the prolonged time required for removal of the reaction medium, which led to acetolysis of the silyl ether group of **16**. Therefore, the work-up procedure was modified in order to neutralize the reaction with triethylamine before concentration. This modified procedure enabled us to prepare compound **16** on a 150 gram scale without

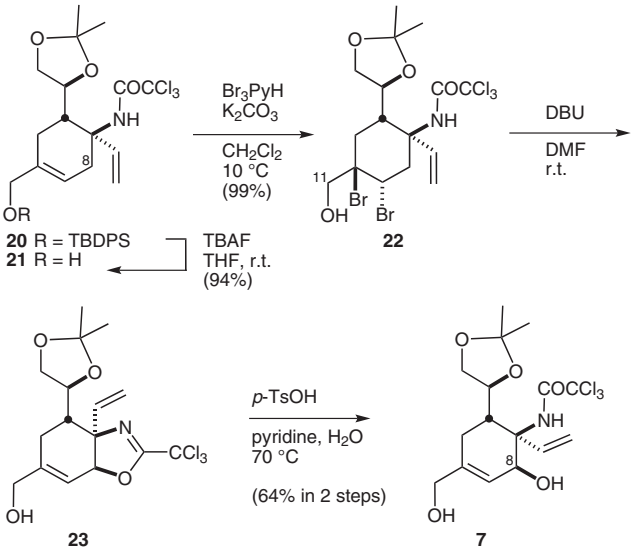
forming the undesired product **17**. For the reduction of bicyclic **16** with the zinc–copper couple in *N*,*N*-dimethylformamide–water, a temperature of 50 °C and a short reaction time (about 10 min; it was necessary to quench the reaction by addition of cold aqueous sodium bicarbonate solution), were found to be critical. Longer reaction times resulted in decreased yields of product **18**. Since the transformation of **18** into trichloroacetamide **20**, including the Overman rearrangement, was successful, on ca. 50 gram scale, we were able to obtain **20** on a 40 gram scale in a single batch.



Scheme 3 Synthesis of trichloroacetamide **20**

Hydroxylation at C-8 of compound **20** was carried out using the neighboring group participation effect of the trichloroacetamide moiety according to the method developed in our laboratory (Scheme 4).[4] Attempted bromination of **20** gave a complex mixture, while bromination of **21**, prepared by desilylation of **20** with tetrabutylammonium fluoride, proceeded at 10 °C to afford dibromide **22**, quantitatively.[13] Treatment of **22** with 1,8-diazabicyclo[5.4.0]undec-7-ene in *N*,*N*-dimethylformamide then gave oxazoline **23**. Finally, hydrolysis of **23** using *p*-toluenesulfonic acid in aqueous pyridine afforded the desired dihydroxylated intermediate **7** in 69% yield over two steps.

In conclusion, we have established a scalable route for the preparation of new advanced intermediate **7** for the synthesis of tetrodotoxin and its analogues. This compound is expected to play an important role in expeditious syntheses of various tetrodotoxin derivatives possessing hydroxy groups at C-11 and C-8 for biochemical investigations, and efforts in this direction are in progress.



Scheme 4 Procedure for hydroxylation at C-8

Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are uncorrected. Infrared spectra were obtained using a Jasco FT/IR-8300 spectrophotometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with Bruker ARX-400 (at 400 MHz) or Varian Gemini-2000 (at 300 MHz) spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker ARX-400 (at 100 MHz) or Varian Gemini-2000 (at 75 MHz) spectrometers. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Elemental analyses were performed by the Analytical Laboratory at the Graduate School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin layer chromatography 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 soln as developing agents. Cica-Merck silica gel (60, particle size 0.063–0.2 mm A STM) was used for column chromatography. Unless otherwise noted, non-aqueous reactions were carried out under N_2 or Ar. Anhyd CH_2Cl_2 and Et_2O were purchased from Kanto Chemical Co., Inc. Et_3N and py were dried over anhyd KOH. $BF_3{\cdot}OEt_2$ was distilled from CaH_2. All other commercial reagents were used as received.

1-Methyl-1-ethenylcyclopropane (Isoprene Monoxide) (12)

A three-necked flask (1 L), equipped with a mechanical stirrer, a dropping funnel and a thermometer was charged with H_2O (190 mL) and cooled in an ice-bath. Isoprene (82 mL, 0.840 mol) was added and the mixture stirred for 15 min. Powdered NBS (313 g, 1.76 mol) was added portionwise, with vigorous stirring over 30 min whilst maintaining the internal temperature <5 °C. After stirring for 1 h, 30% aq NaOH soln (100 mL) was added dropwise over 30 min and stirring was continued for 1 h. The mixture was partitioned and the aq layer extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (100 mL) and then transferred to a distillation apparatus. The solvent was removed under vacuum (760 mmHg) with oil-bath heating at 50 °C, and the remaining material was distilled at 760–230 mmHg with oil-bath heating at 75 °C to give **12** (38.7 g, 82%) as a colorless liquid.

***tert*-Butyl-(2-methylenebut-3-enyloxy)diphenylsilane (13)**

A three-necked flask (2 L), equipped with a dropping funnel, a reflux condenser and a gas inlet adapter was purged with argon. Freshly distilled hexamethyldisilazane (135 mL, 0.639 mol) and anhyd Et_2O (350 mL) were added, and the soln was cooled to –78 °C.

n-BuLi (1.60 M in hexanes, 368 mL, 0.589 mol) was added via the dropping funnel over 50 min. The resulting suspension was stirred for 30 min at r.t., isoprene monoxide (**12**) (41.3 g, 0.491 mol) was added via cannula over 15 min at r.t., and the mixture then heated at reflux for 24 h. After cooling in an ice-bath, the mixture was slowly poured onto ice-cold 2 M HCl (800 mL), and stirred vigorously for 1.5 h. The organic layer was separated, and the aq layer extracted with Et_2O (500 mL, then 2 × 400 mL). The combined organic phase was washed with sat. aq $NaHCO_3$ soln (200 mL) and brine (200 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure (ca. 500 mmHg at 30 °C) to give the crude isoprenol (674 g) as a yellow oil. To a soln of the crude isoprenol (674 g) and imidazole (100 g, 1.47 mol) in DMF (1.0 L) was added TBDPSCl (158 mL, 0.614 mol) at r.t. After being stirred for 30 min, the reaction mixture was quenched with sat. aq $NaHCO_3$ soln (250 mL) and H_2O (750 mL), and then extracted with Et_2O (500 mL then 400 mL). The combined organic extract was washed with H_2O (2 × 1.5 L) and brine (200 mL), and dried over anhyd Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by column chromatography [silica gel (1.2 kg), Et_2O–hexane, 0:1→1:100→1:75→1:50] to give TBDPS ether **13** (105 g, 66% over 2 steps) as a colorless oil.

IR (NaCl, film): 3072, 2931, 2858, 1597, 1473, 1428, 1391, 1113, 902 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, *t*-Bu), 4.38 (m, 2 H, CH_2OTBDPS), 4.98 (d, *J* = 11 Hz, 1 H, CH_AH$_B$=CH), 5.05 (d, *J* = 18 Hz, 1 H, CH$_A$$H_B$=CH), 5.17 (m, 1 H, C$H_AH_B$=C), 5.50 (m, 1 H, CH$_A$$H_B$=C), 6.38 (dd, *J* = 18, 11 Hz, 1 H, CH$_A$H$_B$=C*H*), 7.35–7.48 (m, 6 H, Ph), 7.67–7.73 (m, 4 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 26.7, 63.0, 113.2, 114.9, 127.8, 129.7, 133.6, 135.6, 136.6, 144.6.

Anal. Calcd for $C_{21}H_{26}OSi$: C, 78.21; H, 8.13. Found: C, 78.35; H, 8.40.

(1*S*,4*R*,5a*S*,9a*R*)-5a-Bromo-8-[(*tert*-butyldiphenylsilyloxy)methyl]-1,2,5a,6,9,9a-hexahydro-1,4-epoxy-3-benzoxepin-5(4*H*)-one (14a)

Bromolevoglucosenone (**10**) (65.9 g, 0.321 mol, dried by azeotropic removal of H_2O with toluene) in a three-necked flask (3 L), equipped with a mechanical stirrer, was dissolved in anhyd CH_2Cl_2 (800 mL) under Ar. The mixture was cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (81.4 mL, 0.642 mol) and a soln of diene **13** (125 g, 0.386 mol, dried by azeotropic removal of H_2O with toluene) in anhyd CH_2Cl_2 (200 mL) were added dropwise via cannula over 30 min. After stirring for 15 h, sat. aq $NaHCO_3$ soln (700 mL) was added slowly. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel (1.2 kg), EtOAc–hexane, 1:25→1:15→1:10] to afford bromoketone **14a** (152 g, 89%) as a colorless oil.

$[\alpha]_D^{24}$ –11.1 (*c* 0.904, $CHCl_3$).

IR (NaCl, film): 2931, 2857, 1736, 1473, 1428, 1113, 998, 924, 824 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*-Bu), 2.13 (dd, *J* = 16, 6 Hz, 1 H, CH_AH$_B$CH), 2.41 (dd, *J* = 16, 8 Hz, 1 H, CH$_A$-H_BCH), 2.67 (br d, *J* = 16 Hz, 1 H, CH_AH$_B$CBr), 2.83 (dd, *J* = 8, 6 Hz, 1 H, C*H*), 3.02 (dd, *J* = 16, 5.5 Hz, 1 H, CH$_A$CH_BCBr), 3.85 (dd, *J* = 7.5, 5.5 Hz, 1 H, OCH_AH$_B$CHO), 4.14 (br s, 2 H, CH_2OTBDPS), 4.41 (d, *J* = 5.5 Hz, 1 H, OCH$_A$$H_B$CHO), 4.51 (d, *J* = 7.5 Hz, 1 H, OCH$_2$C*H*O), 5.25 (s, 1 H, OC*H*O), 5.78 (m, 1 H, C=C*H*), 7.34–7.40 (m, 6 H, Ph), 7.62–7.74 (m, 4 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 26.7, 30.0, 36.6, 48.4, 55.9, 66.1, 67.2, 79.0, 100.1, 119.1, 127.8, 129.8, 133.5, 135.6, 140.2, 195.2.

Anal. Calcd for $C_{27}H_{31}BrO_4Si$: C, 61.47; H, 5.92. Found: C, 61.46; H, 5.95.

(1*S*,4*R*,5*R*,5a*S*,9a*R*)-5a-Bromo-8-[(*tert*-butyldiphenylsilyloxy)methyl]-1,2,4,5,5a,6,9,9a-octahydro-1,4-epoxy-3-benzoxepin-5-ol (15)

To an ice-cold soln of bromoketone **14a** (101 g, 191 mmol) in CH_2Cl_2 (150 mL) and MeOH (1.5 L) was added $NaBH_4$ (2.89 g, 76.5 mmol) portionwise. After stirring for 15 min, AcOH (20 mL) was added and the reaction mixture evaporated. The residue was dissolved in H_2O (600 mL) and Et_2O (600 mL), and the organic layer separated. The aq layer was extracted with Et_2O (3 × 350 mL), and the combined organic layer washed with brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude bromohydrin **15** (99.9 g) as a yellow oil. This material was used in the next step without further purification. A small quantity was purified by column chromatography (silica gel, EtOAc–hexane, 1:10→1:5) to give an analytically pure sample.

$[\alpha]_D^{24}$ –43.2 (*c* 1.38, $CHCl_3$).

IR (NaCl, film): 3528, 3071, 2957, 2857, 1473, 1428, 1391, 1238, 1078, 988, 823 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 2.33 (br d, *J* = 8 Hz, 2 H, CH_2C=CH), 2.49 (d, *J* = 12.5 Hz, 1 H, O*H*), 2.75 (dq, *J* = 17, 2.5 Hz, 1 H, C=CHCH_AH$_B$), 2.95 (td, *J* = 8, 1.5 Hz, 1 H, C*H*), 3.02 (dd, *J* = 17, 6 Hz, 1 H, C=CHCH$_A$$H_B$), 3.11 (dd, *J* = 12.5, 2 Hz, 1 H, C*H*OH), 3.73 (dd, *J* = 7.5, 5 Hz, 1 H, OCH_ACH$_B$CHO), 4.07 (s, 2 H, CH_2OTBDPS), 4.25 (dd, *J* = 5, 1.5 Hz, 1 H, OCH$_2$C*H*O), 4.68 (d, *J* = 7.5 Hz, 1 H, OCH$_A$$H_B$CHO), 5.34 (d, *J* = 2 Hz, 1 H, OC*H*O), 5.53 (m, 1 H, C=C*H*), 7.34–7.47 (m, 6 H, Ph), 7.63–7.74 (m, 4 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 26.7, 29.3, 40.2, 44.4, 66.6, 67.2, 70.5, 73.8, 78.3, 101.7, 117.8, 127.7, 129.8, 133.5, 135.6, 136.4.

Anal. Calcd for $C_{27}H_{33}BrO_4Si$: C, 61.24; H, 6.28. Found: C, 61.24; H, 6.02.

Diastereomers (16)

To a soln of crude bromohydrin **15** (99.9 g) in Ac_2O (1 L), at 0 °C, was added TFA (50 mL) over 10 min. The mixture was allowed to warm to r.t. and stirring was continued for 1.5 h. Et_3N (69.0 mL, 491 mmol) was added at 0 °C and the resulting mixture stirred for 30 min, and then concentrated in vacuo. The residue was dissolved in H_2O (500 mL) and EtOAc (500 mL) and partitioned. The aq layer was extracted with Et_2O (3 × 300 mL) and the combined organic layer washed with H_2O (2 × 300 mL) and brine (3 × 200 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography [silica gel (750 g), EtOAc–hexane, 1:10→1:5→1:2) to afford triacetate **16** (110 g, 86% over 2 steps) as a diastereomeric mixture (**16a**:**16b** = 10:1 by ^1H NMR). A small quantity of the mixture was separated by flash column chromatography (silica gel, EtOAc–hexane, 1:5) to give diastereomers **16a** and **16b** as yellow amorphous solids.

(1*S*,3*R*,4*R*,4a*S*,8a*R*)-1-[(Acetyloxy)methyl]-4a-bromo-7-[(*tert*-butyldiphenylsilyloxy)methyl]-3,4,4a,5,8,8a-hexahydro-1*H*-2-benzopyran-3,4-diol 3,4-Diacetate (16a)

$[\alpha]_D^{31}$ +38.7 (*c* 1.02, $CHCl_3$).

IR (NaCl, film): 3072, 2932, 2858, 1748, 1473, 1428, 1370, 1232, 1154, 1112, 1047, 1015, 965, 824 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, *t*-Bu), 1.99 (br d, *J* = 20 Hz, 1 H, CH_AH$_B$C=CH), 2.06 (s, 3 H, OAc), 2.15 (s, 3 H,

OAc), 2.20 (s, 3 H, OAc), 2.56 (br d, J = 20 Hz, 1 H, CH_AH_B-C=CH), 2.68 (dd, J = 11, 6 Hz, 1 H, C*H*), 2.75 (br d, J = 20 Hz, 1 H, C=CHCH_AH_B), 3.60 (br d, J = 20 Hz, 1 H, C=CHCH_AH_B), 3.90 (ddd, J = 11, 4, 3 Hz, 1 H, OCH_2CHO), 4.05 (d, J = 15 Hz, 1 H, CH_AH_BOTBDPS), 4.10 (d, J = 15 Hz, 1 H, CH_AH_BOTBDPS), 4.15 (dd, J = 12, 3 Hz, 1 H, OCH_AH_BCHO), 4.20 (dd, J = 12, 4 Hz, 1 H, OCH_AH_BCHO), 5.08 [d, J = 1 Hz, 1 H, C(Br)C*H*OAc], 5.63 (br s, 1 H, C=C*H*), 6.04 (d, J = 1 Hz, 1 H, OC*H*OAc), 7.34–7.47 (m, 6 H, Ph), 7.64–7.70 (m, 4 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 20.7, 20.8, 21.1, 24.4, 26.8, 34.1, 38.5, 64.3, 65.4, 66.8, 69.8, 71.6, 91.9, 116.4, 127.6, 129.67, 129.70, 133.2, 133.4, 135.46, 135.52, 168.0, 169.3, 170.5.

Anal. Calcd for $C_{33}H_{41}BrO_8Si$: C, 58.84; H, 6.13. Found: C, 58.99; H, 6.04.

(1*S*,3*S*,4*R*,4a*S*,8a*R*)-1-[(Acetyloxy)methyl]-4a-bromo-7-[(*tert*-butyldiphenylsilyloxy)methyl]-3,4,4a,5,8,8a-hexahydro-1*H*-2-benzopyran-3,4-diol 3,4-Diacetate (16b)

$[\alpha]_D^{31}$ +20.5 (*c* 0.58, $CHCl_3$).

IR (NaCl, film): 2932, 2858, 1751, 1473, 1428, 1369, 1232, 1158, 1112, 1071, 823 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 2.01 (br d, J = 18 Hz, 1 H, CH_AH_BC=CH), 2.06 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.24 (s, 3 H, OAc), 2.54 (br d, J = 18 Hz, 1 H, CH_A-H_BC=CH), 2.59 (dd, J = 11, 6 Hz, 1 H, C*H*), 2.89 (br d, J = 19.5 Hz, 1 H, C=CHCH_AH_B), 3.06 (br d, J = 19.5 Hz, 1 H, C=CHCH_AH_B), 3.65 (ddd, J = 11, 4.5, 3 Hz, 1 H, OCH_2CHO), 4.04 (d, J = 14 Hz, 1 H, CH_AH_BOTBDPS), 4.10 (d, J = 14 Hz, 1 H, CH_AH_BOTBDPS), 4.20 (d, J = 4.5 Hz, 1 H, OCH_AH_BCHO), 4.21 (d, J = 3 Hz, 1 H, OCH_AH_BCHO), 5.29 [d, J = 1 Hz, 1 H, C(Br)C*H*OAc], 5.60 (br s, 1 H, C=C*H*), 6.09 (d, J = 1 Hz, 1 H, OC*H*OAc), 7.34–7.47 (m, 6 H, Ph), 7.63–7.70 (m, 4 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 20.8, 23.8, 26.8, 34.4, 38.2, 64.5, 64.8, 66.7, 71.9, 73.2, 89.4, 114.9, 127.7, 129.72, 129.73, 133.4, 133.4, 134.0, 135.47, 135.51, 168.6, 169.9, 170.5.

Anal. Calcd for $C_{33}H_{41}BrO_8Si$: C, 58.84; H, 6.13. Found: C, 58.82; H, 6.04.

(1*S*,8a*S*)-1-[(Acetyloxy)methyl]-7-[(*tert*-butyldiphenylsilyloxy)methyl]-3,5,8,8a-tetrahydro-1*H*-2-benzopyran-3-ol (18)

A flask (5 L), equipped with a mechanical stirrer, was charged with a soln of triacetate **16** (72.0 g, 107 mol) in DMF (400 mL). A mixture of DMF (860 mL) and H_2O (200 mL) was added followed immediately by zinc–copper couple (70 g). The reaction vessel was immersed into an oil-bath at 50 ºC, and following vigorous stirring for 10 min, ice-cold EtOAc (700 mL), sat. aq $NaHCO_3$ soln (100 mL) and ice (500 g) were added sequentially. The mixture was filtered through a pad of Super-Cel, and the solid rinsed with EtOAc. The filtrate was separated and the aq layer was extracted with EtOAc (1 L, then 0.8 L). The combined organic layer was washed with H_2O (2 × 2.5 L, then 2 L) and brine (200 mL), dried over anhyd Na_2SO_4 and evaporated to give crude hemiacetal **18** (55.2 g) which was used in the next step without further purification. A small quantity of this material was purified by column chromatography (silica gel, Et_2O–hexane, 1:2→1:1) to afford an analytically pure sample of **18** as a diastereomeric mixture (ca. 1:10).

$[\alpha]_D^{22}$ +19.8 (*c* 0.84, CH_2Cl_2).

IR (NaCl, film): 3431, 3072, 2931, 2858, 1744, 1590, 1473, 1428, 1365, 1236, 1157, 1113, 824 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major isomer) = 1.06 (s, 9 H, *t*-Bu), 1.72 (m, 1 H, CHCH_AH_BC=CH), 2.10 (s, 3 H, OAc), 2.19 (dd, J = 17, 6.5 Hz, 1 H, CHCH_AH_BC=CH), 2.39 (m, 1 H, C*H*), 2.75–2.99 (m, 2 H, C=CHCH_2C=CH), 3.96 (ddd, J = 10, 5.5, 2.5 Hz, 1 H, OCH_2CHO), 4.05 (br s, 2 H, CH_2OTBDPS), 4.19 (dd, J = 12, 5.5 Hz, 1 H, OCH_AH_BCHO), 4.30 (dd, J = 12.5, 2.5 Hz, 1 H, OCH_AH_BCHO), 5.45 (br s, 1 H, OC*H*OH), 5.66 (br s, 2 H, C=C*H*CH_2C=CH, C=CHCH_2C=C*H*), 7.34–7.47 (m, 6 H, Ph), 7.63–7.70 (m, 4 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major isomer) = 19.2, 20.8, 26.8, 28.2, 31.0, 33.2, 64.4, 67.1, 70.7, 89.3, 119.1, 119.4, 127.7, 129.7, 133.6, 134.2, 135.6, 139.2, 171.1.

Anal. Calcd for $C_{29}H_{36}O_5Si$: C, 70.70; H, 7.37. Found: C, 70.70; H, 7.48.

(*Z*)-2-{(6*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-6-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-cyclohexen-1-ylidene}ethanol (19)

$LiAlH_4$ (8.13 g, 214 mmol) was placed in a three-necked flask (2 L), equipped with a mechanical stirrer and an inlet adapter. Anhyd Et_2O (560 mL) was added under an Ar atm, the resulting suspension cooled to 0 °C and a soln of crude hemiacetal **18** (55.2 g) in Et_2O (100 mL) was added via cannula over 5 min. After stirring for 20 min at 0 ºC, H_2O was carefully added dropwise until evolution of H_2 gas ceased. H_2O (300 mL) and sat. aq tartaric acid soln (300 mL) were added and the mixture stirred for 5 min. Sat. aq potassium sodium tartrate soln (200 mL) was added, and vigorous stirring was continued for a further 20 min. The resulting suspension was filtered, the solid added to EtOAc (300 mL), and the suspension stirred vigorously and filtered again. The filtrate was partitioned and the aq layer extracted with EtOAc (2 × 400 mL). The combined organic layer was washed with brine (300 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude intermediate triol (47.4 g) as a pale-yellow oil. The crude triol (47.2 g) was dissolved in acetone (711 mL), and $Me_2C(OMe)_2$ (13.1 mL, 107 mmol) and *dl*-CSA (330 mg, 1.42 mmol) were added. The resulting soln was stirred at r.t. for 40 min, and then sat. aq $NaHCO_3$ soln (30 mL) and H_2O (500 mL) were added. The reaction mixture was extracted with EtOAc (500 mL, then 300 mL) and the combined organic layer washed with brine (200 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel (500 g), EtOAc–hexane, 1:10→1:6→1:3] to afford allylic alcohol **19** (39.6 g, 75% over 3 steps) as a pale-yellow oil.

$[\alpha]_D^{24}$ +4.52 (*c* 1.15, CH_2Cl_2).

IR (NaCl, film): 3440, 2932, 2858, 1473, 1428, 1371, 1212, 1156, 1112, 1067, 824 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 1.34 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.81 (d, J = 18 Hz, 1 H, CHCH_AH_B-C=CH), 2.23 (br d, J = 18 Hz, 1 H, CHCH_AH_BC=CH), 2.32 (d, J = 8 Hz, 1 H, O*H*), 2.73 (br d, J = 20 Hz, 1 H, C=CHCH_AH_BC=CH), 2.98 (dd, J = 10, 6 Hz, 1 H, C*H*), 3.04 (br d, J = 20 Hz, 1 H, C=CHCH_AH_BC=CH), 3.61 (t, J = 8 Hz, 1 H, OCH_AH_BCHO), 3.91 (dt, J = 11.5, 8 Hz, 1 H, CH_AH_BOH), 4.00 (m, 2 H, CH_2OTBDPS), 4.02 (dd, J = 8, 6 Hz, 1 H, OCH_AH_BCHO), 4.11 (ddd, J = 10, 8, 6 Hz, 1 H, OCH_2CHO), 4.27 (dd, J = 11.5, 8 Hz, 1 H, CH_AH_BOH), 5.64 (br s, 1 H, C=C*H*CH_2C=CH), 5.86 (td, J = 8, 2 Hz, 1 H, C=C*H*CH_2OH), 7.34–7.48 (m, 6 H, Ph), 7.62–7.69 (m, 4 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 25.4, 26.4, 26.8, 28.1, 31.2, 38.8, 56.9, 67.2, 69.0, 75.0, 109.3, 120.6, 124.7, 127.7, 129.8, 133.6, 133.8, 135.6, 140.1.

Anal. Calcd for $C_{30}H_{40}O_4Si$: C, 73.13; H, 8.18. Found: C, 73.11; H, 8.26.

***N*-{(1*R*,6*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-6-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-ethenyl-3-cyclohexen-1-yl}trichloroacetamide (20)**

To a soln of allylic alcohol **19** (44.9 g, 91.1 mmol) in anhyd CH_2Cl_2 (673 mL) at –40 °C were added DBU (16.0 mL, 114 mmol) and trichloroacetonitrile (Cl_3CCN) (11.4 mL, 114 mmol). After stirring at –40 °C for 90 min, the cold-bath was removed, and sat. aq NH_4Cl

soln (300 mL) was added. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was suspended in Et_2O and passed through a short column [neutral silica gel (150 g), eluting with Et_2O]. The filtrate was concentrated to give the crude intermediate trichloroacetimidate (57.6 g) as a yellow oil which was used in the next step without further purification. A small quantity of the material was purified by column chromatography (neutral silica gel, EtOAc–hexane, 1:25) to give an analytically pure sample. A suspension of the crude trichloroacetimidate (57.6 g) and K_2CO_3 (5.8 g) in xylene (1.2 L) was heated at reflux for 15 h. The reaction mixture was cooled to r.t. and then filtered through a pad of Super-Cel. The filtrate was diluted with toluene (500 mL) and concentrated in vacuo. The residue was purified by column chromatography [silica gel (500 g), EtOAc–hexane, 1:50→1:25→1:15] to afford trichloroacetamide **20** (48.5 g, 84% over 2 steps) as a colorless oil.

Data for the Intermediate Trichloroacetimidate

$[\alpha]_D^{30}$ +47.6 (*c* 0.67, CH_2Cl_2).

IR (NaCl, film): 3343, 3072, 2932, 2858, 1661, 1473, 1428, 1370, 1289, 1212, 1156, 1112, 1071, 973, 824 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 1.33 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.85 (d, *J* = 17.5 Hz, 1 H, CHCH_AH$_B$-C=CH), 2.25 (br d, *J* = 17 Hz, 1 H, CHC$H_A$$H_B$C=CH), 2.73 (br d, *J* = 20 Hz, 1 H, C=CHCH_AH$_B$C=CH$_2$), 2.99 (dd, *J* = 9.5, 6 Hz, 1 H, C*H*), 3.08 (br d, *J* = 20 Hz, 1 H, C=CHC$H_A$$H_B$C=CH$_2$), 3.66 (dd, *J* = 8, 6.5 Hz, 1 H, OCH_AH$_B$CHO), 4.02 (dd, *J* = 8, 6.5 Hz, 1 H, OCH$_A$$H_B$CHO), 4.01 (m, 2 H, C$H_2$OTBDPS), 4.16 (dt, *J* = 9.5, 6.5 Hz, 1 H, OCH$_2$C*H*O), 4.77 (ddd, *J* = 12.5, 6, 1.5 Hz, 1 H, C=CHCH_AH$_B$O), 5.01 (ddd, *J* = 12.5, 8, 1 Hz, 1 H, C=CHCH$_A$-H_BO), 5.63 (m, 1 H, C=C*H*), 5.72 (ddd, *J* = 8, 6, 2 Hz, 1 H, C=C*H*CH$_2$O), 7.34–7.48 (m, 6 H, Ph), 7.62–7.69 (m, 4 H, Ph), 8.26 (br s, 1 H, N*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 25.4, 26.80, 26.84, 28.8, 32.1, 39.7, 65.3, 67.2, 68.6, 75.6, 91.6, 109.1, 118.5, 120.6, 127.6, 129.7, 133.5, 133.6, 134.1, 135.5, 142.5, 162.7.

Anal. Calcd for $C_{32}H_{40}Cl_3NO_4Si$: C, 60.33; H, 6.33; N, 2.20. Found: C, 60.33; H, 6.27; N, 2.22.

Data for Trichloroacetamide 20

$[\alpha]_D^{25}$ +37.8 (*c* 1.89, $CHCl_3$).

IR (NaCl, film): 3315, 3072, 2932, 2858, 1728, 1526, 1473, 1428, 1373, 1261, 1159, 1113, 1069, 925, 822 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 1.38 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.59 (m, 1 H, CH_AH$_B$C=CH), 1.77 (dd, *J* = 17, 5 Hz, 1 H, CH$_A$$H_B$C=CH), 2.01 (ddd, *J* = 12, 10, 5 Hz, 1 H, C*H*), 2.28 (br d, *J* = 18 Hz, 1 H, C=CHCH_AH$_B$), 3.41 (dd, *J* = 18, 5 Hz, 1 H, C=CHCH$_A$$H_B$), 3.56 (m, 1 H, OCH$_2$C*H*O), 3.96–4.08 (m, 2 H, OCH_2CHO), 4.06 (br s, 2 H, CH_2OTBDPS), 5.28 (dd, *J* = 17, 1 Hz, 1 H, CH_AH$_B$=CH), 5.32 (dd, *J* = 11, 1 Hz, 1 H, CH$_A$$H_B$=CH), 5.62 (br d, *J* = 5 Hz, 1 H, C=C*H*), 5.74 (dd, *J* = 17, 11 Hz, 1 H, CH$_2$=C*H*), 7.33–7.48 (m, 6 H, Ph), 7.62–7.69 (m, 4 H, Ph), 9.23 (br s, 1 H, N*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 25.4, 26.2, 26.5, 26.8, 35.5, 44.0, 60.2, 66.8, 68.8, 76.3, 93.8, 110.1, 116.2, 119.6, 127.7, 129.8, 133.6, 134.0, 135.6, 160.5.

Anal. Calcd for $C_{32}H_{40}Cl_3NO_4Si$: C, 60.33; H, 6.33; N, 2.20. Found: C, 60.12; H, 6.40; N, 2.06.

***N*-{(1*R*,6*S*)-6-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-hydroxymethyl-1-ethenylcyclohex-3-en-1-yl}trichloroacetamide (21)**

To a soln of TBDPS ether **20** (8.16 g, 12.8 mmol) in THF (150 mL) was added TBAF (1 M in THF, 14.7 mL, 14.7 mmol). After stirring at r.t. for 70 min, sat. aq NH_4Cl soln (50 mL) and H_2O (50 mL) were added and the reaction mixture was extracted with EtOAc (150 mL, then 2 × 200 mL). The combined organic layer was washed with brine (200 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel (150 g), EtOAc–hexane, 1:3→1:1→1:0] to afford allylic alcohol **21** (4.82 g, 94%) as a colorless oil.

$[\alpha]_D^{31}$ +57.7 (*c* 1.84, $CHCl_3$).

IR (NaCl, film): 3308, 2986, 2904, 1725, 1640, 1531, 1437, 1412, 1373, 1341, 1259, 1159, 1066, 1004, 924, 846, 822 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.73 (m, 1 H, CH_AH$_B$C=CH), 1.91 (dd, *J* = 18, 5 Hz, 1 H, CH$_A$$H_B$C=CH), 2.07 (ddd, *J* = 12, 9.5, 5 Hz, 1 H, C*H*), 2.31 (d, *J* = 18 Hz, 1 H, C=CHCH_AH$_B$), 3.46 (dd, *J* = 18, 5 Hz, 1 H, C=CHCH$_A$$H_B$), 3.64 (t, *J* = 8 Hz, 1 H, OCH_AH$_B$CHO), 3.94–4.14 (m, 4 H, CH_2OH, OCH$_A$$H_BCHO, OCH_AH_B$C*H*O), 5.29 (dd, *J* = 17.5, 1 Hz, 1 H, CH=CH_AH$_B$), 5.33 (dd, *J* = 10.5, 1 Hz, 1 H, CH=CH$_A$$H_B$), 5.69 (br d, 1 H, C=C*H*), 5.80 (dd, *J* = 17.5, 10.5 Hz, 1 H, C*H*=CH$_A$H$_B$), 9.27 (br s, 1 H, N*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 26.2, 35.5, 44.1, 60.0, 66.3, 68.9, 76.3, 93.7, 110.1, 116.4, 120.8, 133.4, 134.6, 160.6.

Anal. Calcd for $C_{16}H_{22}Cl_3NO_4$: C, 48.20; H, 5.56; N, 3.51. Found: C, 48.11; H, 5.56; N, 3.46.

***N*-{(1*R*,2*S*,4*R*,5*S*)-4,5-Dibromo-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-hydroxymethyl-1-ethenylcyclohexyl}trichloroacetamide (22)**

Allylic alcohol **21** (4.69 g, 11.8 mmol) was dissolved in anhyd CH_2Cl_2 (120 mL), cooled to 10 °C, and K_2CO_3 (3.20 g, 23.5 mmol) and pyridinium tribromide ($PyHBr_3$) (7.52 g, 23.5 mmol) were added. The reaction mixture was stirred at 10 °C for 35 min, and then treated with sat. aq NH_4Cl soln (100 mL) and H_2O (50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layer washed with aq 3% $CuSO_4$ soln (2 × 150 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel (50 g), EtOAc–hexane, 1:10→1:5→1:1] to afford dibromide **22** (6.48 g, 99%) as a white amorphous solid.

$[\alpha]_D^{29}$ +33.4 (*c* 0.77, $CHCl_3$).

IR (NaCl, film): 3494, 3318, 2988, 2935, 1724, 1522, 1456, 1435, 1373, 1247, 1222, 1160, 1067, 960, 928, 846, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.56 (ddd, *J* = 15, 3, 2.5 Hz, 1 H, CHCH_AH$_B$), 1.83 (dd, *J* = 15, 12.5 Hz, 1 H, CHCH$_A$$H_B$), 2.28 (t, *J* = 7 Hz, 1 H, O*H*), 2.55 (ddd, *J* = 12.5, 9.5, 3 Hz, 1 H, C*H*), 2.97 [dd, *J* = 16, 4.5 Hz, 1 H, CH(Br)CH_AH$_B$], 3.60 (m, 1 H, OCH_AH$_B$CHO), 3.62 [dd, *J* = 16, 2.5 Hz, 1 H, CH(Br)CH$_A$$H_B$], 3.93 (dd, *J* = 12.5, 7 Hz, 1 H, CH_AH$_B$OH), 4.03 (dd, *J* = 12.5, 7 Hz, 1 H, CH$_A$$H_B$OH), 4.05–4.12 (m, 2 H, OCH$_A$$H_BCHO, OCH_AH_B$C*H*O), 4.82 (dt, *J* = 4.5, 2.5 Hz, 1 H, C*H*Br), 5.35 (d, *J* = 17 Hz, 1 H, CH=CH_AH$_B$), 5.37 (d, *J* = 11 Hz, 1 H, CH=CH$_A$$H_B$), 6.72 (dd, *J* = 17, 11 Hz, 1 H, C*H*=CH$_A$H$_B$), 8.78 (br s, 1 H, N*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 26.5, 30.0, 39.2, 44.9, 50.5, 61.4, 69.0, 72.1, 75.5, 76.1, 93.6, 110.3, 116.0, 134.0, 160.7.

Anal. Calcd for $C_{16}H_{22}Br_2Cl_3NO_4$: C, 34.41; H, 3.97; N, 2.51. Found: C, 34.49; H, 3.91; N, 2.54.

{(3a*R*,4*S*,7a*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a-ethenyl-2-trichloromethyl-3a,4,5,7a-tetrahydrobenzooxazol-6-yl}methanol (23)

To a soln of dibromide **22** (6.48 g, 11.6 mmol) in DMF (115 mL) was added DBU (5.19 mL, 34.8 mmol). After stirring at r.t. for 30 min, the reaction vessel was cooled in an ice-bath and sat. aq NH_4Cl soln (50 mL) and H_2O (20 mL) were added. The mixture was extracted with EtOAc (3 × 300 mL), and the combined organic layer washed with H_2O (3 × 300 mL) and brine (100 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give crude oxazoline **23**. The crude material was used in the next reaction without further purification.

***N*-{(1*R*,2*S*,6*S*)-6-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-ethenyl-2-hydroxy-4-(hydroxymethyl)-3-cyclohexen-1-yl}trichloroacetamide (7)**

To a soln of crude oxazoline **23** (4.36 g) in py (100 mL) and H_2O (20 mL) was added *p*-TsOH·H_2O (2.53 g, 13.0 mmol). After stirring at 70 ºC for 2 h, ice and sat. aq $NaHCO_3$ soln (20 mL) were added. The mixture was extracted with EtOAc (4 × 100 mL) and the combined organic layer washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in EtOAc and passed through a short column [silica gel (10 g), eluting with EtOAc], and then concentrated. Repeated crystallization of the crude product (from EtOAc–hexane) afforded diol **7** (2.93 g, 64% over 2 steps) as white needles.

Mp 171.0–172.5 °C; $[\alpha]_D^{29}$ +99.4 (*c* 1.08, $CHCl_3$).

IR (KBr): 3305, 2986, 2920, 1722, 1637, 1541, 1411, 1373, 1227, 1161, 1064, 931, 855, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.66 (dd, *J* = 18, 12 Hz, 1 H, CH_AH$_B$C=CH), 1.94 (dd, *J* = 18, 5.5 Hz, 1 H, CH$_A$$H_B$C=CH), 2.11 (br s, 1 H, CH$_2$O*H*), 2.35 (ddd, *J* = 12, 9.5, 5.5 Hz, 1 H, C*H*), 2.76 (br d, *J* = 5 Hz, 1 H, CHO*H*), 3.66 (t, *J* = 8 Hz, 1 H, OCH_AH$_B$CHO), 3.97–4.15 (m, 4 H, CH_2OH, OCH$_A$$H_BCHO, OCH_AH_B$C*H*O), 4.99 (br t, *J* = 5 Hz, 1 H, C*H*OH), 5.36 (dd, *J* = 10.5, 1 Hz, 1 H, CH_AH$_B$=CH), 5.38 (dd, *J* = 17.5, 1 Hz, 1 H, CH$_A$$H_B$=CH), 5.65 (dd, *J* = 17.5, 10.5 Hz, 1 H, CH$_A$H$_B$=C*H*), 5.91 (br d, *J* = 5.5 Hz, 1 H, C=C*H*), 9.26 (br s, 1 H, N*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 26.3, 26.6, 38.3, 65.3, 65.6, 65.7, 68.9, 75.9, 93.5, 110.3, 117.9, 121.4, 132.2, 139.4, 161.3.

Anal. Calcd for $C_{16}H_{22}Cl_3NO_5$: C, 46.34; H, 5.35; N, 3.38. Found: C, 46.33; H, 5.25; N, 3.37.

Acknowledgment

We are grateful to Mr. S. Kitamura (analytical laboratory of this school) for elemental analyses. This work was supported financially by a Grant-in-Aid for Scientific Research (B) and G-COE from MEXT, and the Naito Foundation.

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