Total Synthesis of Two Possible Diastereomers of Natural 6-Chlorotetrahydrofuran Acetogenin and Its Stereostructural Elucidation

Hiroyoshi Takamura,* Tomoya Katsube, Kazuki Okamoto, and Isao Kadota[a]

Abstract: The first total synthesis of two possible diastereomers of natural 6-chlorotetrahydrofuran acetogenin **1** has been achieved. The synthetic route features 5-*exo-tet* cyclization, (*Z*)-selective Wittig reaction and Julia olefination for the construction of conjugated diene and enyne moieties, and stereoselective chlorination. Comparison of their ^{1}H and ^{13}C NMR data and specific rotation with those of the natural product elucidated the absolute configuration of natural (–)-6-chlorotetrahydrofuran acetogenin **1**.

6-Chlorotetrahydrofuran acetogenins **1–4** (Figure 1) were isolated from the organic extract of the red alga *Laurencia glandulifera* by Vagias and co-workers in 2009.[1] The planar structures of **1–4**, which are characterized by the conjugated enyne, 2,5-disubstituted-3-functionalized tetrahydrofuran, and conjugated diene in **1**/alkene in **2–4**, were established by the measurement of HRFABMS, IR, and UV, and the detailed analysis of ^{1}H–^{1}H COSY, HSQC, and HMBC spectra. The geometries of the enyne (C3/C4), diene (C11/C12 and C13/C14 in **1**), and alkene (C11/C12 in **2–4**) portions were determined by the coupling constants in their ^{1}H NMR data. In addition, the relative configurations at the C7, C9, and C10 positions in the tetrahydrofuran rings were elucidated by the NOE observations. However, the stereochemistries at other chiral centers, which are positions of C6 in **1–4** and C13 in **2–4**, have remained to be clarified. As a part of our program toward the stereostructural elucidation of natural 6-chlorotetrahydrofuran acetogenins **1–4** by the chemical synthesis, we herein report the total synthesis of two possible diastereomers of **1** and its stereochemical determination.[2]
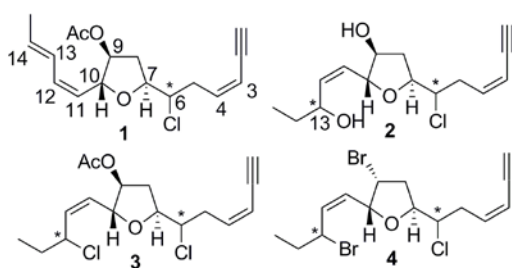

Figure 1. Relative configurations of 6-chlorotetrahydrofuran acetogenins **1–4**. Stereochemistries at the asterisked carbon are unknown.

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We planned to synthesize two possible diastereomers of 6-chlorotetrahydrofuran acetogenin **1**, that is, C6-stereoisomers **1a** and **1b**, by using the synthetic route wherein these compounds could be derived by branching from the common synthetic intermediate at the late-stage of synthesis (Scheme 1). Thus, we envisioned that the target compounds **1a** and **1b** could be obtained by stereoinverted and stereoretentive chlorination of alcohol **5**, respectively. The conjugated enyne and diene motifs of **5** could be possibly introduced by (*Z*)-selective olefinations, respectively. 2,5-*Trans*-disubstituted-3-oxygenated tetrahydrofuran **6** could be synthesized via 5-*exo-tet* cyclization of epoxy alcohol **7**.[3,4]
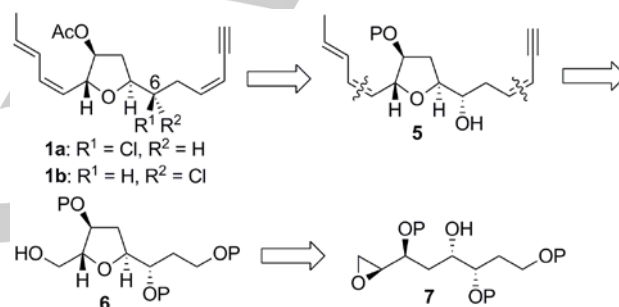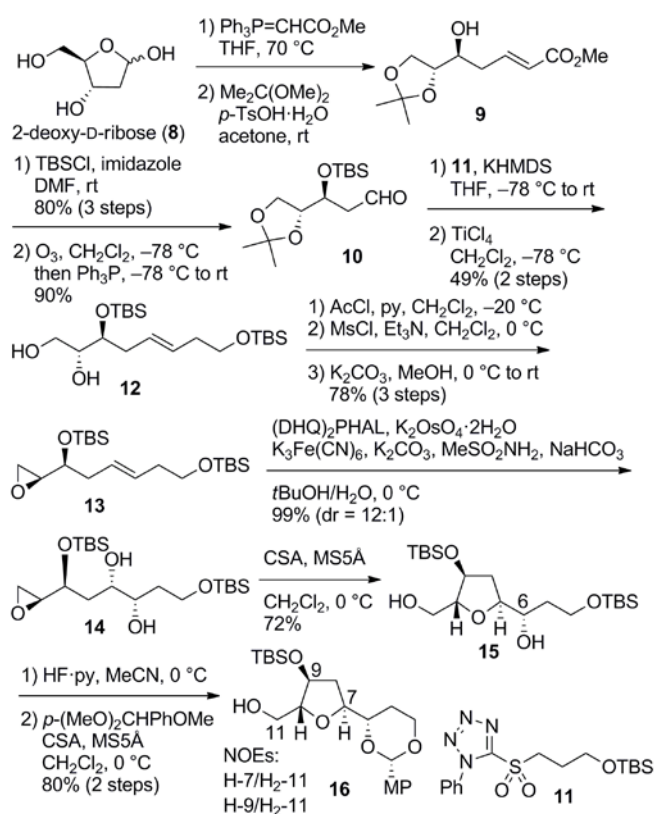

Scheme 1. Retrosynthetic analysis of C6-stereoisomers **1a** and **1b**. Ac = acetyl, P = protective group.

We initially investigated stereoselective construction of the tetrahydrofuran ring. Thus, Wittig reaction of 2-deoxy-D-ribose (**8**) and selective protection of the 1,2-diol moiety as the acetonide gave alcohol **9** (Scheme 2).[5] Protection of **9** as the *tert*-butyldimethylsilyl (TBS) ether followed by ozonolysis provided the known aldehyde **10**.[6] The aldehyde **10** was coupled with 1-phenyl-1*H*-tetrazol-5-yl (PT)-sulfone **11**[7] by Julia–Kocienski olefination[8] to produce the desired (*E*)-alkene, which underwent acetonide deprotection with TiCl$_4$[9] to provide diol **12**. Selective acetylation of the primary hydroxy group of **12** and mesylation of the obtained secondary alcohol gave the corresponding acetate. Removal of the acetyl moiety and subsequent epoxidation were carried out with K$_2$CO$_3$ in MeOH to afford terminal epoxide **13**. The vicinal diol portion of **14** was introduced by Sharpless asymmetric dihydroxylation[10] using (DHQ)$_2$PHAL as the chiral ligand, wherein the diastereoselectivity of 12:1 was obtained. The epoxy diol **14** underwent 5-*exo-tet* cyclization in the presence of camphorsulfonic acid (CSA)/MS5Å to furnish the desired product **15** in 72% yield. Selective removal of the primary TBS part with HF·py and subsequent protection of the resulting 1,3-diol as the *p*-methoxybenzylidene acetal yielded the tetrahydrofuran **16**. The stereochemistry of the tetrahydrofuran ring was verified by the observed NOEs of H-7/H$_2$-11 and H-9/H$_2$-11.[11]

Scheme 2. Synthesis of tetrahydrofuran **16**. THF = tetrahydrofuran, Ts = toluenesulfonyl, TBS = *tert*-butyldimethylsilyl, DMF = dimethylformamide, rt = room temperature, KHMDS = potassium hexamethyldisilazide, py = pyridine, Ms = methanesulfonyl, (DHQ)$_2$PHAL = bis(dihydroquinino)phthalazine, CSA = camphorsulfonic acid, MS = molecular sieves, MP = *p*-methoxyphenyl, NOE = nuclear Overhauser effect.

Having constructed the tetrahydrofuran moiety, we next focused on the stereoselective introduction of the conjugated diene and enyne portions. Thus, as described in Scheme 3, after the alcohol **16** was oxidized to the corresponding aldehyde with 2-azaadamantane *N*-oxyl (AZADO),[12] Wittig reaction between the aldehyde and phosphonium bromide **17**[13] was conducted by using potassium hexamethyldisilazide (KHMDS) as the base at –78 °C, which was the optimized conditions obtained in the model study, to produce (11*Z*,13*E*)-conjugated diene **18** in 56% yield in two steps. The formation of geometric isomers of **18** was not observed in this reaction. The resulting stereochemistries of **18** were established by the coupling constants ($^3J_{11,12}$ = 11.1 Hz and $^3J_{13,14}$ = 12.9 Hz). The acetal moiety of **18** was removed with AcOH and subsequent selective oxidation of the obtained diol **19** with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO)[14] gave the corresponding aldehyde. Treatment of the aldehyde with benzothiazol-2-yl (BT)-sulfone **20**[15] according to the one-pot Julia olefination[8b,8c,16] procedure which was reported by Bonini and co-workers[17] provided the desired (*Z*)-enyne as a single geometric isomer.[18] Deprotetion of the TMS-acetylene afforded conjugated enyne **21** in 50% yield in three steps. The (*Z*)-configuration of **21** was unambiguously determined by the observed coupling constant ($^3J_{3,4}$ = 11.0 Hz). Next, we investigated the installation of the C6-chlorine atom with the

configurational inversion and finally found that the Nakata's two-step transformation, chloromethanesulfonation[19] and halogenation, [18b,20] worked well to furnish chlorinated product **22** as a single diastereomer. The TBS ether **22** was deprotected with *p*-TsOH·H$_2$O to give alcohol **23** in 62% yield in three steps.[21] Finally, the alcohol **23** was acetylated to produce the first target compound **1a**.
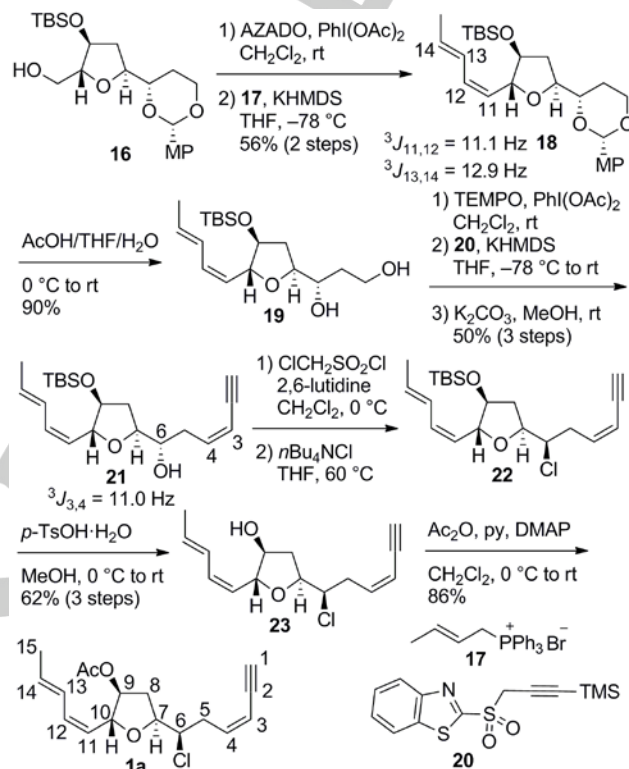
Scheme 3. Completion of the total synthesis of **1a**. AZADO = 2-azaadamantane *N*-oxyl, TEMPO = 2,2,6,6-tetramethylpiperidinyloxy, TMS = trimethylsilyl, DMAP = 4-dimethylaminopyridine.

We next tried the stereoretentive chlorination of the alcohol **21** under the conditions of SOCl$_2$/DMF[22] and POCl$_3$/DMF,[23] which would lead to the synthesis of the second target compound **1b**. However, the expected chlorinated product was not obtained at all. Therefore, we decided to synthesize **1b** by the double stereoinversion. Thus, the stereochemistry at the C6 position of the diol **19** was inverted under the Mitsunobu conditions[24] with *p*-NO$_2$PhCO$_2$H/Ph$_3$P/diethyl azodicarboxylate (DEAD)[25] to provide the bis-*p*-nitrobenzoate, which underwent methanolysis with K$_2$CO$_3$ in MeOH to give diol **24** (Scheme 4).[26] Subsequently, transformation of **24** to **1b** was examined by using a sequence analogous to that used for the synthesis of **1a**. Thus, selective oxidation of the diol **24** with TEMPO,[14] one-pot Julia olefination[8b,8c,16] of the resulting aldehyde with BT-sulfone **20**,[15,17,18] and removal of the TMS moiety afforded conjugated enyne **25**. The resultant (*Z*)-geometry of **25** was verified by the coupling constant ($^3J_{3,4}$ = 10.8 Hz). Chloromethanesulfonation[19] of the alcohol **25** followed by treatment of the obtained sulfonate with *n*Bu$_4$NCl gave chloro enyne **26**.[18b,20] Deprotection of the

TBS ether **26** with HF·py and acetylation of alcohol **27** furnished the second target compound **1b**.
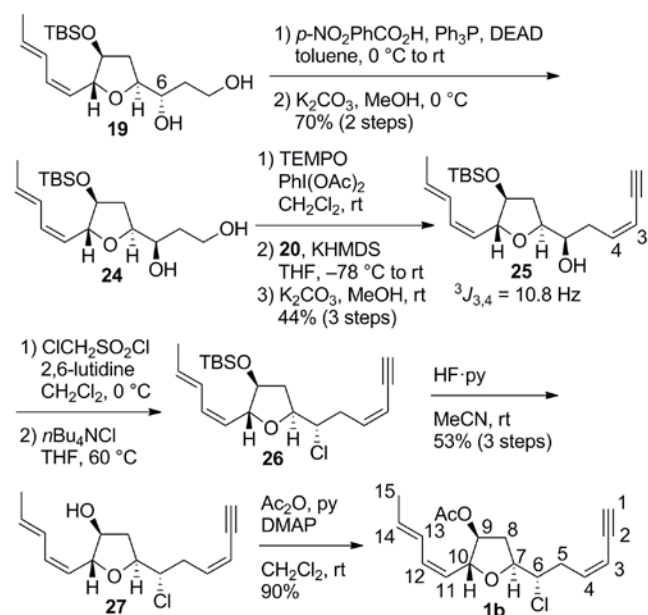
Scheme 4. Completion of the total synthesis of **1b**. DEAD = diethyl azodicarboxylate.

With the target compounds **1a** and **1b** in hand, we next analyzed their 2D NMR spectra and compared their ^{1}H and ^{13}C NMR data with those reported for natural product **1**.[1,27] The ^{1}H and ^{13}C NMR data of the synthetic **1b** were found to be almost identical to those of the natural product. On the other hand, the ^{1}H and ^{13}C NMR data of the synthesized **1a** were different from those of the natural product. It was observed that the chemical shift differences between the natural product and **1a** were especially critical around the C6 position in both the ^{1}H and the ^{13}C NMR data. In addition, there was a significant discrepancy in the coupling constant of $^3J_{6,7}$ between the natural product (5.0 Hz) and **1a** (8.0 Hz).[28] The sign of the specific rotation of **1b**, $[\alpha]_D^{23} = +31.5$ ($c = 0.10$, CHCl$_3$), was opposite to that of the natural product, $[\alpha]_D^{20} = -10.0$ ($c = 0.07$, CHCl$_3$).[1,29] From these results, we concluded that (−)-6-chlorotetrahydrofuran acetogenin **1** isolated from nature is the enantiomer of **1b**.

In conclusion, we have succeeded in the total synthesis of two possible diastereomers of natural product **1**, **1a** and **1b**. The key transformations are 5-*exo-tet* cyclization, (*Z*)-selective Wittig reaction and Julia olefination, and stereoinverted chlorination. Comparison of the NMR data and specific rotations between the natural product and the synthetic products **1a** and **1b** elucidated the absolute configuration of natural (−)-6-chlorotetrahydrofuran acetogenin **1**. The unknown stereochemistries at the C6 positions of natural products **2–4** would be predictable by utilizing the NMR data of the synthetic products **1a** and **1b**. Further synthetic study of other 6-chlorotetrahydrofuran acetogenins toward the structural determination is currently underway.
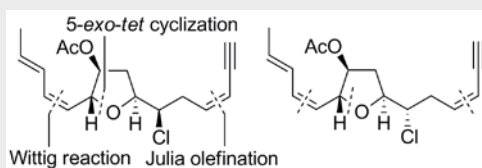
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[26] When the alcohol **21** was subjected to the Mitsunobu reaction, the elimination proceeded as a side reaction and the desired *p*-nitrobenzoate was not obtained.

[27] See the Supporting Information for details.

[28] The coupling constant of $^3J_{6,7}$ in the synthetic **1b** was 5.1 Hz.

[29] The purity of the synthetic product **1b** was unambiguously verified by its NMR data. Since the natural product is not available for us at present, it is difficult to discuss the absolute value difference of specific rotations between the synthetic product **1b** and the natural product.

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