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SYNTHESIS OF (–)-TULIPARIN B UTILIZING 2-BROMO-1-ALKENES CONVENIENTLY SYNTHESIZED FROM THE 3-*O*-SUBSTITUTED 1,2-DIBROMOALKANE SYSTEM BY REGIOSELECTIVE ELIMINATION

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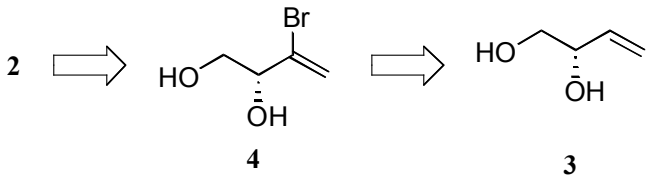
Abstract - Synthesis of (–)-tulipalin B with a variety of biological properties including cutaneous allergenic activity, was accomplished by using the 2-bromo-1-alkenes synthesized by the regioselective HBr elimination reaction of 3-acyloxy-1,2-dibromoalkanes.

INTRODUCTION

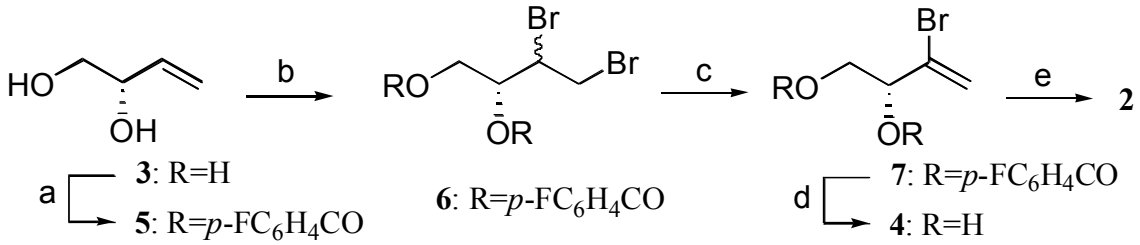
Tuliparins A (**1**) and B (**2**) (Figure 1), the simplest substance in naturally occurring α-alkylidene-γ-lactones, were isolated from bulbs of the common tulip, *Tulipa gesneriana* L.,[1] and leaves, stems, and flowers of *T. sylvestris* and *T. turkestanica*.[2] These two lactones appear to function as a defensive agent against infection of the tulip plant by common pathogenic soil fungi, such as *Fusarium oxysporum*[3] and *Botrytis* sp.[4] In addition, **1** has been recognized to possess the inductive activity of allergic contact dermatitis (ACD).[5] Although the β-hydroxy-γ-lactone (**2**) had been claimed to have no activity of the ACD induction, correction was made by Benezra and co-worker that **2** was a contact sensitizer as a result of open epicutaneous testing on sensitized Guinea pigs.[6] As part of the investigation of the molecular mechanism of ACD, synthesis of **2** was achieved by using some methodologies.[7] The first total synthesis of (–)-**2** was achieved using diazomethylketone synthesis and the Wittig reaction from isopropylidene-D-glyceraldehyde.[7a] Benezra and co-worker,[7b] and Momose and co-workers[7c] synthesized (–)-**2** from (*S*)-(–)-dimethyl malate as a chiral pool. Especially, the latter synthesis recorded the highest total yield of (–)-**2** (19% yield from (*S*)-(–)-methyl 3,4-dihydroxybutanoate[8]), to our knowledge. Leahy and co-workers accomplished the synthesis of (–)-**2** (total yield was 11 %) in the shortest steps involving the asymmetric Baylis-Hillman reaction from commercially available *cis*-2-butene-

Tuliparin A (**1**) Tuliparin B (**2**)

Figure 1. Structures of tuliparins.



Scheme 1



Scheme 2. *Reagent and conditions*: a. *p*-FC_6H_4COCl, Py., $CHCl_3$, rt (99%). b. Py•HBr_3, Py., $CHCl_3$, rt (96%) . c. DBU, DMF, 60 °C (100%). d. NH_4OH, MeOH, rt (96%). e. $Ni(Ph_3P)_2(CO)_2$, THF, reflux (21%).

1,4-diol diacetate.[7d,7e] In addition, several syntheses of α-alkylidene-γ-lactones from natural sources have been also investigated.[9]

Recently, we reported that the high-yield conversion of 3-acyloxy-1,2-dibromoalkanes into 2-bromo-1-alkenes under mild basic conditions proceeded through the highly regioselective HBr-elimination.[10] 2-Bromo-1-alkenes[10,11] have been utilized as substrates of transition metal-mediated coupling reactions[12,13] and radical reaction,[14] and as precursors of vinyllithiums[15] and vinyl Grignard reagents,[13] and α-halo ketones.[16] With such versatile availability, an effective synthetic protocol of 2-bromo-1-alkenes promises effective assembly of biologically active natural products.[10] We describe herein the synthesis of optically active **2** employing our regioselective elimination reaction from commercially available (*S*)-1-butene-3,4-diol (**3**) in 5 steps.

RESULTS AND DISCUSSION

In our retrosynthetic analysis (Scheme 1), **2** would be constructed from the bromoalkene (**4**) by using the carbonyl insertion reaction. The bromoalkene moiety of **4** can be produced by bromination of alkene (**3**), followed by the regioselective HBr elimination reaction.[10] With such prospects in mind, synthesis of **2** was commenced with acylation of **3** (Scheme 2). As regioselectivity and yield of our HBr elimination reaction were regulated by the electron-withdrawing effect of *O*-functional groups at the C-3 position of the 1,2-dibromoalkane chain,[10] we selected a *p*-fluorobenzoyl group, possessing a strong electron-withdrawing effect, as an acyl moiety. Diacylation of the diol (**3**) gave diacylate (**5**) in 99% yield, followed by bromination with Py•HBr_3 to yield the dibromide (**6**) in 96% yield, as *ca*. 3 : 2 mixture of the corresponding diastereomers. Highly regioselective elimination of the vicinal dibromide possessing the acyloxy group at the adjacent position, with DBU[10] provided the 2-bromo-1-alkene derivative (**7**) in quantitative yield (**7**: its isomers = >99 : 1). The 1,3-acyl migration by the attack of the acyloxy group to

the vicinal dibromide was not observed during this elimination reaction. Mild hydrolysis under NH_4OH conditions, which scarcely affected the bromoalkene moiety, afforded **4** in 96% yield. The following carbonylation of the bromoalkene system to give the α-methylenelactone was a crucial step. Attempts for the expected lactonization with the Pd-mediated carbonyl insertion, were unsuccessful. Accordingly, we investigated construction of a five-membered lactone system with bis(triphenylphosphine)nickel dicarbonyl,[12c,12d] a safe and convenient reagent as compared with nickel carbonyl. After several examinations,[17] the desired lactone (**2**) was obtained in 21 % yield[18] under the Semmelhack protocol[12d] employing bis(triphenylphosphine)nickel dicarbonyl in THF at reflux temperature for 2 min. The total yield of this synthesis was 19% yield in 5 steps, although the final step has not been optimized. Moreover, our method was the second shortest-step synthesis to Leahy's method.[7d] The synthetic **2** was identical to the natural product under the full range of spectroscopic data.

In conclusion, the synthesis of (–)-tulipalin B (**2**), possessing a variety of biological properties including the induction of ACD, was accomplished by utilizing the 2-bromo-1-alkene synthesis by regioselective HBr elimination reaction. This method was the second shortest-step to Leahy's method. Moreover, our method showed the highest total yield of (–)-**2** from **3** among all of the synthetic approaches reported.

EXPERIMENTAL

General. All reactions were carried out under an argon atmosphere unless otherwise noted. Optical rotations were measured on a JASCO DIR-360 digital polarimeter with sodium (D line) lamp. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on JNM-GX400 spectrometers in deuteriochloroform solvent using tetramethylsilane as an internal standard, otherwise stated. HRMS spectra were obtained on JEOL GCMATE BU20 spectrometers. Preparative and analytical TLC were carried out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical Silica 60N (spherical, neutral, 63-210 μm) was used for column chromatography.

*3,4-Bis(4-fluorobenzoyloxy)-1-butene (**5**).*

To a solution of (*S*)-1-butene-3,4-diol (**3**) (200 mg, 2.3 mmol) in $CHCl_3$ (2 mL) were successively added pyridine (538 mg, 6.8 mmol) and 4-fluorobenzoyl chloride (858 mg, 5.4 mmol) at 0 °C; the mixture was stirred at ambient temperature for 2 days. The mixture was diluted with $CHCl_3$, and washed with 1 M aq. HCl, H_2O, and brine. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) to yield **5** (750 mg, 99%) as a colorless oil: $[\alpha]_D^{22}$ –14.6° (*c* 1.0, $CHCl_3$); IR (film) 1730, 1604, 1505 cm^{-1}; ^{1}HNMR δ 4.52 (1H, dd, *J* = 7.2, 12.4 Hz), 4.58 (1H, dd, *J* = 4.0, 12.4 Hz), 5.39 (1H, dd, *J* = 1.2, 10.8 Hz), 5.51 (1H, dd, *J* = 1.2, 17.2

Hz), 5.89 (1H, m), 5.98 (1H, ddd, *J* = 5.6, 10.8, 17.2 Hz), 7.08 (2H, td, *J* = 2.0, 9.2 Hz), 7.12 (2H, td, *J* = 2.0, 9.2 Hz) , 8.02 (2H, ddd, *J* = 2.0, 6.4, 9.2 Hz), 8.08 (2H, ddd, *J* = 2.0, 6.4, 9.2 Hz); ^{13}CNMR δ 65.3, 72.8, 115.4, 115.5, 115.6, 115.7, 119.2, 125.8, 126.0, 132.0, 132.09, 132.13, 132.21, 132.22, 164.47, 164.49, 165.1, 167.0; HRMS calcd for $C_{18}H_{14}O_4F_2$ (M^+) 332.0860, found *m/z* 332.0867.

*1,2-Dibromo-3,4-bis(4-fluorobenzoyloxy)butane (**6**).*

To a solution of **5** (711 mg, 2.1 mmol) in $CHCl_3$ (10 mL) were successively added pyridine (440 mg, 5.6 mmol) and Py•HBr_3 (760 mg, 2.4 mmol) at 0 °C; the mixture was stirred at ambient temperature for 2 days. The mixture was diluted with $CHCl_3$, and washed with 1 M aq. HCl, H_2O, sat. aq. $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) to yield **6** (1.01 g, 96%, about 3 : 2 diastereomixture) as a colorless oil: $[\alpha]_D^{20}$ +28.0° (*c* 1.0, $CHCl_3$); IR (film) 1730, 1603, 1506 cm^{-1}; ^{1}HNMR δ 3.74 (0.6H, t, *J* = 10.5 Hz), 3.82-3.90 (1.4H, m), 4.51-4.74 (2.6H, m), 4.83 (0.4H, dd, *J* = 3.6, 12.5 Hz), 5.85 (0.4 H, m), 5.97 (0.6H, m), 7.08-7.18 (4H, m), 7.99-8.14 (4H, m); ^{13}CNMR δ 31.2, 32.3, 49.6, 50.0, 63.6, 65.1, 69.0, 71.8, 115.5, 115.6, 115.67, 115.70, 115.74, 115.8, 115.88, 115.92, 125.0, 125.2, 125.4, 125.5, 132.18, 132.21, 132.27, 132.30, 132.4, 132.47, 132.49, 132.6, 163.96, 163.97, 164.6, 164.83, 164.84, 168.4, 167.1, 167.3; HRMS calcd for $C_{18}H_{14}O_4{}^{79}BrF_2$ (M^+–Br) 411.0043, found *m/z* 411.0041.

*2-Bromo-3,4-bis(4-fluorobenzoyloxy)-1-butene (**7**).*

To a solution of **6** (900 mg, 1.8 mmol) in DMF (9 mL) was added DBU (295 mg, 1.9 mmol) at 0 °C; the mixture was stirred at 60 °C for 1 h. The mixture was diluted with Et_2O and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : EtOAc = 7 : 1) to yield **7** (750 mg, quantitative yield) as a colorless oil: $[\alpha]_D^{20}$ –18.8° (*c* 1.0, $CHCl_3$); IR (film) 1730, 1628, 1604, 1508 cm^{-1}; ^{1}HNMR δ 4.69 (2H, d, *J* = 5.2 Hz), 5.81 (1H, d, *J* = 2.4 Hz), 5.90 (1H, t, *J* = 5.2 Hz), 6.13 (1H, d, *J* = 2.4 Hz), 7.07-7.26 (4H, m), 8.02 (2H, dd, *J* = 5.2, 8.8 Hz), 8.09 (2H, dd, *J* = 5.2, 8.8 Hz); ^{13}CNMR δ 64.0, 74.5, 115.5, 115.6, 115.7, 115.8, 121.1, 125.3, 125.6, 126.7, 132.1, 132.2, 132.3, 132.4, 163.9, 164.6, 164.8, 167.1; HRMS calcd for $C_{18}H_{13}O_4F_2$ (M^+–Br) 331.0782, found *m/z* 331.0763.

*2-Bromo-1-buten-3,4-diol (**4**).*

To a solution of **7** (593 mg, 1.4 mmol) in MeOH (3 mL) was added 28% NH_4OH aq. (1 mL) at 0 °C; the mixture was stirred at ambient temperature for 2 days. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) to yield **4** (231 mg, 96 %) as a colorless oil: $[\alpha]_D^{20}$ +2.4° (*c* 1.0, $CHCl_3$); IR (film) 3365, 1628 cm^{-1}; ^{1}HNMR δ 2.09 (1H, br),

2.79 (1H, br), 3.75 (1H, dd, J = 6.4, 11.6 Hz), 3.82 (1H, dd, J = 4.0, 11.6 Hz), 4.31 (1H, m), 5.70 (1H, s), 6.05 (1H, s); ^{13}CNMR δ 64.6, 75.9, 118.3, 132.0. Calcd for $C_4H_7O_2Br$: C, 28.77; H, 4.22. Found: C, 28.78; H, 4.26.

*(–)-Tulipalin B (**2**).*

To a solution of bis(triphenylphosphine)nickel dicarbonyl (300 mg, 0.47 mmol) and Et_3N (58 mg, 0.57 mmol) in THF (2 mL) was added **4** (50 mg, 0.30 mmol) at reflux temperature; the mixture was stirred at the same temperature for 2 min. The mixture was cooled to ambient temperature, diluted with hexane (2 mL), and charged on a silica gel column (hexane : EtOAc = 7 : 1 – 1 : 3). All fractions including the targeted compound were concentrated *in vacuo*. The residue was purified by preparative TLC (hexane : acetone = 3 : 1) to yield **2** (7.2 mg, 21 %) as a colorless oil: $[\alpha]_D^{20}$ –80.0° (*c* 1.0, $CHCl_3$) [lit.,[1] $[\alpha]_D^{20}$ –82° (*c* 1.0, $CHCl_3$)]; IR (film) 3398, 1759, 1668 cm^{-1}; ^{1}HNMR δ 2.27 (1H, d, J = 6.0 Hz), 4.20 (1H, dd, J = 3.6, 10.0 Hz), 4.53 (1H, dd, J = 6.4, 10.0 Hz), 4.98 (1H, m), 6.04 (1H, d, J = 2.4 Hz), 6.48 (1H, d, J = 2.4 Hz); ^{13}CNMR δ 67.6, 73.5, 126.7, 137.6, 169.2; ; HRMS calcd for $C_5H_5O_3$ (M^+–H) 113.0239, found *m/z* 113.0248. Calcd for $C_4H_7O_2Br$: C, 52.63; H, 5.30. Found: C, 52.23; H, 5.39.

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17. No effect was observed upon changing the reaction time and employing the bases such as Cs_2CO_3, K_2CO_3, DABCO, DBU, pyridine, or $PhNMe_2$. When the insertion reaction was performed in such solvents as toluene, dioxane, CH_3NO_2, or DMF, **2** was provided in extremely low yield (0-3%). The reaction did not proceed at low temperature.
18. A byproduct, showing the same moving as that of **3**, was observed by analytical TLC. However, that disappeared during a work-up procedure, probably owing to chelation with degradation products of the Ni reagent.