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SYNTHESIS OF TULIPALIN B AND 1-*O*-METHYL-6-TULIPOSIDE B

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Abstract – Toward the total synthesis of 6-tuliposide B, facile synthesis of tulipalin B and 1-*O*-methyl-6-tuliposide B (Methyl 6-*O*-((*S*)-3',4'-dihydroxy-2'-methylenebutanoyl)-*β*-D-glucopyranoside) has been achieved.

INTRODUCTION

Tulip cultivars produce antimicrobial substances as secondary metabolites in the flowers, stem, leaves and bulb. These metabolites were identified as 6-tuliposide A (6-*O*-(4'-hydroxy-2'-methylenbutanoyl)-D-glucopyranose), 6-tuliposide B (**1**), tulipalin A (α-methylene-γ-butyrolactone) and tulipalin B (**2**).[1] Tulipalins and tuliposides except **1**, are known as causative agents of contact dermatitis, generally called "tulip finger".[2] Recently, we revealed the potent antimicrobial activity of **1** against Gram-positive, Gram-negative bacteria and certain fungicide-tolerant strains except a yeast and anther-specific distribution of this particular natural product. These observations suggested that a novel defense strategy evolved in tulips to protect pollens from bacterial pollution in the reproductive process by anther-specific production of **1**.[3] To verify these observations and survey the potential of **1** as an antimicrobial agent against multidrug-resistant microorganisms, we have been studying the total synthesis of

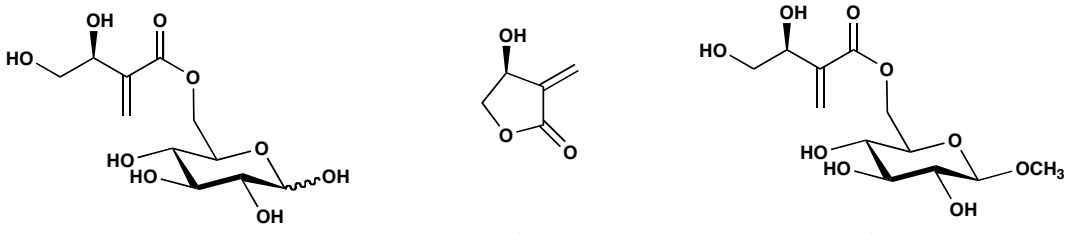


Figure 1

This paper is dedicated to Professor Satoshi Õmura in celebration of his 70th birthday.

6-tuliposide B (**1**). Only one synthetic study of the benzyltetraacetyl derivative of 1-tuliposide B, but not total synthesis of **1**, has been reported,[4] probably because 6-tuliposide B (**1**) as well as its derivatives are extremely labile and its chemical behavior has not been well elucidated. In this paper, we describe the synthesis of tulipalin B (**2**) and 1-*O*-methyl tuliposide B (**3**) shown in Figure 1.

RESULTS AND DISCUSSION

The synthesis of (-)-tulipalin B (**2**) and 1-*O*-methyl-6-tuliposide B (**3**) was achieved using the Baylis-Hillman (BH) reaction as a key step. The BH reaction is known as a convergent reaction to give 3-hydroxy-2-methylene-propionate in moderate yield.[5] In a search for the optimum conditions of the BH reaction using 2-[(*tert*-butyldimethylsilyl)oxy]-acetaldehyde (**4**),[6] we first conducted a study on the synthesis of (±)-tulipalin B. The BH reaction of **4** with methyl acrylate (**5**) afforded **6a** and TBDMS migrated product (**6b**) as shown in Table 1.

Table 1. Baylis-Hillman reaction of methyl acrylate (**5**) with 2-[(*tert*-butyldimethylsily)oxy]-acetaldehyde (**4**).

4 **5** **6a** **6b**

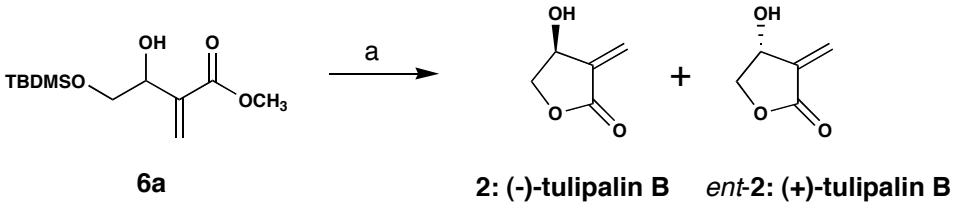
Entry	Conditions[a]	Yield (%)	
		6a	**6b**
1	DABCO (1 equiv.), dioxane : H_2O = 1 : 1,[7] rt, 1 h	0	0
2	Tributylphosphine (0.2 equiv.), THF, rt,[8] 1 week	0	0
3	DABCO (1 equiv.), THF, rt, 50 d	28	-[b]
4	DABCO (1 equiv.), DMSO,[9] 5 d	30	-[b]
5	3-Hydroxyquinuclidine (3-HQD) (1 equiv.), THF, rt,[10] 40 d	29	-[b]
6	3-HDQ (1 equiv.), acetone, rt, 20 d	18	2
7	3-HQD (1 equiv.), DMF, rt, 43 h	32	10
8	3-HQD (1 equiv.), DMSO, rt, 33 h	30	14

a: Three equivalents of **5** were used. *b*: Not isolated.

As in the case of Entry 1, the conditions using another solvent containing water (THF : H_2O = 1 : 1) did not afford any desired compound, probably because of instability of aldehyde (**4**) against water. Therefore, acceleration of the BH reaction by water cannot be used in this study. An aprotic solvent such as DMSO and DMF accelerated the reaction (Entry 3 *vs*. Entry 4; Entry 5 *vs*. Entry 7 or Entry 8).

Mildly acidic treatment of **6a** afforded (±)-tulipalin B (**2**, *ent*-**2**) as shown in Scheme 1.[11] Since the two enantiomers (**6a*S*** and **6a*R***) were completely separable by using analytical chiral-HPLC (DAICEL Chiralcel® OD-H, eluent:

2-propanol : hexane = 1 : 99, retention time: 43.31 min and 46.03 min), formal total synthesis of natural (-)-tulipalin B (**2**) and its enantiomer (*ent*-**2**) was achieved. Although several total syntheses of (±)-tulipalin B and (-)-tulipalin B have been described,[4,12] the present synthesis is an easy and efficient method of preparing both enantiomers to test their biological properties.

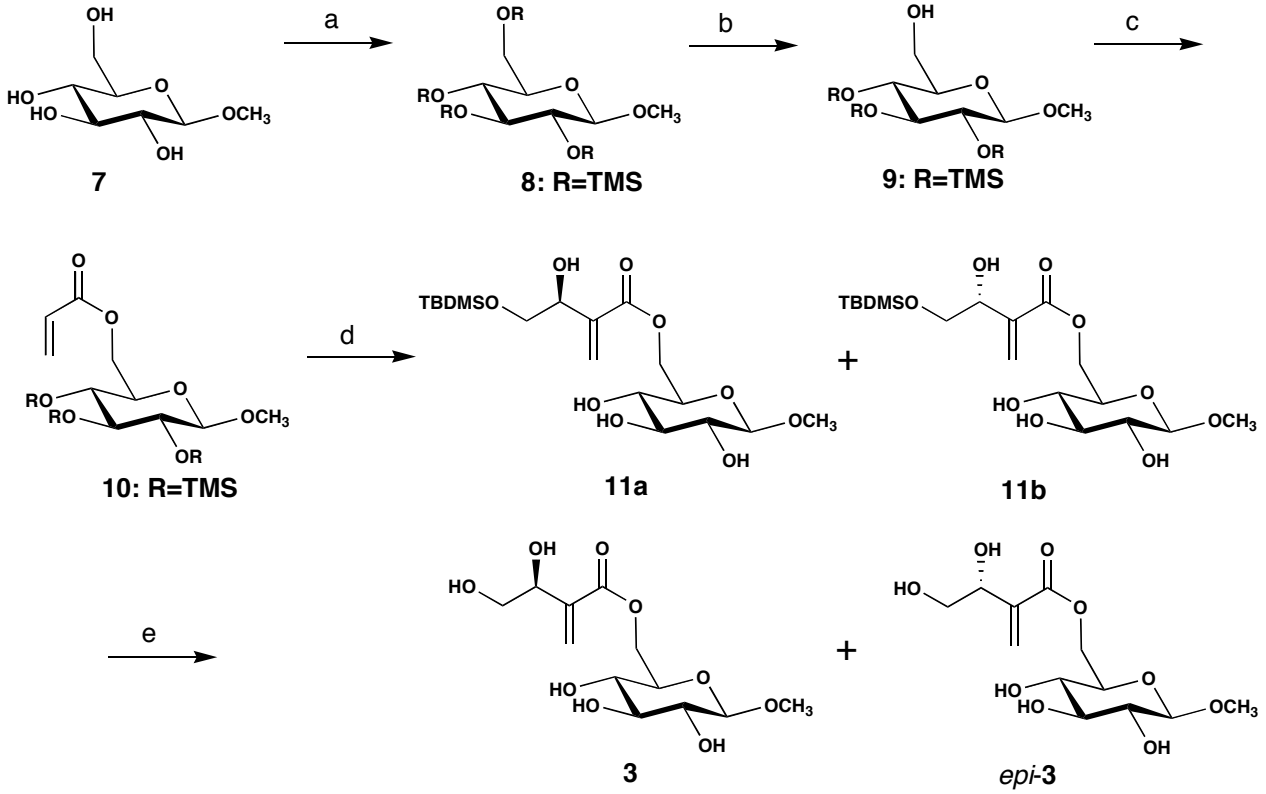


6a **2: (-)-tulipalin B** ***ent*-2: (+)-tulipalin B**

Reagent and conditions: a) TFA, $CHCl_3$, rt, 7d, 100%.

Scheme 1

Methyl 2,3,4-tris-*O*-trimethylsilyl-*β*-D-glucopyranoside (**9**) was prepared from methyl *β*-D-glucopyranoside (**7**) in two steps as described previously.[13] Esterfication of **9** with acryloyl chloride under the influence of triethylamine furnished methyl 6-*O*-acryloyl-2,3,4-tris-*O*-trimethylsilyl-*β*-D-glucopyranoside (**10**) in 97%. The BH reaction of **10** with aldehyde (**4**) yielded adducts (**11a**) and (**11b**), which lost all TMS groups in the glucose moiety.[14]



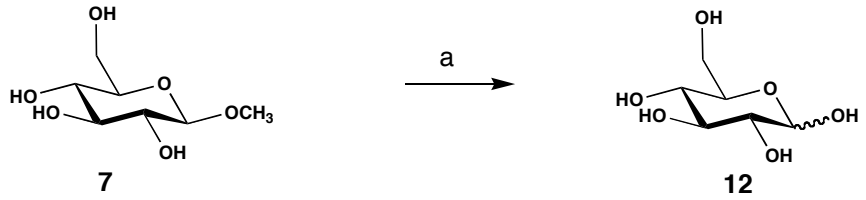
Reagent and conditions: a) TMSCl, py, 0°C, 6h, 99%; b) K_2CO_3, MeOH, 0°C,1h, 78%; c) acryloyl chloride, Et_3N, CH_2Cl_2, 97%; d) **4**, 3-HQD (1equiv.), DMSO, rt, 30% (diastereomeric ratio = 51.4 : 48.6); e) TBAF : AcOH = 1 : 2, THF, rt, 3h, quant.

Scheme 2

The two diastereomers, (**11a**) and (**11b**), were completely separable by analytical chiral HPLC (DAICEL

Chiralcel® OD-H, eluent: 2-propanol : hexane = 1 : 19, retention time: 30.75 min (48.6%) and 38.30 min (51.4%)), and treatment of the mixture of **11a** and **11b** with tetrabutylammonium fluoride (TBAF)-AcOH in THF afforded **3** and its epimer (*epi*-**3**) without lactonization in quantitative yield. Thus, formal synthesis of **3** and *epi*-**3** was achieved.[15]

Although demethylation of **3** and *epi*-**3** was attempted by using *β*-glucosidase or under mildly acidic conditions, neither tuliposide B (**1**) nor its epimer (*epi*-**1**) was detected. The conditions used were as follows: i) cellulase from *Trichoderma viride* (1000 unit/mg for filter paper), ii) *β*-glucosidase from almonds (2.6 unit/mg for salicin), iii) cellulase from *Aspergillus niger* (25 unit/mg for carboxymethyl cellulose), iv) cellulase from *Rizopus* mold (0.2 unit/mg for cellulose). Demethylation of methyl *β*-D-glucopyranoside (**7**) as a model reaction proceeded to give D-glucopyranose (**12**) in 90% yield (Scheme 3). The reaction was completed within 15 min, whereas disappearance of **3** and *epi*-**3** using the same conditions was not completed even after 24 hours and lactonization proceeded to afford (-)-tulipalin B (**2**) and (+)-tulipalin B (*ent*-**2**). An attempted demethylation using Dowex 50 worked in a similar way to give **2** and *ent*-**2**.



Reagent and conditions: a) **7**: 1 mmol/1.5 mL citrate buffer soution (pH 5.0), *β*-glucosidase from almonds (2 mg/mL solution): 200μl, 30°C, 15 min, 90%.

Scheme 3

In conclusion, we have succeeded in preparing (±)-tulipalin B (**2**) and a diastereomeric mixture of 1-*O*-methyl-6-tuliposide B (**3**) and its epimer (*epi*-**3**) in short steps. Although 6-tuliposide B (**1**) itself could not be prepared, a separable diasteromeric mixture of **3** and *epi*-**3** was prepared for the first time, which could be used for the study of the defense mechanism of tulip reproduction and the development of a new antimicrobial agent against multidrug-resistant microorganisms. Asymmetric total synthesis of 6-tuliposide B (**1**) and 1-tuliposide B[16] is now underway on the basis of the above observations.

ACKNOWLEDGEMENTS

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11. TBDMS migrated product (**6b**) could be converted to **2** using the same conditions in good yield.
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13. Preparation of methyl 2,3,4-tris-*O*-trimethylsilyl-α-D-glucopyranoside: D. T. Hurst and A. G. McInnes, *Can. J. Chem.*, 1965, **43**, 2004.
14. Although the minor spots on the TLC were thought to be the TBDMS migrated products as in the case of the BH reaction of **4** with **5**, enough amount of the compounds for the structural determination were not obtained.
15. Satisfactory spectroscopic data were obtained. Since the chemical shifts of major signals (**3**) but not of minor signals (*epi*-**3**) in ^{13}C NMR were fairly close to the data of the β anomer of **1** reported by Christensen,[1] it was indicated that the chiral acryloyl derivative (**10**) provided preferentially the desired diastereoselectivity during the BH reaction albeit the selectivity was not sufficient.
16. Although the structure of 1-tuliposide B was proposed by Tschesche *et al.*, the NMR data are not reasonable.[1]