

HETEROCYCLES, Vol. 69, 2006, pp. 63 - 67. © The Japan Institute of Heterocyclic Chemistry
Received, 10th May, 2006, Accepted, 16th June, 2006, Published online, 20th June, 2006. COM-06-S(O)11

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

Kengo Shigetomi,¹ Takao Kishimoto,¹ Kazuaki Shoji,² and Makoto Ubukata^{1*}

¹Division of Applied Bioscience, Research Faculty of Agriculture, Hokkaido University, Sapporo 060-8589, Japan; e-mail: m-ub@for.agr.hokudai.ac.jp

²Agricultural Experiment Station, Toyama Agricultural Research Center, Yoshioka, Toyama 939-8153, Japan

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'-methylenebutanoyl)-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

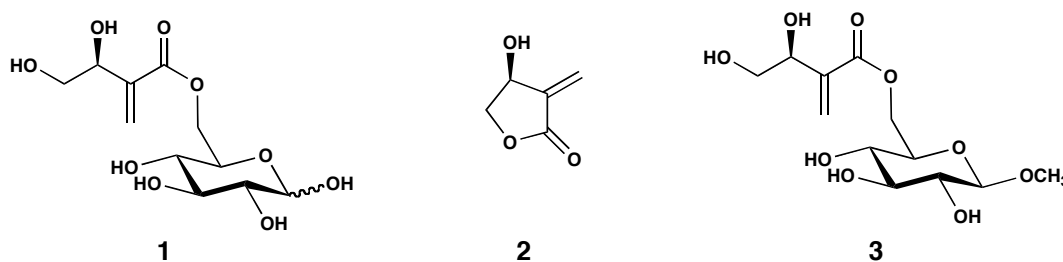


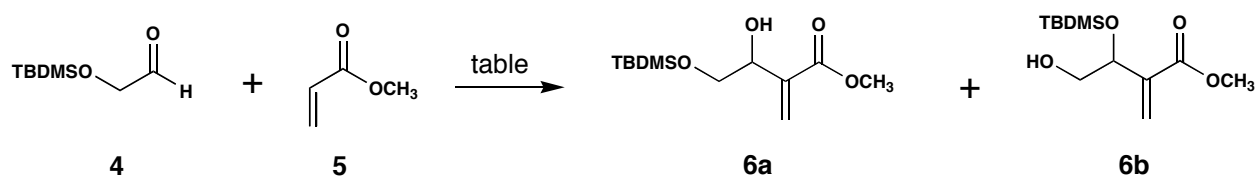
Figure 1

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*-butyldimethylsilyl)oxy]-acetaldehyde (**4**).



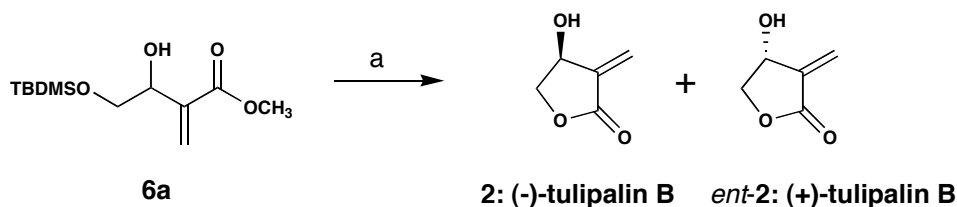
Entry	Conditions ^a	Yield (%)	
		6a	6b
1	DABCO (1 equiv.), dioxane : H ₂ O = 1 : 1, ⁷ rt, 1 h	0	0
2	Tributylphosphine (0.2 equiv.), THF, rt, ⁸ 1 week	0	0
3	DABCO (1 equiv.), THF, rt, 50 d	28	^b
4	DABCO (1 equiv.), DMSO, ⁹ 5 d	30	^b
5	3-Hydroxyquinuclidine (3-HQD) (1 equiv.), THF, rt, ¹⁰ 40 d	29	^b
6	3-HQD (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 : H₂O = 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 (**6aS** and **6aR**) were completely separable by using analytical chiral-HPLC (DAICEL Chiralcel[®] OD-H, eluent:

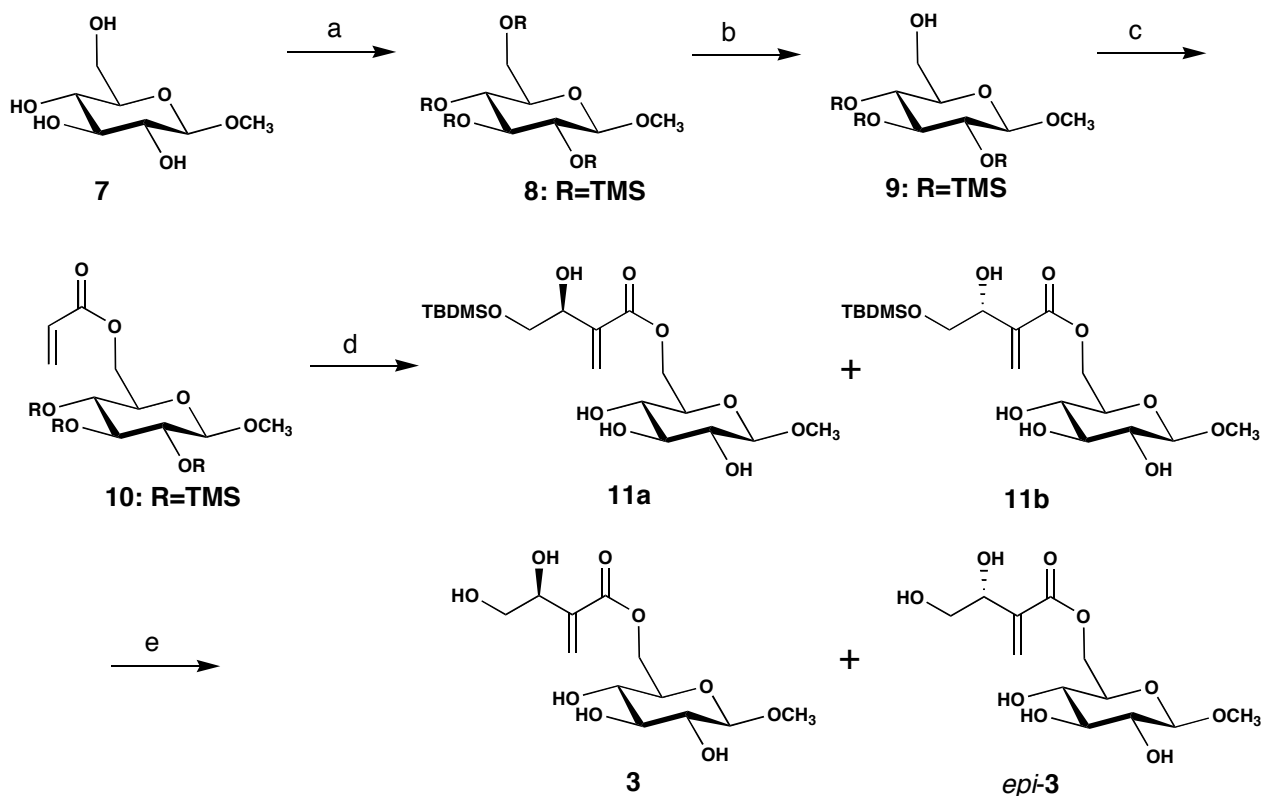
2-propanol : hexane = 1 : 99, retention time: 43.31 min and 46.03 min), formal total synthesis of natural (-)-tulipalin B (**2**) and its enantiomer (*ent*-**2**) was achieved. Although several total syntheses of (\pm)-tulipalin B and (-)-tulipalin B have been described,^{4,12} the present synthesis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



Reagent and conditions: a) TFA, CHCl₃, 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 Esterification 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



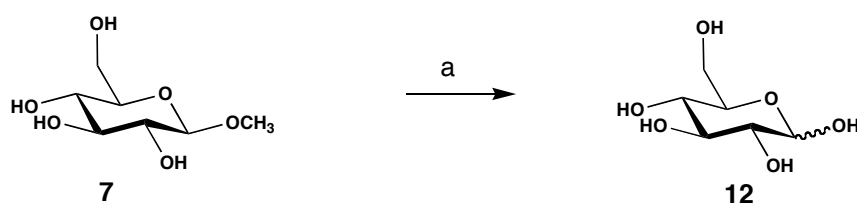
Reagent and conditions: a) TMSCl, py, 0°C, 6h, 99%; b) K₂CO₃, MeOH, 0°C, 1h, 78%; c) acryloyl chloride, Et₃N, CH₂Cl₂, 97%; d) **4**, 3-HQD (1equiv.), DMSO, rt, 30% (diastereomeric ratio = 51.4 : 48.6); e) TBAF : AcOH = 1 : 2, THF, rt, 3h, quant.

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 solution (pH 5.0), β -glucosidase from almonds (2 mg/mL solution): 200 μ L, 30°C, 15 min, 90%.

Scheme 3

In conclusion, we have succeeded in preparing (\pm)-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 diastereomeric 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 B¹⁶ is now underway on the basis of the above observations.

ACKNOWLEDGEMENTS

This work was supported by Grant-in-Aid for Scientific Research on Priority Area "Creation of Biologically Functional Molecules" from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES AND NOTES

1. R. Tschesche, F. J. Kämmerer, and G. Wulff, *Chem. Ber.*, 1969, **102**, 2057; R. Tschesche, F. J.

- Kämmerer, and G. Wulff, and F. Schönbeck, *Tetrahedron Lett.*, 1968, **6**, 701; A. Slob, *Phytochemistry*, 1973, **12**, 811; A. Slob, B. Jekel, B. de Jong, and E. Schlattmann, *ibid.*, 1975, **14**, 1997; L. P. Christensen, *ibid.*, 1999, **51**, 969.
- G. A. W. Verspyck Mijnsen, *Br. J. Dermatol.*, 1969, **81**, 737; B. Santucci, M. Picardo, C. Iavarone, and C. Trogolo, *Contact Dermatitis*, 1985, **12**, 215; J. C. Mitchell and G. Dupuis, *Br. J. Dermatol.*, 1971, **84**, 139; B. M. Hausen, E. Prater, and H. Schubert, *Contact Dermatitis*, 1983, **9**, 46.
 - K. Shoji, M. Ubukata, K. Momonoi, T. Tsuji, and T. Morimatsu, *J. Japan. Soc. Hort. Sci.*, 2005, **74**, 469.
 - J. P. Corbet and C. Benezra, *J. Org. Chem.*, 1981, **46**, 1141
 - E. Ciganek, 'The catalyzed α -hydroxylation and α -aminoalylation of activated olefins (The Morita-Baylis-Hillman reaction),' *Organic Reactions*, 1997, **51**, pp. 201-350.
 - D. Enders and T. Schusseler, *Synthesis*, 2002, **15**, 2280; J. A. Lafontaine, D. P. Provencal, C. Gardelli, and J. W. Leahy, *J. Org. Chem.*, 2003, **68**, 4215.
 - C. Yu, B. Liu, and L. Hu, *J. Org. Chem.*, 2001, **66**, 5413.
 - K. Morita, Z. Suzuki, and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815; S. Rafel, J. W. Leahy, *J. Org. Chem.*, 1997, **62**, 1521.
 - K.-S. Yang and K. Chen, *Org. Lett.*, 2000, **2**, 729.
 - S. E. Drewes, S. D. Freese, N. D. Emslie, and G. H. P. Roos, *Synth. Commun.*, 1988, **18**, 1565; F. Ameer, S. E. Drewes, S. Freese, and P. T. Kaye, *Synth. Commun.*, 1988, **18**, 495.
 - TBDMS migrated product (**6b**) could be converted to **2** using the same conditions in good yield.
 - C. R. Hutchinson, *J. Org. Chem.*, 1974, **39**, 1854; A. Tanaka, *Agric. Biol. Chem.*, 1980, **44**, 199; C. Papageorgiou and C. Benezra, *J. Org. Chem.*, 1985, **50**, 1145.
 - 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.
 - 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.
 - 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.
 - Although the structure of 1-tuliposide B was proposed by Tschesche *et al.*, the NMR data are not reasonable.¹