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Efficient transformation of 7,14-dihydroxy-*ent*-kaurenes to novel *ent*-abietanes having *cis*-fused α-methylene γ-lactones under Mitsunobu reaction conditions and their cytotoxicities

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ABSTRACT

Transformation of plant-origin 7,14-dihydroxy-*ent*-kaurenes to *ent*-abietanes having a *cis*-fused α-methylene γ-lactones was accomplished efficiently under the Mitsunobu reaction conditions. The yields of the desired products were apparently influenced by the steric hindrance at C-1. The cytotoxic activity on P388 murine leukemia cells of the *ent*-abietanes having *cis*-fused α-methylene γ-lactones produced were assayed.

1. Introduction

Only a limited number of *ent*-abietane diterpenoids have been reported,[1–14] including tetracyclic *ent*-abietanes jolkinolides A–F from *Euphorbia jolkini* (Euphorbiaceae),[7–9] helioscopinolides A–L from *Euphorbia helioscopia* (Euphorbiaceae),[10–13] and taibaihenryiin C (**1**), having a unique diterpene skeleton with a δ,ε-unsaturated *cis*-fused α-methylene γ-lactone in the molecule, from *Rabdosia henryi* (Labiatae) (Fig. 1).[14] Of them, jolkinolide D (**5**) is known to inhibit tumor invasion into the basement membrane tissue[15,16] and to induce apoptosis in tumor cells and jolkinolide B (**3**) is known to induce neuroendocrine differentiation of human prostate LNCaP cancer cell line.[17] However, the synthetic methods reported for the preparation of *ent*-abietanes are quite limited.[18–20] On the other hand, over four hundred *ent*-kaurene diterpenoids have been isolated from plants, of which those having an α,β-unsaturated ketone substructure are attracting much attention as pharmaceutical lead compounds.[21] In those *ent*-kaurenes, 7β-hydroxy group seemed to increase the cytotoxic activity. So, previously, we tried to prepare 7β-hydroxy-bearing *ent*-kaurenes of stronger cytotoxicity from protected 7α-hydroxy-bearing *ent*-kaurenes by the Mitsunobu reaction. The results demonstrated, however that the reaction caused skeletal modification to produce *ent*-abietane series, instead of giving 7β-hydroxy-bearing *ent*-kaurene skeleton. By applying this findings, as reported in our previous communication,[22] we transformed 7,14-dihydroxy-*ent*-kaurene diterpenoids, i.e., excisanin A (**7**), kamebanin (**9**), and kamebakaurin (**10**) obtained from *Rabdosia* plants in moderate yield[23] to *ent*-abietanes having a δ,ε-unsaturated *cis*-fused α-methylene γ-lactone. The present paper describes semisynthesis of pharmaceutically interesting *ent*-abietanes by first protecting the hydroxyl groups of 7,14-dihydroxy-*ent*-kaurene diterpenoids from *Rabdosia*, i.e., **7**, rabdokunmin C (**8**), **9**, and **10**, with different protective groups and then subjecting them to the skeletal transformation under the Mitsunobu reaction. As shown in Scheme 1, **A** may be derived from **B** under the Mitsunobu reaction conditions: conversion of 7-hydroxyl group to an oxyphosphonium ion intermediate, nucleophilic attack by the oxygen atom of 14-hydroxy group on the carbonyl carbon at C-15, and the elimination of triphenylphosphine oxide may occur in succession under the Mitsunobu reaction conditions to afford the corresponding

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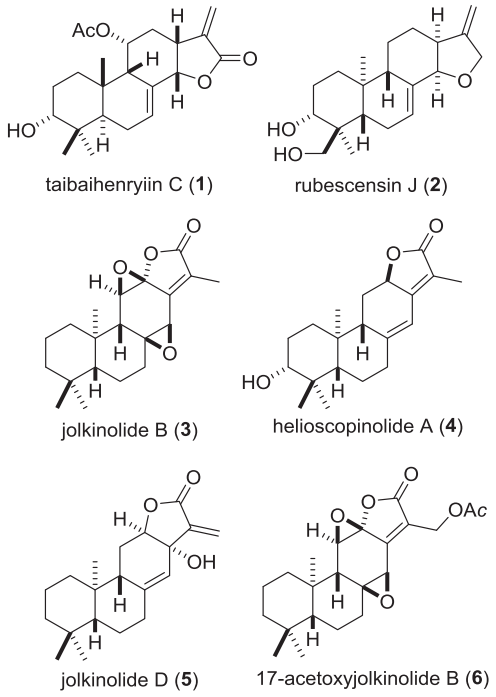
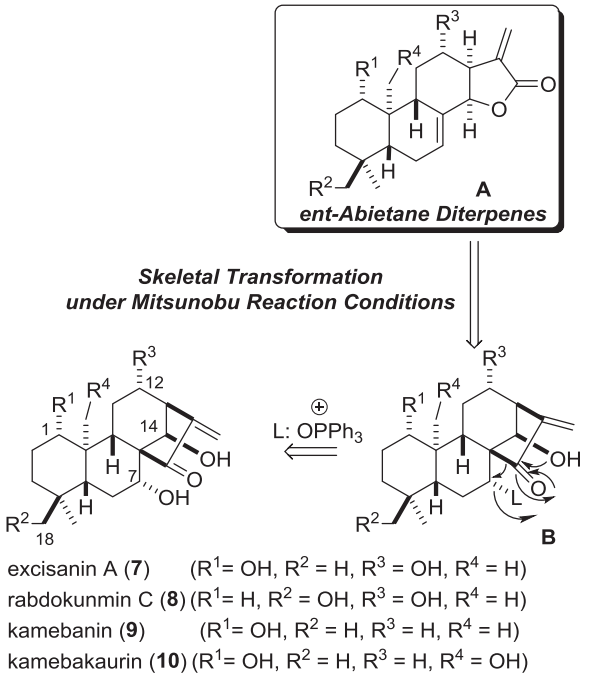


Fig. 1. Structures of naturally occurring diterpenes having tetracyclic *ent*-abietane skeletons (**1**–**6**).

ent-abietanes. In this case, usual intermolecular Mitsunobu reaction does not take place, apparently because the steric hindrance around C-7 makes the nucleophilic attack on C-7 by a carboxylate anion difficult. The effect of selective protection of polyoxygenated *ent*-kaurenoids (**7**, **8**, **9**, and **10**) gave interesting results. In this paper, we specifically discuss the effects of 1-, 12-, 18-substituents of *ent*-kaurenes on this rearrangement reaction and demonstrated the scope of this reaction. Since pyrophosphorylation of 7-hydoxyl group is possible in plants, the present transformation of *ent*-kaurenes to *ent*-abietanes under the Mitsunobu reaction conditions



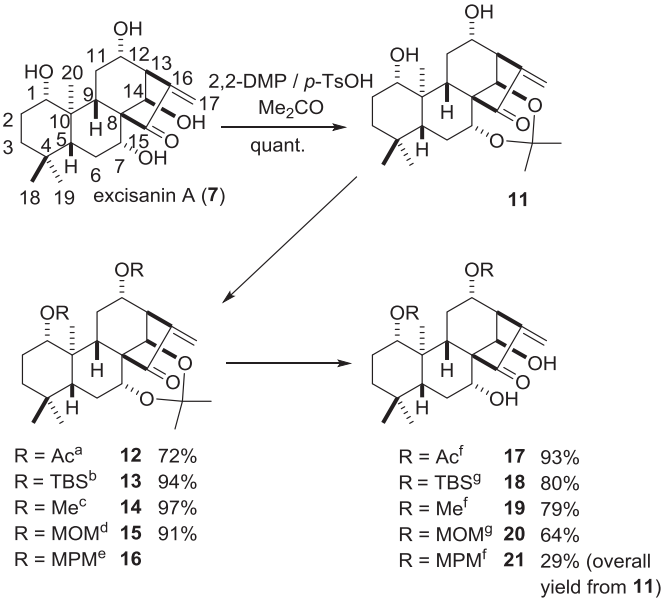
Scheme 1. Synthetic strategy of *ent*-abietanes from 1,14-dihydroxy-*ent*-kaurenes (**7**–**10**).

may be regarded as biomimetic: this view may be supported by the fact that *ent*-abietane and *ent*-kaurene diterpenoids are often isolated from the same plants.[1,3] The cytotoxic activity of the *ent*-abietanes thus obtained were also evaluated.

2. Results and discussion

2.1. Preparation of substrates for transformation under Mitsunobu reaction conditions

Substrates for the transformation were prepared from *ent*-kaurenes **7**, **8**, **9**, and **10** according to the procedures given in Schemes 2–5, respectively. Each consisted of three steps, including protection of 7- and 14-hydroxyls by acetalization, protection of the other hydroxyls, and deprotection of 7-*O*,14-*O*-acetal. In the case of excisanin A (**7**), after acetalization of 7,14-dihydroxy groups by the reported manner,[24,25] 1- and 12-hydroxyls were protected by acetylation,[26] silylation,[26] methylation, methoxymethylation, and *p*-methoxyphenylmethylation. Then, deacetalization of resulting 7-*O*,14-*O*-acetalized products **12**–**16**, having different protecting groups at 1-*O* and 12-*O*, were carried out in 1 N HCl–THF–MeOH or I_2 in MeOH to afford the corresponding 7,14-dihydroxy-*ent*-kaurenes **17**–**21**, in moderate to good yields (Scheme 2).



Reagents and conditions: (a) Ac_2O / pyridine / rt; (b) TBSOTf / 2,6-lutidine / CH_2Cl_2 / 0 °C; (c) NaH / THF / rt then MeI / rt; (d) MOMCl / $^iPr_2NEt$ / CH_2Cl_2 / rt; (e) NaH / THF / rt then *p*-methoxybenzyl bromide / rt; (f) 1N HCl / MeOH / THF / rt; g) I_2 / MeOH / 50°C.

Scheme 2. Preparation of protected 1,14-dihydroxy-*ent*-kaurenes (**17**–**21**) from excisanin A (**7**).

In the case of rabdokunmin C (**8**), its acetalization was accomplished by the use of acetone and PSA, because the conventional combination of 2,2-dimethylpropane (DMP) and *p*-toluenesulfonic acid (PSA) produced a complex mixture (Scheme 3). Acetylation, methoxymethylation, and *p*-methoxyphenylmethylation of the resulting acetalized product **22** was carried out in the usual manner to give, after deacetalization, the corresponding protected 7,14-dihydroxy-*ent*-kaurenes (**26**–**28**) in moderate to good yields (Scheme 3). The protected kamebanin derivatives (**33**–**35**) were prepared by practically the same procedure as that used in Scheme 2 for excisanin A (Scheme 4).