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MICROWAVE-AIDED ONE-POT DEHYDRATION OF THE ALCOHOL DERIVED FROM (–)-SHIKIMIC ACID FOR EFFICIENT SYNTHESIS OF PERICOSINES

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Abstract – Dehydrating conditions of shikimate-derived alcohol **7**, an early intermediate in the synthesis of the pericosine family of marine natural products, were examined. The triflate **8** was effectively converted to cyclohexadiene **9** with excess 4-*N*,*N*-dimethylaminopyridine (DMAP) at room temperature for 24 h. The reaction time was dramatically shortened by heating under microwave (MW) irradiation, preventing formation of the Diels–Alder type byproduct **14**. Furthermore, the MW-aided one-pot dehydration of alcohol **7** with Tf_2O and DMAP (2.4 eq.) to form diene **9** was realized.

Isolation of pericosines A–E (**1–4, 6**) and D_o (**5**), metabolites of the fungus *Periconia byssoides* OUPS-N133, originally isolated from the sea hare *Aplysia kurodai*, was reported by Numata and co-workers.[1,2] These compounds have unique C_7 cyclohexenoid structures[3] with condensed functional groups on the six-membered ring (Figure 1). We have been studying syntheses of pericosines with the primary aim of confirming their relative or absolute configurations.[4-8]

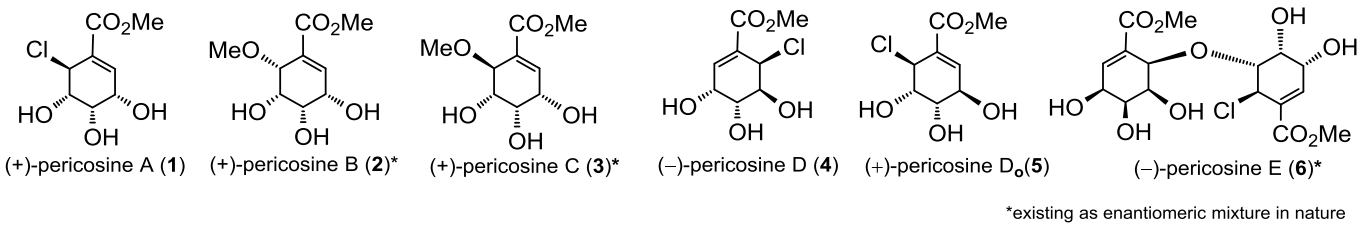
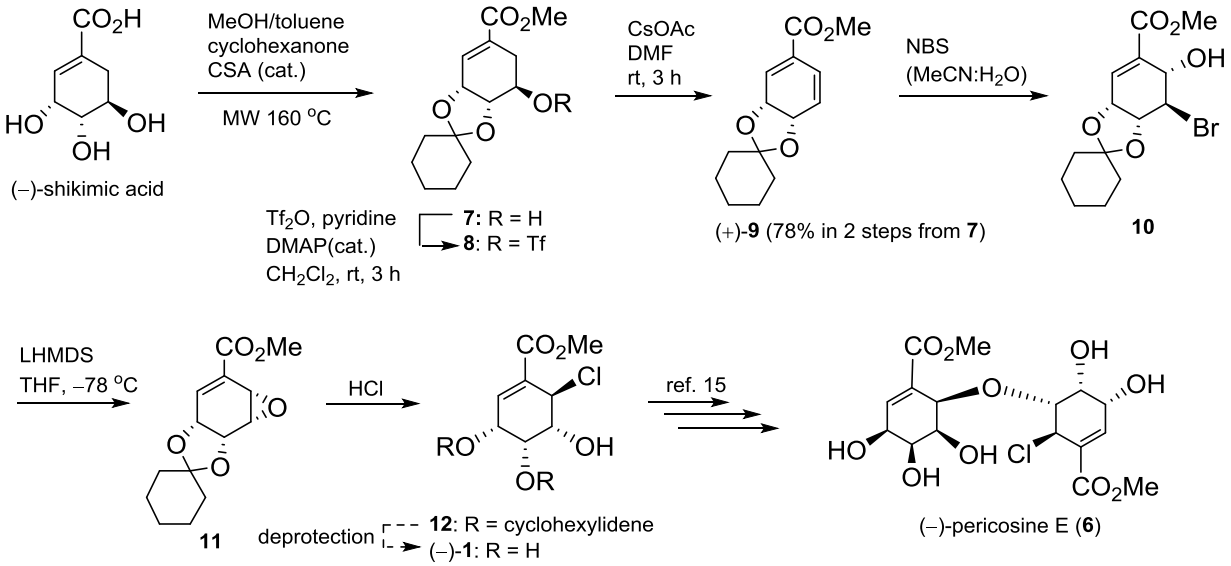


Figure 1. Structure of naturally occurring pericosines

Since pericosine A (**1**) has shown remarkable growth inhibition against several human cancer cell lines,[1,2] several other research groups have also taken on the challenge of the total syntheses of pericosines.[9-14] Recently, our interest has been in developing more efficient synthetic processes towards pericosines, which will enable more effective searching for biologically active compounds.[6,15] Our efforts afforded a microwave (MW)-aided one-pot synthesis of alcohol **7** from (–)-shikimic acid, a regioselective bromohydrination of cyclohexadiene **9** (Scheme 1), and a regioselective epoxidation of **9**. They also led to the first total synthesis of (–)-pericosine E (**6**).[15] Chlorohydrin **12** participated as a key intermediate in this total synthesis and is, of course, a precursor of (–)-**1** (Scheme 1).

Following this, our interest was focused on a one-pot synthesis of diene **9** from **7**, since it had been observed that a small amount of **9** was formed during *O*-trifluoromethansulfonylation of the 5-hydroxyl group in **7**. The two-step dehydration included use of cesium acetate (CsOAc) as a base and *N*,*N*-dimethylformamide (DMF) as a solvent.[6,15,16] These, however, are not ideal conditions as CsOAc is harmful and extremely hygroscopic, and DMF has a high boiling point because of which it must be removed during extraction through several washes with water or brine. Therefore, a CsOAc- and DMF-free dehydration process is desirable. This paper describes optimization of the conditions for the elimination step to convert **8** to **9** and a one-pot operation for the transformation of alcohol **7** into diene **9**.



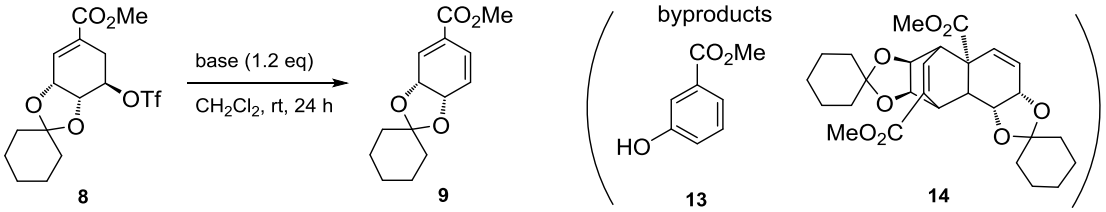
Scheme 1. Synthetic route to pericosine intermediates **11** and **12**

Initially, two commercially available dehydrating reagents, Martin sulfurane dehydrating agent[17] and Burgess reagent,[18] were tested for the direct dehydration of alcohol **7**. The Martin sulfurane dehydrating agent did not react with **7** in CH_2Cl_2 at room temperature. Reaction of **7** with the Burgess reagent under the same conditions led to a complex mixture, which did not contain **9**. Due to these unfruitful attempts, our

study was redirected to modify the reaction conditions of our previous method for the preparation of **9**. It had been shown that alcohol **7** could be successfully converted to triflate **8** at room temperature in a few hours (Scheme 1). In this reaction, pyridine was essential, since the reaction in the absence of pyridine did not afford **8**, and 4-*N*,*N*-dimethylaminopyridine (DMAP) participates as an effective catalyst.

Subsequently, attention was directed to the CsOAc- and DMF-free elimination step to convert **8** to **9**. Various bases were tested for this process, the results of which are summarized in Table 1. All reactions were carried out at room temperature for 24 h. Neither pyridine nor *N*,*N*-diisopropyl-*N*-ethylamine (DIPEA, known as Hünig's base) promoted the reaction (entries 1 and 3, respectively). The stronger base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected the aromatization of **8** to form methyl 3-hydroxybenzoate (**13**) (entry 4). Triethylamine and DMAP (1.2 eq.) gave desired diene **9** (entries 2 and 5, respectively), with the reaction with DMAP giving a slightly improved yield. Examination of the pK_a values of the protonated bases[20] suggests that basicity does not affect the reaction. An improved yield was obtained with excess DMAP (2.4 eq.) (entry 6). Entry 7 is a trial reaction at the same concentration as that of entry 6 with respect to DMAP (1.2 eq.) in CH_2Cl_2. This gives a similar yield to entry 5. From the results of entries 5–7, excess DMAP was proven to be necessary for smooth elimination. However, the reason for this is not clear. The optimum conditions given in entry 6 will be used in the following study. A closely related study had been reported on dehydration of steroidal alcohols with Tf_2O and DMAP (3 eq.).[19] The reaction with 3 equivalents of DMAP did not increase the chemical yield (entry 8).

Table 1. Elimination with Various Bases



8 9 13 14

entry	base	(p*K*a of H^+base)[20]	**9**, yield (%)	recovery of **8** (%)
1	pyridine	5.2	0[a]	
2	Et_3N	10.6	14	73
3	DIPEA	11	0[a]	
4[b]	DBU	12	16	7
5[c]	DMAP	9.2	63	11
6[d]	DMAP		71	9
7[e]	DMAP		65	20
8[f]	DMAP		63	

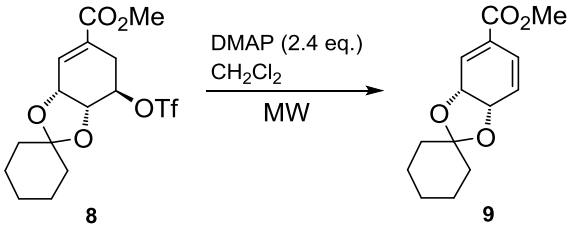
a. Since the reaction did not proceed, recovery of starting material **8** was not purified.

b. The aromatized product **13** was obtained in 67%. c. Byproduct 14 was obtained in only 4% yield.

d. DMAP (2.4 eq.) was used. e. DMAP (1.2 eq.) was used in 1/2 volume of CH_2Cl_2. f. DMAP (3.0 eq.) was used.

The major problem with the optimal conditions (entry 6) is the long reaction time required for the reaction (24 h). MW irradiation was suggested as a solution to overcome this issue. MW-aided reactions have often been used in our recent synthetic studies to reduce reaction time dramatically.[21-25] However, another problem may arise when using MW irradiation at higher temperatures for the preparation of **9** because **9** is known to be unstable.[16,26] Indeed, some byproduct **14**, which is formed by Diels–Alder reaction between two molecules of **9**, was observed in the preparation of bromohydrin **10** from **9** in our recent synthetic study on the total synthesis of pericosine E (**6**).[15] Results of the MW-aided reactions are summarized in Table 2. MW irradiation over long times (30 min) (entries 2–4) afforded trace amounts of the predicted byproduct **14**, but a shortened irradiation time prevented the formation of **14**. Irradiation at 120 °C for 5 min afforded desired **9** in 85% yield with no formation of **14** (entry 8). As references, experiments with conventional heating in 1,2-dichloroethane were listed in entries 1 and 5. The reaction in 30 min yielded **9** in 86% yield (entry 1) but the reaction did not complete in 5 min (entry 5).

Table 2. Microwave-Aided Elimination with DMAP



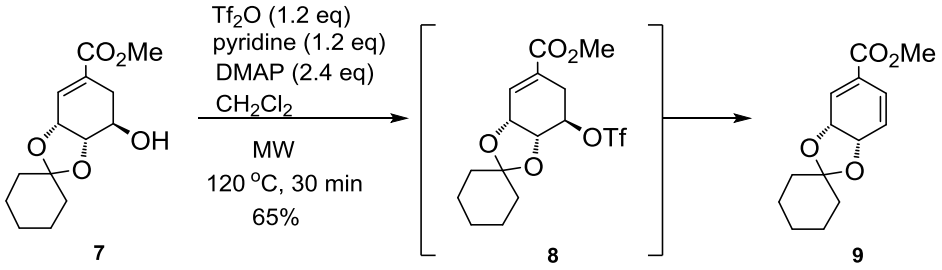
8 **9**

entry	temp. (°C)	time (min.)	**9**, yield (%)	recovery of **8** (%)
1[a]	80	30	86	-
2[b]	80	30	76	-
3[b]	100	30	72	-
4[b]	120	30	67	-
5[a]	80	5	46	34
6	80	5	57	35
7	100	5	75	13
8	120	5	85	-

a. Conventional heating in 1,2-dichloroethane as a solvent.

b. Trace amount of **14** was observed in the ^{1}H-NMR spectra of crude reaction mixture.

Finally, we performed the one-pot dehydration of **7** to **9** using the MW method. It was found that conversion of **7** to **8** did not proceed in the presence of catalytic DMAP without pyridine. Following this, the one-pot synthesis of **9** was examined with Tf_2O (1.2 eq), pyridine (1.2 eq), and DMAP (2.4 eq) in CH_2Cl_2 under MW irradiation (Scheme 2). The best result was obtained under MW irradiation at 120 °C for 30 min, which afforded **9** in 65% yield. When the same reaction mixture was reacted under MW irradiation at 120 °C for 5 min or at 100 °C for 30 min, significant amounts of unreacted **7** were observed in the ^{1}H-NMR spectrum of the crude residue. Prolonged reaction time to 30 min might be required for the conversion of **7** to triflate **8**.



Scheme 2. One-pot dehydration from alcohol **7** to diene **9**

In conclusion, DMAP was proven to be an effective base for the elimination of the trifluoromethanesulfonyloxy group in **8** to afford **9**. MW irradiation shortened the reaction time**,** and irradiating for just 5 min prevented the formation of Diels–Alder byproduct **14**. One-pot dehydration of **7** to **9** was realized with Tf_2O (1.2 eq.), pyridine (1.2 eq.), and DMAP (2.4 eq.) by a MW-aided reaction at 120 °C for 30 min. This one-pot procedure reduced the reaction time to one-twelfth that of the previous two-step processes. The procedure described in this paper will be useful for the synthesis of pericosines and other related biologically active analogues.

EXPERIMENTAL

NMR spectra were recorded at 27 °C on Agilent 300- and 400-MR-DD2 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Liquid column chromatography was conducted over silica gel (Nacalai, silica gel 60, mesh 70–230 or 230–400). Analytical TLC was performed on precoated Merck glass plates (silica gel 60 F_{254}) and compounds were detected by dipping the plates in an ethanol solution of phosphomolybdic acid, followed by heating. All microwave-aided reactions were carried out with Biotage Initiator® (Switzerland). Dry CH_2Cl_2, pyridine, and DMAP were purchased from Wako Pure Chemical Industries (Osaka, Japan). Tf_2O was purchased from Nakalai Tesque, Inc. (Kyoto, Japan). Martin sulfurane dehydrating agent and Burgess reagent were purchased from Sigma Aldrich Co. LLC. (St. Louis, MO, USA). (−)-Shikimic acid was purchased from Carbosynth, Ltd. (UK).

Elimination with Various Bases: Table 1

General Procedure (Table 1, entry 5): To a solution of triflate **8** (130 mg, 0.33 mmol) in dry CH_2Cl_2 (20 mL), under an argon atmosphere, was added DMAP (72 mg, 0.39 mmol) at 0 °C with stirring. The reaction mixture was then allowed to warm to room temperature followed by stirring for 24 h. After quenching with aq. NH_4Cl, the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (hexane:EtOAc = 6:1) to give **9** (51 mg, 63%) and **14** (6.5 mg, 8%*) with

recovery of **7** (14 mg, 11%).

*Mol ratio to **8** or **9** is 4% since 2 mol of **7** should be consumed to give 1 mol of **14**.

Microwave-Aided Elimination with DMAP: Table 2

General Procedure (Table 2, entry 1): To a solution of triflate **8** (24 mg, 0.059 mmol) in dry CH_2Cl_2 (4 mL) contained in a MW reactor vial, was added DMAP (17 mg, 0.14 mmol). The sealed vessel was heated under MW irradiation at 80 °C for 30 min. After cooling, the reaction mixture was neutralized by slow addition of aqueous HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (hexane:EtOAc = 6:1) to give **9** (11 mg, 76%).

Microwave-Aided One-pot Dehydration from 7 to 9

To a solution of alcohol **7** (48 mg, 0.18 mmol), pyridine (20 μL, 0.25 mmol), and DMAP (53 mg, 0.43 mmol) in dry CH_2Cl_2 (4 mL), contained in a MW reactor vial, was added a solution of Tf_2O (36 μL, 0.22 mmol) in CH_2Cl_2 (1 mL) at 0 °C with stirring. The sealed vessel was heated under MW irradiation at 120 °C for 30 min. After cooling in an ice bath, the reaction mixture was neutralized by slow addition of aqueous HCl and extracted with CH_2Cl_2 (3 ×10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (hexane:EtOAc = 6:1) to give **9** (29 mg, 65%).

* The one-pot dehydration experiment in 2.2 mmol scale showed 59% yield.

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