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Biomimetic synthesis of grandione from demethylsalvicanol via hetero-Diels–Alder type dimerization and structure revision of grandione

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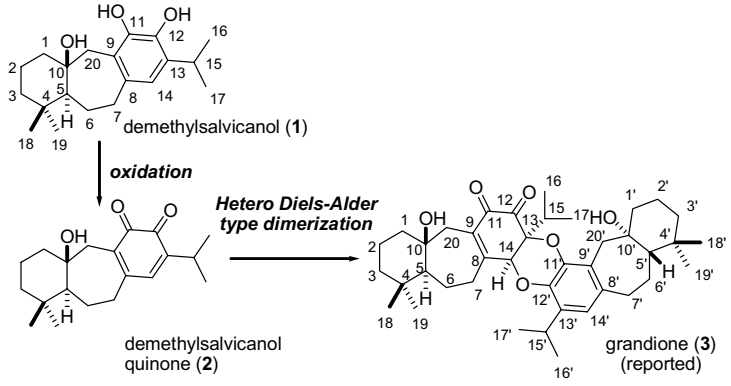
Abstract—Grandione, a unique isetexane diterpene dimer, was synthesized from demethylsalvicanol via the solid state hetero-Diels–Alder type dimerization reaction. By X-ray crystallography, grandione was determined to have the structure, in which the two isopropyl groups on the two monomer units are arranged *syn*. Grandione and some of its analogues showed a moderate cytotoxity on P388 murine leukemia cells.

The present letter describes the synthesis of grandione (**3**),[1] a unique isetexane diterpene dimer, by the plausible biomimetic hetero-Diels–Alder reaction of quinone (**2**) derived from demethylsalvicanol (**1**) having a rearranged 9(10→20)-abeoabietane skeleton. Briefly, the method consists of oxidation of **1** to **2** and dimerization of **2** to **3**. Cytotoxity of grandione (**3**) and its analogues obtained in the present study were also assayed. Grandione (**3**) was originally isolated from *Torreya grandis* (Taxaceae) by Riccio and co-workers in 1999 and its structure was proposed to be a unique heptacyclic diterpene dimer as shown in Scheme 1 by them.[1]

Demethylsalvicanol (**1**)[2] was obtained from aerial parts of *Perovskia abrotanoides* (Labiatae) in 0.37% yield. Gonzalez et al. suggested that the absolute configuration



Scheme 1. Structure of dimeric diterpene, grandione (**3**), and plausible biosynthetic pathway from demethylsalvicanol.

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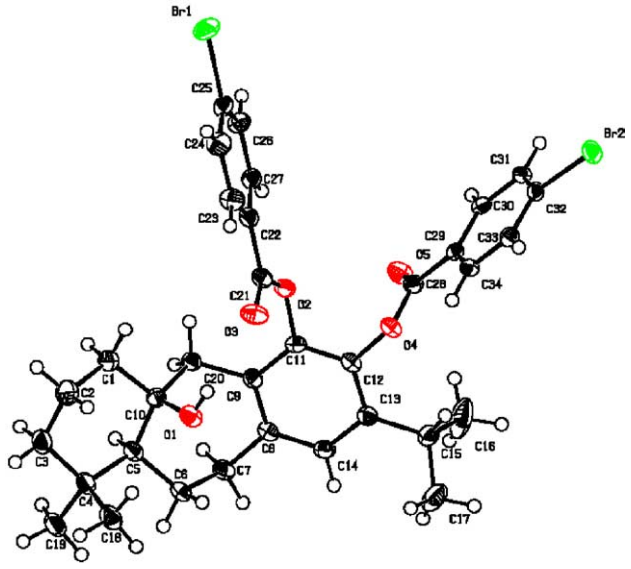


Figure 1. ORTEP representation of dibenzoate **4**.

of compound **1** was 5*S* and 10*S*, on the basis of chemotaxonomic consideration.[2] We converted **1** to its bis(*p*-bromobenzoate) (**4**) in 89% yield and subjected it to X-ray crystallographic analysis,[3] which proved that the absolute configuration of compound **4** was 5*S* and 10*S* (Fig. 1), and accordingly, that the absolute configuration of demethylsalvicanol (**1**) was 5*S* and 10*S*, as suggested.

Table 1. Oxidation of **1** to *o*-quinone **2** with different oxidants

Entry	Oxidants/conditions	Yields[a] of **2**
1	Ag_2O/Et_2O/rt/30 min	81
2	Ag_2CO_3/Et_2O/rt/60 min	Quant.
3	$FeCl_3{\cdot}6H_2O$/acetone/rt/50 min	Many products
4	CrO_3/AcOH/rt/50 min	27
5	Fremy's salt/KH_2PO_4/acetone/60 min	82
6	DDQ/doxane/rt/15 min	80
7	CAN/MeCN/H_2O/rt/10 min	77

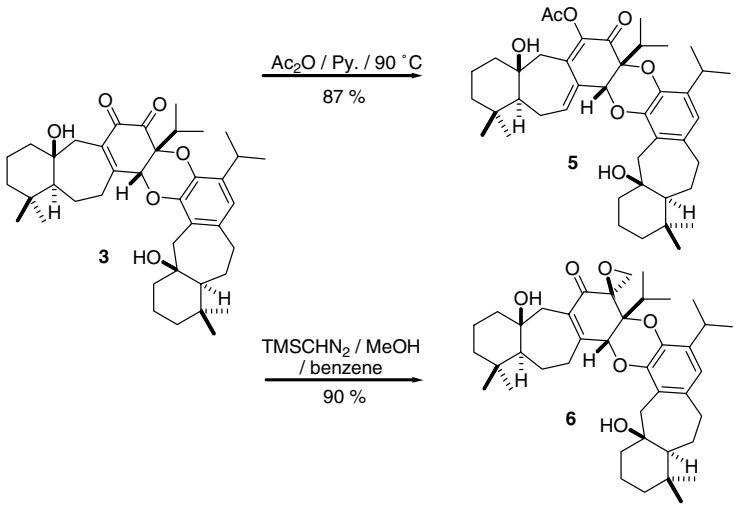
[a] Isolated yields.

Table 2. Hetero-Diels–Alder type dimerization of **2** under different reaction conditions

Entry	Solvent	Temperature (°C)	Time (h)	Product ratio (**2**:**3**)[a]
1	Toluene	40	18	100:0
2	$CHCl_3$	40	18	100:0
3	MeOH	rt	20	96:4
4	None	−20	24	98:2
5	None	−20	408	93:7
6	None	rt	24	92:8
7	None	rt	72	79:21
8	None	rt	113	70:30
9	None	rt	216	62:38
10	None	rt	408	52:48
11	None	40	24	66:34
12	None	40	48	59:41
13	None	40	60	44:56 (54)[b]
14	None	50	60	18:82 (74)[b]
15	None	70	12	20:80 (53)[b]

[a] The ratios were estimated on the basis of ^{1}H NMR spectrum.
[b] Yields of cycloadduct **3** isolated.

Oxidation of demethylsalvicanol (**1**) was carried out under several reaction conditions (Table 1). Oxidation with ferric(III) chloride or chromium(VI) oxide (Table 1, entries 3 and 4) was not effective, but the other procedures gave the corresponding quinone (**2**)[4] in good to excellent yields (Table 1, entries 1, 2, and 5–7). Quinone **2** was then subjected to an intermolecular hetero-Diels–Alder reaction (Table 2). In a solution in toluene, chloroform, or methanol, the reaction apparently did not proceed (Table 2, entries 1–3). When the reaction was performed in solid state[5] at rt or at 40 °C, the yield of the aimed cycloadduct increased as the reaction time increased (Table 2, entries 6–13), and at 50 and 70 °C, the reaction proceeded to give the cycloadduct in good yields (Table 2, entries 14–15). When the temperature was −20 °C, the reaction seemed to be extremely slow (Table 2, entries 4–5). Of the four possible cycloadducts, the hetero-Diels–



Scheme 2. Derivatization of dimer **3**.

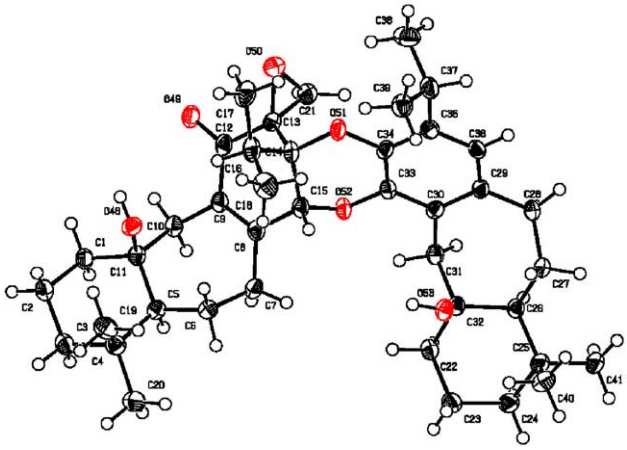


Figure 2. ORTEP representation of **6**.

Alder type dimerization reaction gave only one type of cycloadduct. The present cycloadduct was demonstrated to be identical to the natural grandione **3**, formerly isolated, by the comparison of the ^{1}H and ^{13}C NMR data with those cordially provided by Riccio et al.

The spectral data of the acetate (**5**) and the epoxide (**6**) of the present cycloadduct were also identical to the spectral data of the corresponding derivatives of natural grandione **3** (Scheme 2).[1] Thus, the identity of the present synthetic cycloadduct and natural grandione **3** was established. As the epoxide derivative **6** gave good single crystals, it was subjected to X-ray crystallographic analysis.[6] The ORTEP drawing of **6** is given in Figure 2.

The results showed that the structure of grandione **3** proposed by Riccio et al. was to be revised to that shown in Scheme 3, in which the two isopropyl groups on the two monomer units are arranged *syn*.

Recently, synthesis of natural products via biomimetic Diels–Alder cycloaddition is attracting much attention, as it demonstrates that in some cases the Diels–Alder reaction can proceed nonenzymatically and thus it may provide means for effective construction of unique carbon skeletons.[7] The present study demonstrated that the nonenzymatic biomimetic hetero-Diels–Alder reaction of compound **2** proceeded to produce a natural heptacyclic diterpene dimer, grandione (**3**), efficiently and that the reaction gave primarily one of the four possible cycloadducts. The theoretical calculation of the transition state of the hetero-Diels–Alder reaction is now under investigation.

Compounds **1**–**6** were assayed for their cytotoxity on P388 murine leukemia cells. The IC_{50} values were 0.71, 0.57, 4.3, >100, 6.3, and >100 μg/mL, respectively. Compounds **1**–**3**, and **5** were shown to be active. Thus the 11,12-carbonyl or phenol groups, especially 12-oxygen functional group, may be essential for the cytotoxity (**1**–**3**, **5** vs **4**, **6**).

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References and notes

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3. Crystallographic data for compound **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 279944. Copies of the data can be obtained, free of charge, on application to the Director, CCDC (e-mail: deposit@ccdc.cam.ac.uk).
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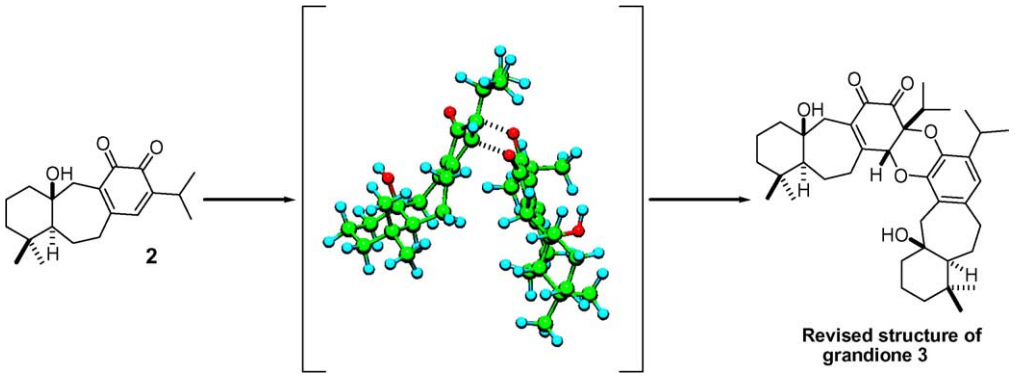

Scheme 3. Transition state of hetero-Diels–Alder type dimerization of **2**.