Received: December 18, 2014 | Accepted: December 29, 2014 | Web Released: January 8, 2015 CL-141168

Total Synthesis of a Monomeric Phloroglucinol Derivative Isolated from *Myrtus communis*

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The first total synthesis of a monomeric phloroglucinol [(1*R**,2*S**)-2-hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocyclohexyl acetate] was achieved by stereoselective reduction of a symmetrical α-ketol as a key step. The corresponding *cis*-stereoisomer of the natural product was synthesized from phloroglucinol via *cis*-dihydroxylation using OsO_4. Comparison of ^{1}H NMR data for synthetic **1** and **2** confirmed the *trans*-stereochemistry of the natural product.

2-Hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocyclohexyl acetate (**1**) was isolated from the essential oil of *Myrtus communis* which has been widely utilized as a traditional medicine.[1] The relative stereochemistry of **1** was proposed as 1*R** and 2*S**. The absolute stereochemistry has not been determined yet. Natural product **1** and related natural products **3**,[2] **4**,[1] and **5**[3] are monomeric phloroglucinols[4] and characterized by the highly oxygenated 2,2,4,4-tetramethylcyclohexane-1,3-dione framework with the vicinal diol moiety (Figure 1). Although syntheses and biological activities of monomeric phloroglucinol **6** and its analogs have been extensively studied,[1,5] those of **1**, **3**, **4**, and **5** have been less studied except for the total synthesis of **3**.[6] We herein report the stereoselective synthesis of *rac*-**1** bearing the *trans*-diol moiety and its *cis*-isomer **2**. The relative stereochemistry of the natural product **1** was confirmed as *trans* by NMR analyses of **1** and **2**.

Retrosynthetic analysis of *rac*-**1** featuring the diastereoselective desymmetrization of **7** is depicted in Scheme 1. We employed a hydroxy group-directing reduction of **7** to the construction of the *trans*-diol moiety of **1**. Ketol **7** could be derived by oxidation of **8**. Triketone **8** could originate from phloroglucinol (**9**) via sequential introduction of the isobutyl side chain and tetramethyl groups.

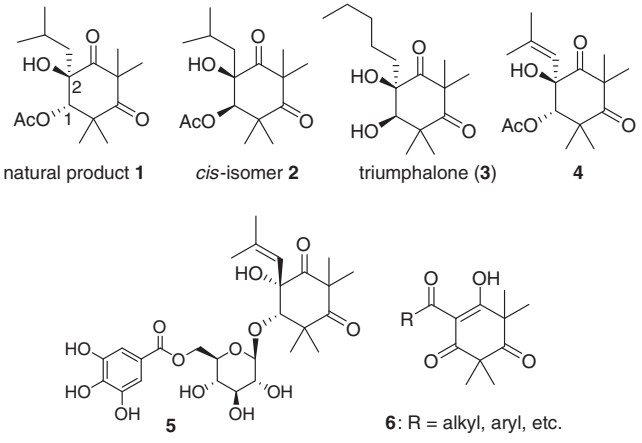
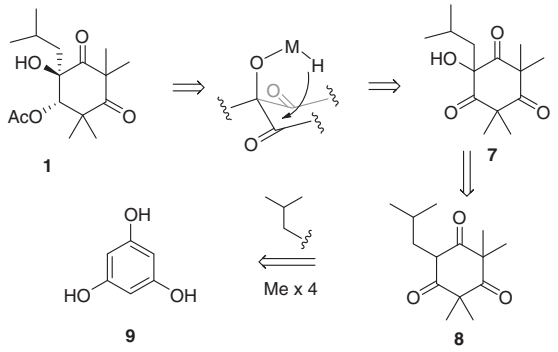
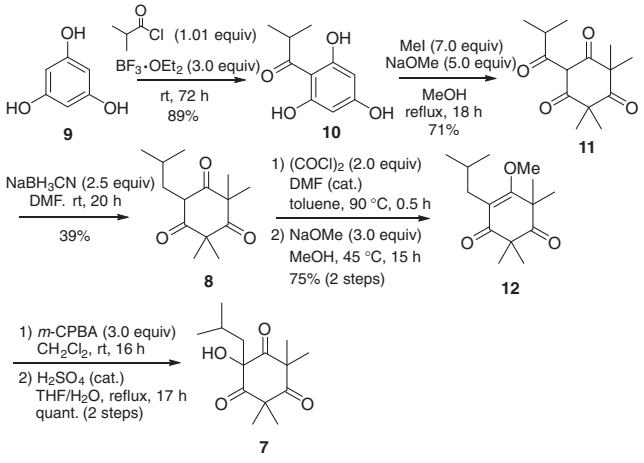


Figure 1. Structure of monomeric phloroglucinols.



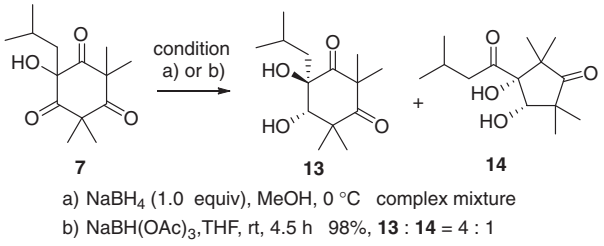
Scheme 1. Retrosynthetic analysis of **1**.



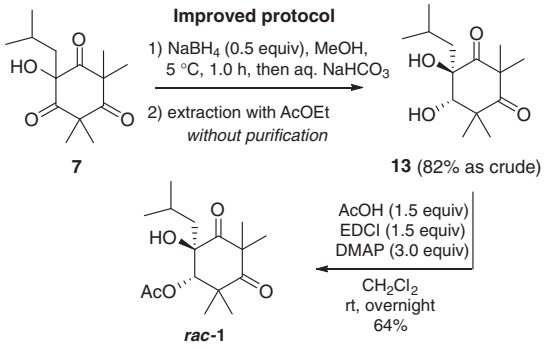
Scheme 2. Synthesis of symmetrical α-ketol **7**.

α-Ketol **7** was prepared from phloroglucinol (**9**) in seven steps (Scheme 2). Treatment of **9** with isobutyryl chloride in the presence of BF_3·OEt_2 gave **10** in 89% yield.[6] Tetramethylation of **10** with an excess of MeI gave **11** in 71% yield. Chemoselective reduction of **11** with $NaBH_3CN$[7] gave ketone **8** in 39% yield. Triketone **8** was converted to **12** in 75% yield over two steps. The hydroxylation of **12** was achieved by epoxidation with *m*-CPBA followed by an acidic hydrolysis to give ketol **7** in quantitative yield.

We next investigated the stereoselective reduction of **7**. Treatment of **7** with $NaBH_4$ (1.0 equiv) in MeOH at 0 °C resulted in a complex mixture of **13** and highly polar tri- and tetraols (Scheme 3). To suppress the undesired over-reduction pathway, $NaBH(OAc)_3$ was employed as an alternative reagent. As expected, the reduction smoothly took place without over-reduction. However, a 4:1 mixture of the desired *trans*-diol **13** and unexpected cyclopentanone **14** which would arise from **13** by the ring constructive α-ketol rearrangement was obtained.[8]



Scheme 3. Initial attempts for the key reduction of **7**.



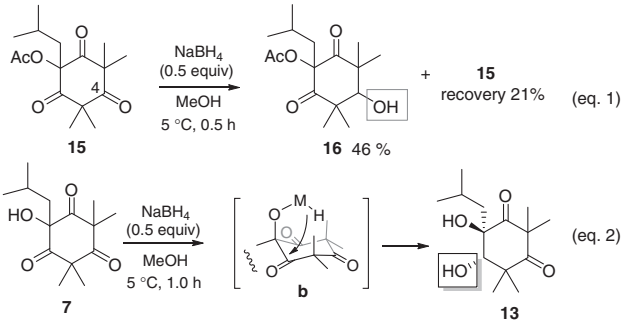
Scheme 4. Total synthesis of *rac*-**1**.

The stereochemistry of **13** was confirmed by comparison of the NMR data of the corresponding acetate **1** with those of *cis*-**2** which was prepared by the stereochemically defined synthetic route via *cis*-dihydroxylation (Scheme 6 and Table 1). The relative stereochemistry of cyclopentanone **14** was putatively assigned as *cis* by NOESY experiment (Supporting Information).

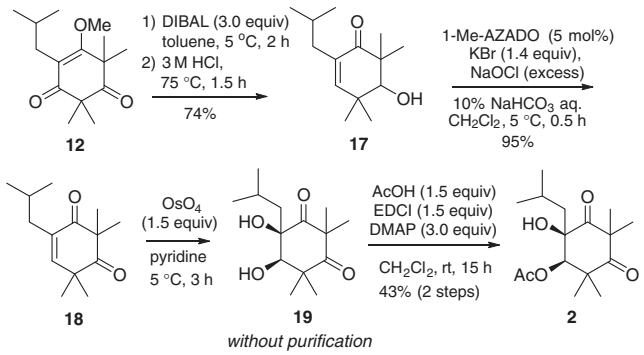
We have reported that the α-ketol rearrangement of **3** was accelerated in a protic solvent.[6] It was postulated that a small amount of AcOH or triacetoxyborane derived from $NaBH(OAc)_3$ would participate as a catalyst in the α-ketol rearrangement of **13**.[9] In line with this hypothesis, we carefully examined the reaction conditions and established an improved protocol to provide *trans*-diol **13** in an efficient manner. Treatment of **7** with 0.5 equiv of $NaBH_4$, followed by quenching of the reaction mixture with $NaHCO_3$, extraction with AcOEt, and concentration in vacuo gave crude **13** in 82% yield. ^{1}H NMR data of the crude material revealed the presence of **13** as a sole product (Supporting Information). The total synthesis of *rac*-**1** was achieved by the successive acetylation without purification of **13** (Scheme 4). The ^{1}H- and ^{13}C NMR data for synthetic *rac*-**1** was identical to those of the reported data (Table 1 and Table SI-1).[1]

Interestingly, the carbonyl group at C4 of acetate **15** was predominantly reduced to give **16** as a single isomer, when **15** was treated with 0.5 equiv of $NaBH_4$ at 0 °C (Scheme 5, eq 1).[10] This result clearly showed that the loss of the directing effect remarkably influenced the regioselectivity. Based on this result, we proposed a reaction mechanism for the stereoselective reduction of **7** involving the hydroxy group-directing effect (Scheme 5, eq 2). Reaction of ketol **7** with $NaBH_4$ initially provides a putative intermediate **b**. Stereoselective formation of **13** would be ascribed to the preferential intramolecular hydride attack from the upper face in the intermediate **b**.

To confirm the relative stereochemistry of **1**, the NMR data for *rac*-**1** and its *cis*-isomer **2** were compared. *cis*-Isomer **2** was

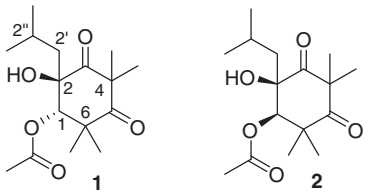


Scheme 5. Equation 1: Reduction of acetate **15**; Equation 2: Proposed reaction mechanism for the stereoselective reduction of **7**.



Scheme 6. Synthesis of **2** from **12**.

Table 1. ^{1}H NMR data of natural product **1**, synthetic *rac*-**1** and *rac*-**2**



	Natural product **1**[a]	**1**[b]	**2**[b]
C2″-Me	0.89 (d)	0.82 (d)	0.70 (d)
C2″-Me	0.90 (d)	0.84 (d)	0.85 (d)
C2″-H	1.84 (m)	1.78 (m)	1.65 (m)
C2′-CH_2	1.43 (dd)	1.38 (dd)	1.18 (dd)
	1.71 (dd)	1.64 (dd)	1.46 (dd)
C1-H	5.44 (s)	5.38 (s)	5.35 (s)
C4 and C6	1.42 (s)	1.35 (s)	1.27 (s)
4 × Me	1.33 (s)	1.27 (s)	1.27 (s)
	1.15 (s)	1.08 (s)	1.25 (s)
	1.10 (s)	1.04 (s)	1.01 (s)
–C(=O)CH_3	1.58 (s)	1.53 (s)	1.59 (s)
OH	2.80 (s)	2.75 (s)	3.89 (s)

[a]400 MHz (C_6D_6), ref 1. [b]600 MHz (C_6D_6).

prepared from **12** in accordance with the previous synthetic procedure for triumphalone (**3**) (Scheme 6).[6] Enol ether **12** was reduced with DIBAL, followed by hydrolysis under acidic conditions to give α,β-unsaturated ketone **17**. Oxidation of **17**

using 1-Me-AZADO[11] provided ketone **18** in 95% yield. Treatment of **18** with a stoichiometric amount of OsO_4 gave *cis*-diol **19** which exerted mostly the same reactivity as **13** in regard to the facile α-ketol rearrangement to **14**.[12] Therefore, the crude **19** was successively acetylated without purification under the mild conditions using DMAP as a weak base to furnish **2** in 43% yield.

^{1}H NMR data of natural product **1**,[1] synthetic **1** and its *cis*-isomer **2** in C_6D_6 are depicted in Table 1. ^{1}H NMR data for *cis*-**2** was not identical to naturally occurring **1** and synthetic **1**. In addition, ^{13}C NMR data of **1** and **2** are distinctly distinguishable (Table SI-1). There results suggest that the relative stereochemistry of naturally occurring **1** is *trans*.

In summary, the first total synthesis of *rac*-**1** in 9 steps from **9** was achieved. The diastereoselective desymmetrization of symmetrical ketone **7** streamlined the synthetic process. The relative stereochemistry of **1** was confirmed by comparison of the NMR data of *rac*-**1** and its *cis*-isomer **2**. Further application to the total synthesis of highly oxidized monomeric phloroglucinols is ongoing in our laboratory.

This work was financially supported by a grant from Scientific Research of Innovative Areas, Chemical Biology of Natural Products[13] from MEXT (No. 23102009) and KAKENHI (Nos. 23228001 and 25282233) from JSPS.

Supporting Information is available electronically on J-STAGE.

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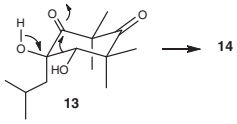
8 We have reported the α-ketol rearrangement of triumphalone (**3**) to give a cyclopentanone derivative with the *cis*-diol moiety. It is interesting to note that *trans*-diol **13** underwent α-ketol rearrangement to give *cis*-**14**. A proposed reaction mechanism is shown below. The reaction mechanism is currently under investigation and will be reported in due course.



9 Examples of acid-catalyzed α-ketol rearrangement: L. A. Paquette, J. E. Hofferberth, *Org. React.* **2003**, *62*, 477. Acid sensitivity of **13** was confirmed by the following supporting evidence: (i) when **13** was subjected to silica gel chromatography, the rearrangement product **14** occurred as a minor product and (ii) treatment of **13** a small amount of 6 M HCl in MeOH at room temperature gave **14** as a single product in 48% yield (see SI).

10 Relative stereochemistry of **16** has not been elucidated.

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