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First total synthesis of a new sesquiterpenoid natural product, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone

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Abstract—An efficient and stereodefined process is described for the first preparation of a new prenyl-benzoylfuranone type sesquiterpenoid, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone. The synthetic strategy is based on nucleophilic addition of organometallic reagents to the functionalized ketoamides elaborated from dihydroxyacetone dimer for the stereoselective construction of the key quaternary carbon center in the target compound. © 2003 Elsevier Science Ltd. All rights reserved.

3-(2,4-Dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone (**1**) together with two structurally related furanyl-substituted compounds, **2** and **3**, was isolated in 1999 by Kojima and co-workers[1] from the roots of *Ferula ferulioides* (Steud.) Korovin (Umbelliferae), which grows in Bulgan Somon of Hovd City, Mongolia (Fig. 1). Closely related new sesquiterpene phenylpropanoids, pallidones, were also isolated in 2000 from the roots of *Ferula pallida* (Umbelliferae).[2] These natural products have been used as a traditional medicine for the treatment of spasm[1] for a long time and were revealed to be a new class of prenyl-benzoylfuranone type sesquiterpenoid derivatives possessing contiguous three stereogenic centers along with a quaternary carbon in the lactone ring after structural characterization by the same group based on comprehensive spectral analysis. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, no report has appeared to date despite those pharmacological activities and attractive structural features. The central feature of this communication is to report the details of the first and expeditious route from dihydroxyacetone dimer for the stereoselective construction of the tetrasubstituted lactone ring with a quaternary carbon center and the total synthesis

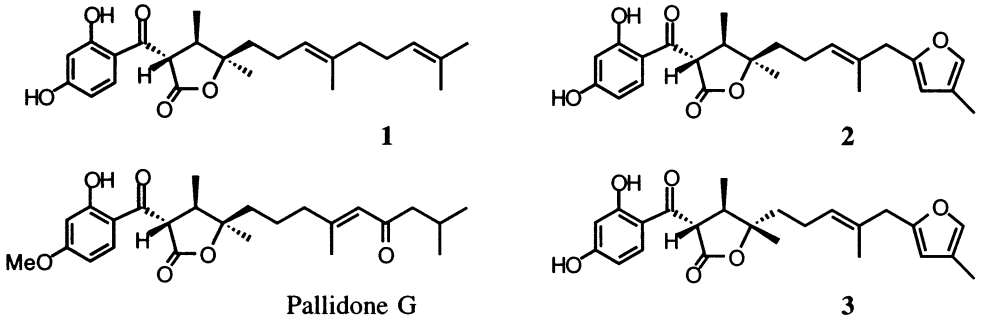

Figure 1.

Keywords: sesquiterpenoid; benzoylfuranone; nucleophilic addition; terpene lactone; dihydroxyacetone.
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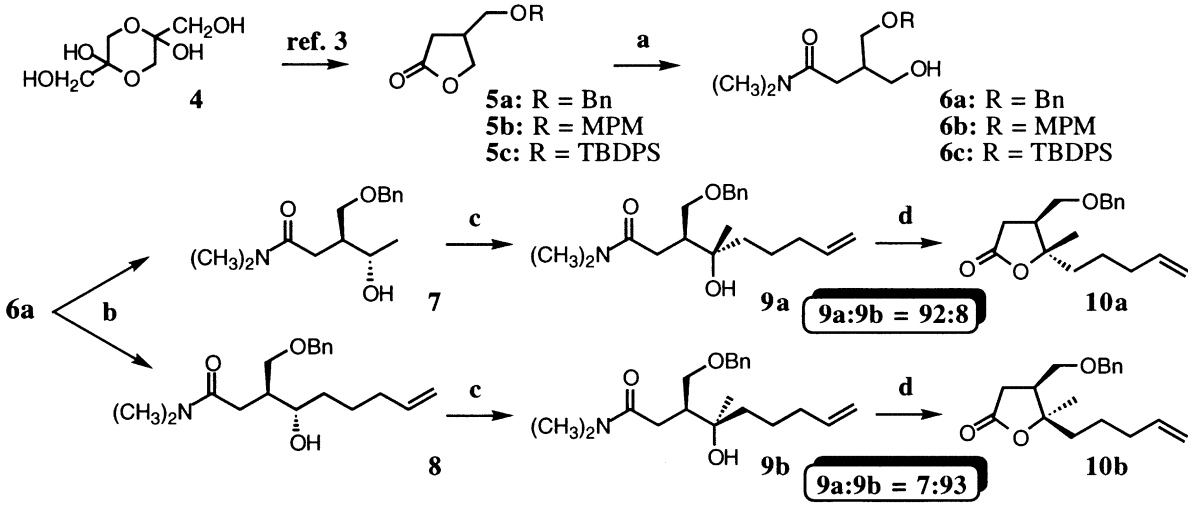
of (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone natural product (**1**).

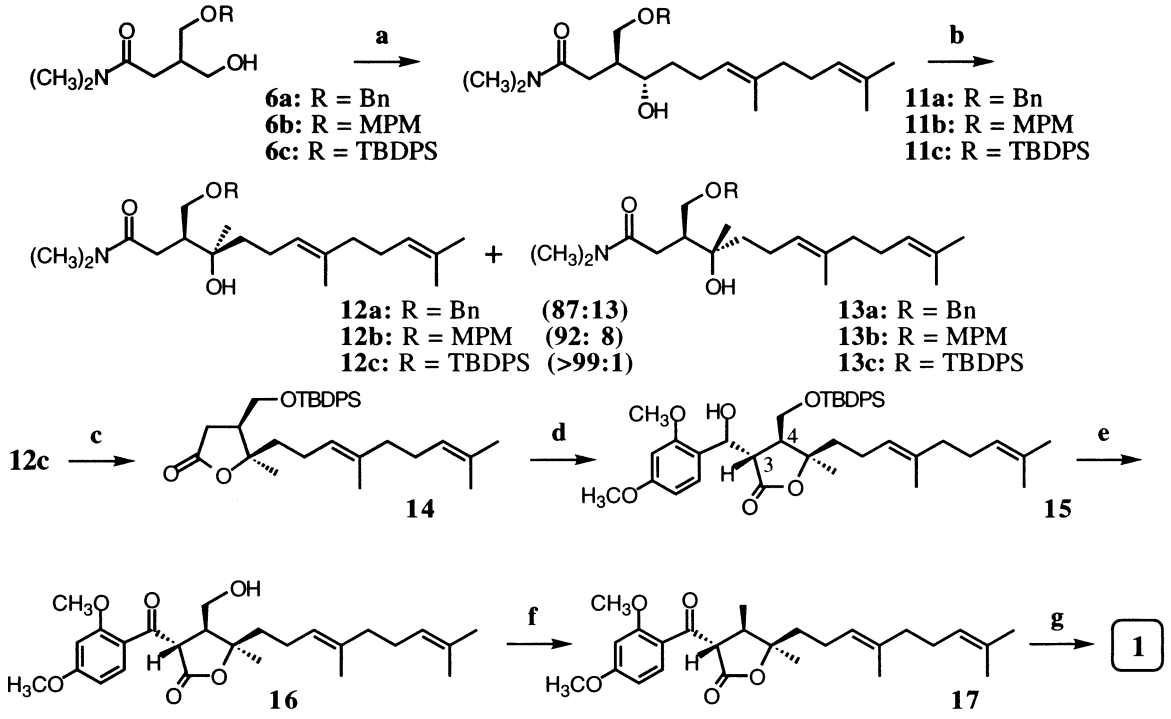
As shown in Scheme 1, the protected mono-terpene lactones **5**, key starting compounds for the synthesis of these terpenoids, were easily prepared from dihydroxyacetone dimer **4** according to our reported procedure.[3] Aminolysis of **5** with Me_2NH opened the lactone ring to give amide alcohols **6** in high yields. Initial experiments have been performed with **6a** in expectation of the stereoselective construction of the quaternary carbon center. Swern oxidation of **6a** followed by the nucleophilic addition of methyl- or pentenyl Grignard reagent in situ gave the amide alcohol **7** and **8**,[4] as a predominant product,[5] respectively. After oxidation with PCC, we were delighted to find that the second alternating Grignard addition to the ketone intermediates in the presence of $CeCl_3$[6] could effect these reactions to afford the desired products **9a** and **9b** in a reverse stereoselective manner[7] at the quaternary center (the former; **9a**:**9b** = 92:8 and the latter; **9a**:**9b** = 7:93, determined by HPLC). These compounds were smoothly cyclized to the corresponding trisubstituted lactones **10a** and **10b**, respectively. Stereochemical results thus obtained can be easily explained in terms of the thermodynamically more stable Cram's non-chelation transition model.[4]

With the above stereochemical outcome in hand, we turned our attention to the total synthesis of (±)-**1**. To begin with, successive treatment of **6a** with Swern oxidation reagents, homogeranylmagnesium bromide elaborated from geraniol in six steps,[8] and PCC, followed by the addition of the second methylmagnesium bromide as described above afforded the amide alcohol **12a** through **11a** as a predominant product with moderate stereoselectivity (**12a**:**13a** = 87:13, determined by HPLC) (Scheme 2). After investigation with three types of mono-protected amide alcohols **6**, a surprising enhancement in stereoselectivity was finally observed upon employing **6c** with the largest TBDPS(*t*-butyldiphenylsilyl) group, leading to the desired isomer **12c** as the single product (determined by HPLC and ^{13}C NMR analysis). Cyclization of **12c** under mild conditions gave the trisubstituted lactone **14** in 76% yield without silyl-deprotection. **14** thus obtained was effected by coupling reaction with 2,4-dimethoxybenzaldehyde in the presence of LiHMDS at low temperature to produce the 3,4-*trans*-adduct **15** alone,[9] including the almost equivalent of stereoisomers at the benzyl position[4] (determined by ^{13}C NMR). Then, **15** was submitted to PCC oxidation again followed by deprotection with Bu_4NF to provide the lactone alcohol **16** in moderate yield. Whereas the deoxygenation reaction of the primary alcohol in **16** with phenylchlorothionoformate[10] or thiocarbonyldiimidazole[11] gave inseparable mixtures, use of Et_3B–Bu_3SnH[12] in the presence of O_2 at 0°C after bromination of the hydroxyl group with CBr_4–PPh_3 dramatically changed the results and brought about the desired deoxygenated product **17** in satisfactory yield. Finally, **17** was subjected to deprotection with Me_3SiI to complete the total synthesis of (±)-**1**. The spectral data of synthesized **1** were completely identical with those of the reported natural compound.[1]

In summary, this work constitutes the first synthesis of the naturally occurring prenyl-benzoylfuranone type of sesquiterpenoid through stereoselective construction of the tetrasubstituted lactones containing a quaternary carbon center from mono-terpene lactones and verifies the structure proposed in the literature for this compound.



Scheme 1. *Reagents and conditions*: (a) Me_2NH, THF; 86% (**6a**); 90% (**6b**); 92% (**6c**); (b) (i) $(COCl)_2$, DMSO, THF, then Et_3N, −78 to −45°C; (ii) methylmagnesium bromide, THF, 0°C; 62% (**7**) (two steps); pentenylmagnesium bromide, THF, 0°C; 54% (**8**) (two steps); (c) (i) PCC, CH_2Cl_2; (ii) pentenylmagnesium bromide, THF, $CeCl_3$, −78°C; 53% (**9a**) (two steps); methylmagnesium bromide, THF, $CeCl_3$, −78°C; 43% (**9b**) (two steps); (d) *p*-TsOH, benzene, 50°C; 77% (**10a**); 68% (**10b**).



Scheme 2. *Reagents and conditions*: (a) (i) $(COCl)_2$, DMSO, THF, then Et_3N, −78 to −45°C; (ii) homogeranylmagnesium bromide, THF, 0°C; 48% (**11a**); 50% (**11b**); quant. (**11c**) (two steps, respectively); (b) (i) PCC, CH_2Cl_2; (ii) methylmagnesium bromide, THF, $CeCl_3$, −78°C; 50% (**12a**); 70% (**12b**); 76% (**12c**) (two steps, respectively); (c) *p*-TsOH, benzene, 50°C; 76%; (d) LiHMDS, 2,4-dimethoxybenzaldehyde, THF, −78°C; quant.; (e) (i) PCC, CH_2Cl_2; (ii) TBAF, THF; 40% (two steps); (f) (i) CBr_4, PPh_3, CH_2Cl_2; 62%; (ii) Et_3B, Bu_3SnH, O_2, CH_2Cl_2; 66%; (g) Me_3SiI, $CHCl_3$, −20°C; 88%.

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