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Stereoselective Synthesis of 7R-Paeonimetaboline-I; Stereoselective Route Towards Paeoniflorigenone

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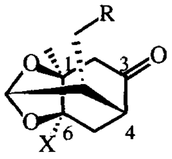
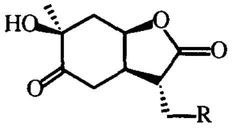
Abstract: Development of a successful synthetic route to the racemic monoterpene 7R-paeonimetaboline-I is reported; extension of this methodology in an approach to synthesis of racemic paeoniflorigenone is also summarized. © 1997 Elsevier Science Ltd.

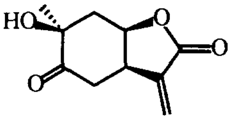
As a result of their intriguing chemical structures and their occurrence in a wide variety of traditional Chinese and Japanese herbal medicines, the monoterpenes in the paeoniflorigenone family recently have been active targets for total synthesis. Prompted by the known use of root extracts of the paeony species *Paeonia Albiflora* PALLAS *var. trichocarpa* BUNGE as an analgesic salve[1] and for the treatment of a variety of other painful afflictions,[2] Japanese researchers have isolated the novel tricyclic monoterpene paeoniflorigenone, **1**,[3] and the structurally-similar bicyclic paeonilactones-A (**2**), -B (**3**), and C (**4**).[4] Related in structure to **1**, the metabolite 7R-paeonimetaboline-I (**5**) has been isolated from bacterial digestion extracts of paeony roots.[5] Study of the pharmacological activity of these materials has shown that **1** causes a blocking effect on the neuromuscular junction in phrenic nerve-diaphragm preparations in mice,[1] and that **4** suppresses both directly and indirectly stimulated muscle twitching of sciatic nerve-sartorius muscle preparations from frogs.[6] Similarly, **5** has been shown to inhibit penetetrazole- and pentylenetetrazole-induced convulsions in rats.[7] As this family of natural products presents such a concentrated array of stereogenic centers and functionality on a highly-oxygenated cyclohexane nucleus, it has generated considerable attention from synthetic chemists. For example, work in our laboratory led to synthesis of **2**, **3**, and **4** in racemic form in 1990,[8] while Japanese colleagues have reported enantiospecific routes to **2**, **3**, **5** and the 7S-epimer of **5** (7S-paeonimetaboline-I[5]) beginning from R-(-)-carvone.[9] Most recently, Hatakeyama, et al. have reported[10] enantiospecific syntheses of (+)-**1** and (+)-**4**, also from R-(-)-carvone, leading us to report on our ongoing work in this area.



1 X=OH, R=$OCOC_6H_5$
5 X=OH, R=H
16 X=H, R=$OCOC_6H_5$



2 R=H
4 R=$OCOC_6H_5$



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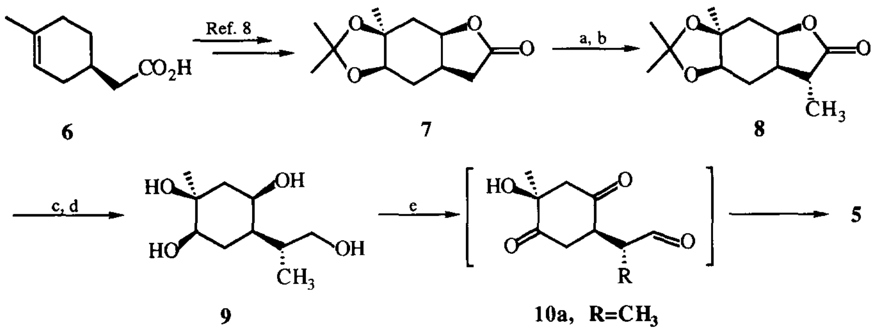
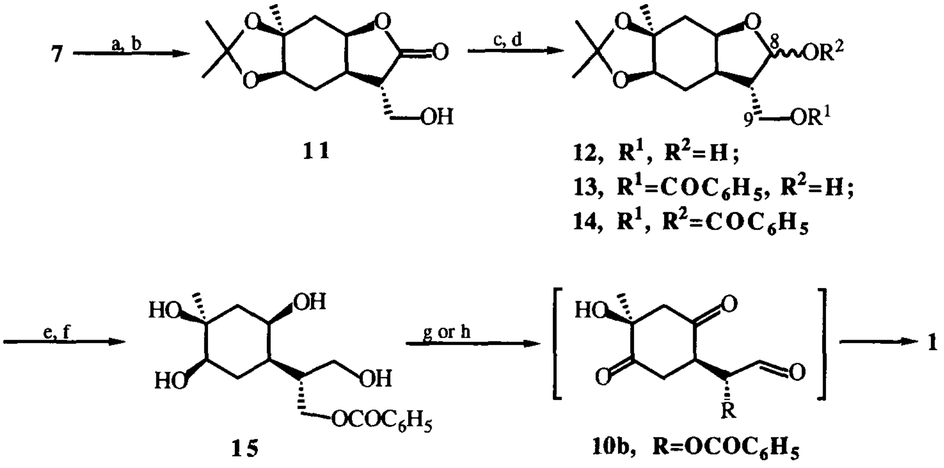
The common thread in our synthetic approaches to **1** and **5** was the preparation of a tertiary alcohol-diketone-aldehyde, of general form **10** (Schemes 1 and 2), that we envisioned would fold, under the proper conditions, to provide the tricyclic acetal-hemiketal structure in the targets. The key requirements for construction of **10** are: a) establishment of a cis-relationship between the C-1 tertiary hydroxyl group and the C-4 side chain; b) placement of ketone moieties at C-6 and C-3 while avoiding aromatization, and c) the flexibility to position either a methyl group, or the benzoate ester of a hydroxymethyl group, at C-7 with the proper R absolute configuration. We set the stage for accomplishing all of these requirements with the synthesis of **7**, the key intermediate in our earlier routes[8] to **2**, **3** and **4**, which is readily available from 4-methyl-3-cyclohexene-1-acetic acid, **6**.[11] The first step in our successful synthesis of 7R-paeonimetaboline, **5**, from **7** was methylation at C-7 (Scheme 1). Lactone enolate generation with LDA was followed by quenching with excess methyl iodide to give methyl lactone **8** (93% yield).[12] As expected, electrophilic attack by methyl iodide was stereoselective for the less sterically encumbered convex face of the lactone enolate, leading to **8** with the desired 7R stereochemistry with >95:5 selectivity (as observed by GCMS). Elaboration via reductive cleavage of the lactone with lithium aluminum hydride (92% yield), liberated primary and secondary hydroxyl groups at C-8 and C-3, respectively. Hydrolysis at reflux under mildly acidic conditions followed, producing tetrol **9**, with exposed tertiary and secondary hydroxyl groups at C-1 and C-6, respectively (83% yield). Final transformation to **5** required oxidation of the secondary alcohols to ketone moieties and of the primary hydroxyl group to its corresponding aldehyde. Our original plan was that all three oxidations could be accomplished under the same reaction conditions and that intramolecular condensation would proceed spontaneously to **5** (presumably *via* intermediate **10a**). Indeed, upon treatment with excess Swern reagent[13] (oxalyl chloride, 4.5 equiv., DMSO, 9.0 equiv., Et_3N, 8.0 equiv.), **9** was observed to produce essentially only the target 7R-paeonimetaboline-I, **5**, albeit in modest yield (45%). Synthetic **5** exhibited spectral properties (^1H-NMR, IR) that matched those reported for natural 7R-paeonimetaboline-I.[5,7] It is noteworthy that the formation of side products via methylthiomethyl ether formation[14] at the C-1 tertiary hydroxyl group (as had complicated our related approaches[8] to **2**, **3**, and **4**) was not observed in this reaction.



Scheme 1: a) LDA, THF, -78 °C; b) CH_3I (93%); c) LAH, Et_2O, 0 °C (92%); d) aq. HCl/THF, reflux (83%); e) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2 -78 °C (45%).

An approach to the synthesis of **1** using an adaptation of this route to **5** was investigated next (Scheme 2). As before, conversion of **7** to its lactone enolate form was accomplished with LDA; subsequent treatment with excess gaseous formaldehyde[15] produced hydroxymethyl lactone **11** (63% yield) with 92:8 selectivity for the desired 7R-epimer (GCMS). Developing a successful strategy for properly adjusting the oxidation states of C-3, C-6, and C-8 while also selectively positioning and maintaining a benzoate ester at the C-9 hydroxyl group proved difficult. In our most effective route, DIBALH reduction of lactone **11**, with inverse addition, proceeded to lactol **12** (77% yield), an intermediate which also was utilized in the synthesis of **1** by Hatakeyama, et al.[10] Lactol **12** was then converted to monobenzoate ester **13** under mild conditions (benzoyl chloride (1.5 eq.), pyridene, 50 °C; 80% yield; both **12** and **13** were present as a 2:1 mixture of C-8 epimers). It should be noted that in the synthetic approach developed Hatakeyama, et al.[10] benzoylation of optically pure **12** under more active conditions (excess benzoyl chloride, Et_3N, DMAP) produced dibenzoate **14** which was then carried on to (+)-**1**. Elaboration of **13** without premature intramolecular acetalization required selective reduction of the C-8 aldehyde, with sodium borohydride, followed by acetonide hydrolysis, with mild aqueous acid, to give tetraol **15** (57% yield, overall). With **15** in hand, the stage was set for final elaboration to **1** *via* oxidation to intermediate **10b**, in analogy to the chemistry presented in Scheme 1. In the event, treatment of **15** with excess Swern reagent (as above), or with $SO_3\cdot$pyr (6 equiv.), under a wide variety of conditions, produced a mixture of products



Scheme 2: a) LDA, THF, -78 °C; b) CH_2O (g) (63%); c) DIBALH, CH_2Cl_2, -78 °C (77%); d) C_6H_5COCl (1.5 eq.), pyr, 50 °C (83%); e) $NaBH_4$, anhyd. CH_3OH, 25 °C; f) aq. HCl/THF, reflux (57%, overall); g) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2 -78 °C; h) $SO_3\cdot$pyr, DMSO, Et_3N, CH_2Cl_2, 25 °C.

with low recovery, none of whose ^{1}H-NMR spectra matched those for **1**. Analysis of spectra of the most abundant of these products identified it as **16** (above), indicating that in this case oxidation at C-6 could not occur before intramolecular acetal formation proceeded, in marked contrast to our experience with oxidation of **9**.

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