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STEREOSELECTIVE SYNTHESIS OF THE PAEONILACTONES A, B AND C

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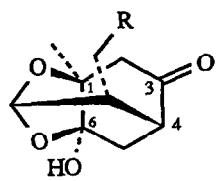
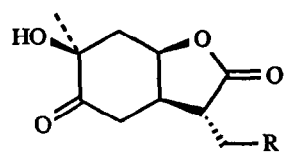
Abstract: The first total syntheses of the title monoterpenes are reported.

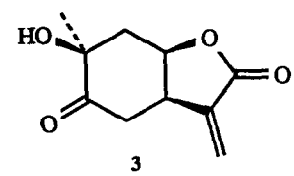
Root extracts from plants of the paeony family have been used extensively in Chinese and Japanese herbal medicine for treatment of a variety of painful afflictions[1] including use in an analgesic salve for soothing muscle pain.[2] Anecdotal evidence of analgesic activity in these extracts has prompted Japanese workers to examine the paeony species *Paeonia Albiflora* PALLAS *var. trichocarpa* BUNGE for pharmacologically active components and has led recently to the isolation of the novel tricyclic monoterpene paeoniflorigenone, **1**,[3] and the structurally related bicyclic systems, the paeonliactones -A (**2**), -B (**3**), and -C(**4**).[4] Pharmacological studies have established that **1** produces a blocking effect on the neuromuscular juction in phrenic nerve-diaphragm preparations from mice,[2] while **4** suppresses both directly and indirectly stimulated muscle twitching of sciatic nerve-sartorius muscle preparations from frogs.[5] Similar in structure to **1**, 7R-paeonimetaboline-I, **5**, a metabolite isolated[6] from bacterial digestion of paeony extracts, inhibits penetetrazole- and pentylenetetrazole-induced convulsions in rats.[7] The interesting anesthetic-like activity of these materials and the unusually high density of stereocenters and oxygen-containing functional groups on their central cyclohexane nuclei makes them challenging targets for synthesis. Herein, we report the first progress made in the synthesis of this monoterpene family with our stereoselective syntheses of the paeonilactones -A (**2**), -B (**3**), and -C (**4**).



1 R=$C_6H_5CO_2$
5 R=H



2 R=H
4 R=$C_6H_5CO_2$



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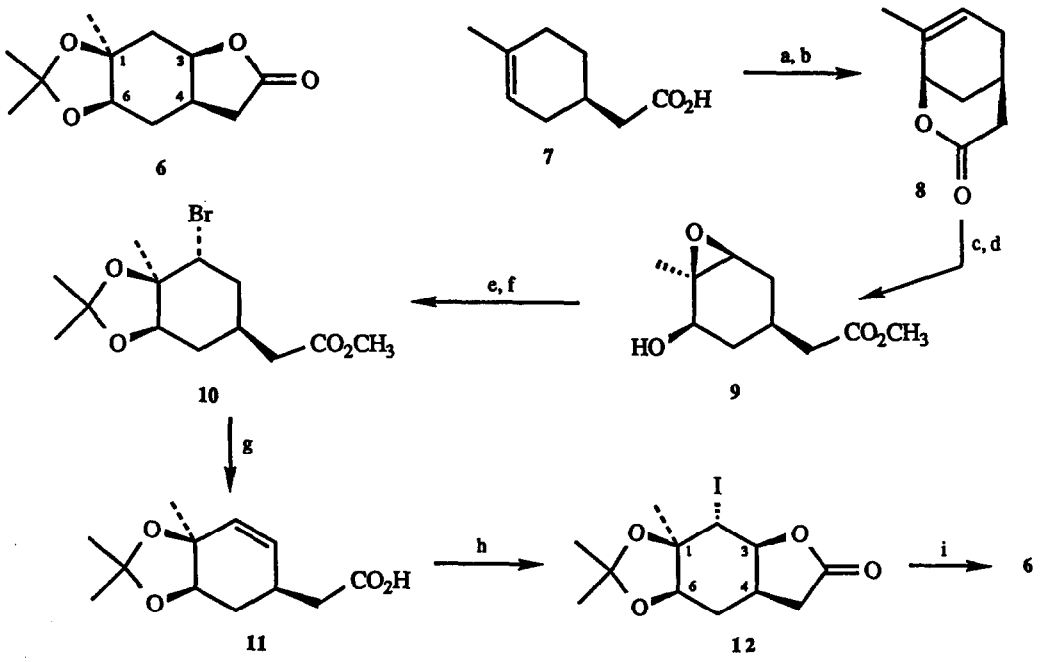
Two central problems confronting synthesis of any member in this class of monoterpenes are exposed in the structure of acetonide-lactone **6**, which we chose as a pivot point in our approach to **2**, **3** and **4**. First is the stereocontrolled establishment of the three cis stereocenters at C-1, C-3 and C-4 on the cyclohexane system and second is the construction of this highly oxidized nucleus under conditions which will avoid aromatization. To surmount these challenges we made electrophilic lactonization reactions[8] central processes in our synthetic approach to **2**, **3** and **4** due to their stereogenic power and inherent mildness. In the first step, kinetic iodolactonization of readily available 4-methyl-3-cyclohexene-1-acetic acid, **7**,[9] using modified bromolactonization condtions of Jew (NIS, KOt-Bu, DMF),[10] accomplished oxygenation at C-6 and set the stage for creating the required C-1 stereochemistry. In this process, the intermediate iodolactone undergoes KOt-Bu-mediated elimination during *in vacuo* concentration of the crude reaction mixture, producing the δ-lactone-olefin **8** in 99% yield (≤ 5% isomeric material, PMR).[11] Classical aqueous iodolactonization conditions (I_2, KI, $NaHCO_3$)[12] gave lower yields (31-48%; yield of iodolactone), while thermodynamic condtions (I_2, KI, CH_3CN),[13] which are acidic, resulted in aromatization.

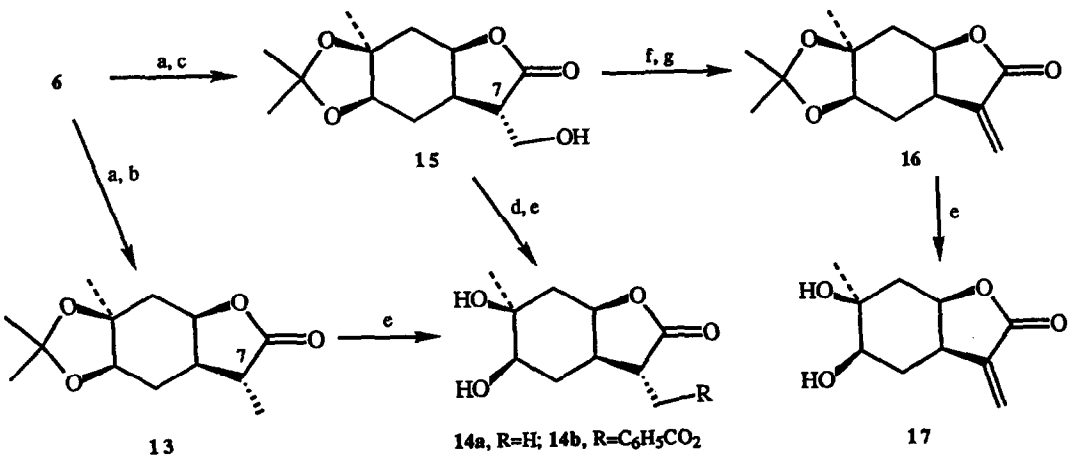


CONDITIONS: a) NIS, KOtBu, DMF; b) rotary evaporation, 50 °C (99% overall); c) Na_2CO_3, CH_3OH (88%); d) MCPBA CH_2Cl_2, 0 °C (96%); e) TMSBr, Ph_3P, $CHCl_3$, -30°C (74%); f) 2,2-dimethoxypropane, acetone, pTSA (87%); g) KOtBu, DMF, reflux (97%); h) $NaHCO_3$, KI, I_2, H_2O (82%); i) nBu_3SnH, THF, reflux (95%).

Since the C-6 hydroxyl in **8** necessarily had been introduced cis to the C-4 center during iodolactonization, this group could be used to direct oxygenation at C-1 cis to the C-4 center. This was accomplished by methanolsis of **8**, followed by MCPBA epoxidation of the intermediate allylic alcohol, to give epoxy-alcohol **9** as a single isomer (PMR) in 85% overall yield. That epoxidation had occured under the stereochemical direction of the C-6 hydroxyl , following the precedent for conformationally-locked cyclohexenols,[14] could be demonstrated by conversion of **9** to acetonide **10**. In a two step process, epoxide **9** was cleaved with TMS-Br,[15] to give a bromo-diol, which was immediately subjected to ketalization. Isolation of **10** (64% overall yield) confirmed both that epoxide cleavage had produced a cis-diol and that epoxidation had proceeded cis to the C-6 hydroxyl. Treatment of the protected cis-diol-bromide **10** with excess KOt-Bu in refluxing DMF then accomplished halide elimination with concomitant ester cleavage affording olefin-acid **11**. Attempted bromide elimination without prior ketalization of the diol system simply resulted in reversion to epoxide **9**. Although obviously stable to basic conditions, **11** was extremely acid-sensitive and aromatized if the acidification step in the workup of the elimination/saponification reaction was not conducted with extreme care at 0 °C.

Elaboration of **11** to our key intermediate lactone **6** utilized a second iodolactonization reaction to oxygenate C-3 with the required cis stereochemistry. Although slow (3 days, 25 °C), classical conditions were found to be the most efficient and produced **12** (82% yield) containing a γ-lactone, as expected under kinetic conditions. Finally, reductive dehalogenation of **12** with tri-n-butyl tin hydride[16] produced lactone **6** (95%) yield .

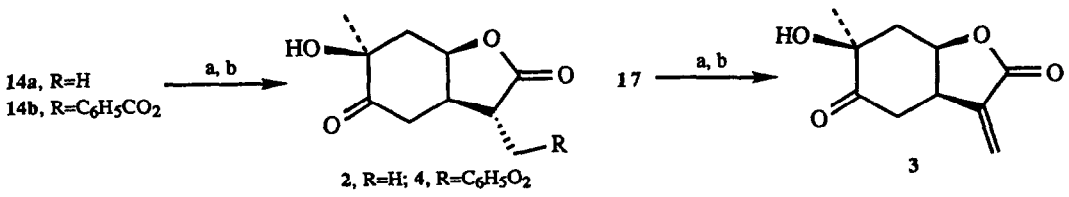
After conversion of **6** to its lactone enolate, elaboration to the target monoterpenes followed either of two paths: enolate reaction with excess methyl iodide gave methyl lactone **13** (93% yield); reaction with excess gaseous formaldehyde[17] gave hydroxymethyl lactone **15** (63% yield). It was anticipated that these substitutions would be stereoselective for the corresponding 7R-substituted products at the lactone α-carbon since the convex face of the lactone enolate should be more accessible to electrophiles. In each case, high selectivity was observed (GCMS: **13**, 95:5; **15**, 92:8) and 7R-configuration was confirmed by conversion to the final targets. Next, hydroxymethyl lactone **15** served as a branch point in parallel routes to **3** and **4**. In the route to **3**, benzoylation of **15** was followed by acetonide hydrolysis in a mildly acidic medium to give the deprotected benzoate ester **14b** (68% overall). Similarly, in



CONDITIONS: a) LDA, THF, -78 °C; b) CH_3I (93%); c) CH_2O (g), -40 °C (63%); d) C_6H_5COCl, pyr (76%); e) HOAc/THF/H_2O (1/1/1), reflux (yields: **13**, 98%; **15**, 89%; **16**, 82%); f) CH_3SO_2Cl, pyr; g) pyr, reflux (83% overall).

the route to **4**, mesylation and mesylate elimination proceeded under literature conditions[18] to construct the protected α-methylene lactone **16** (83% overall), and ketal cleavage under identical conditions gave the corresponding diol **17** in 82% yield. The same hydrolysis conditions with **13** produced diol **14a** in 98% yield.

Final conversion of the intermediate diols **14a**, **14b**, and **17** to each of the corresponding targets **2**, **4**, and **3** required only oxidation of the C-6 hydroxyl to a ketone. In each case, this was accomplished with the mild conditons of Swern[19a] (oxalyl chloride, 2.2 equiv.; DMSO; Et_3N, -78 °C). Although successful, these oxidations were complicated by conversion of roughly half of the products into the corresponding methylthiomethyl ethers of the C-1 tertiary hydroxyl groups.[20] Formation of these common Swern oxidations side-products[19b] could be reversed by exposure of the crude product mixtures to MTM-ether cleavage conditions.[21] For example, the crude product from Swern oxidation of **14a** was isolated and treated immediately with excess mercury(II) chloride and cadmium carbonate in aqueous acetonirile.[21] Upon reisolation and chromatography on silica gel, paeonilactone A, **2**, was obtained in



CONDITIONS: a) oxalyl chloride, DMSO, triethylamine, -78 °C; b) $HgCl_2$, $CdCO_3$, CH_3CN/H_2O (10/1), 60-70 °C; overall yields: **14a**, 51%; **14b**, 60%; **17**, 83%.

51% overall yield. In similar fashion, **14b** and **17** were converted to the paeonilactones -C, **4**, and -B, **3**, in overall yields of 60% and 83%, respectively. The PMR (200 MHz) and infrared spectra of synthetic racemic **2**, **3** and **4** were identical with those previously published.[4] Conversion of the intermediate substituted lactones **15** and **13** to paeoniflorigenone, **1**, and 7R-paeonimetaboline-I, **5**, respectively, are under way and will be reported in a future publication

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