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Diastereoselective and Highly Efficient Radical Approach to (1S,6R) and (1R,6S)-2,2,6-trimethyl-3-oxabicyclo[4.2.0]octadecane, Key Intermediates in the Synthesis of (+) and (-)-Grandisol

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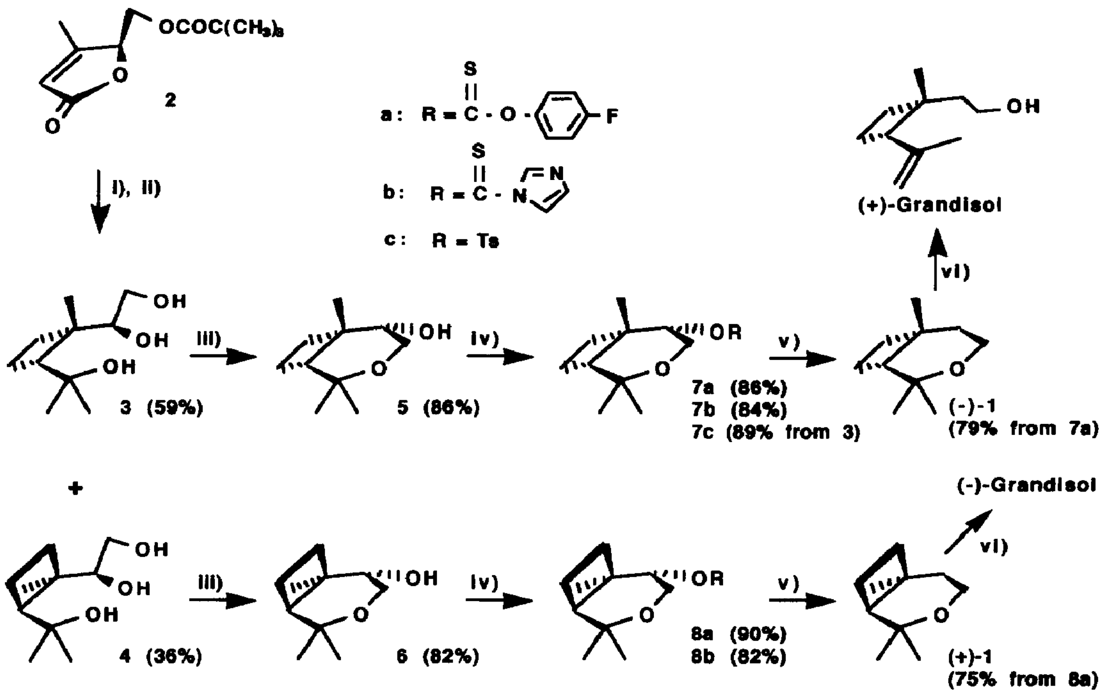
Abstract: The pure enantiomers (1S,6R) and (1R,6S)-2,2,6-trimethyl-3-oxabicyclo[4.2.0]octadecane, key intermediates in the synthesis of (+) and (-)-grandisol are prepared by a highly efficient radical deoxygenation under mild conditions of secondary hydroxyl groups.

The academic target of a high yielding total synthesis of (+)-grandisol and the need for an economically viable preparation for the control of pest insects in agriculture are the reasons for the many syntheses of this pheromone reported to date.[1,2] Recently, yields of ~ 20% have been claimed in some asymmetric approaches.[3] We have reported a highly efficient approach via a diastereoselective [2+2] photocycloaddition of ethylene to an easily available butenolide, being 28% the yield of the formal synthesis of (+)-grandisol.[4] On the other hand, Barton and McCombie demonstrated that secondary alcohols can be deoxygenated in high yield by reduction of suitable thiocarbonyl derivatives at 80-110°C with a trialkyl tin hydride.[5] This deoxygenation proceeds via free radical intermediates and avoids the common side reactions when carbocations are involved, such as rearrangements and eliminations; it also circumvents the steric hindrance and the dipole repulsion that appear in the ionic S_N reactions. We wish to report here a new and highly efficient synthesis of the key intermediates (-)-**1**, and its enantiomer (+)-**1** that have been already described as immediate precursors of (+) and (-)-grandisol respectively. The overall yields are 34% for (-)-**1** (lit:[3b] 25%), and 20% for (+)-**1** (lit:[3b] 17%). The starting material for both is the easily available butenolide **2**.[4]

We have described the diastereoselective photocycloadditition of ethylene to butenolide **2** and the subsequent alkylation with MeLi of the two cycloadducts obtained after their easy separation by flash column chromatography (see scheme).[4] Cyclization of the triols **3** or **4** is accomplished with 1.2 equivalents of TsCl to yield the free alcohols **5** ($\{\alpha\}_D$ -76.51, c:1.32 in $CHCl_3$) and **6** ($\{\alpha\}_D$ +4.56, c:1.09 in $CHCl_3$) respectively; an excess of TsCl over **3** affords **7c** ($\{\alpha\}_D$ -30.85, c:1.75 in $CHCl_3$). To accomplish the Barton and McCombie reduction two different thiocarbonyl derivatives of **5** and **6** are prepared. Treatment of **5** with 4-fluorophenyl chlorothionoformate affords **7a** ($\{\alpha\}_D$ -58.49, c:1.265 in $CHCl_3$), while reaction with *N,N'*-thiocarbonyldiimidazole (TCDI) affords **7b** ($\{\alpha\}_D$ -113.11 , c:1.27 in $CHCl_3$). In a similar way **6** affords **8a** ($\{\alpha\}_D$ +32.0, c:1.00 in $CHCl_3$) and **8b** ($\{\alpha\}_D$ +15.68, c:1.275 in $CHCl_3$). According to the standard procedure, the thiocarbonyl derivatives were heated with tributyltin hydride in refluxing toluene but the yields of the deoxygenated product (-)-**1** ($\{\alpha\}_D$ -19.84, c:1.31 in $CHCl_3$) were only 32% from **7a**. In a similar way, (+)-**1** ($\{\alpha\}_D$ +18.82, c:0.42 in $CHCl_3$) was prepared with low yield from **8a** (60%). We explored different experimental conditions and found that by lowering the temperature of the reaction to 90°C and adding slowly the thiocarbonyl derivatives to the hydride, the yields increased up to 79% (from **7a**) for (-)-**1** and 75% (from **8a**) for (+)-**1**. The overall yields of (-)-**1** and (+)-**1** from the starting butenolide **2** are 34% and 20% respectively. All the described stereoisomers showed 99% enantiomeric purity as checked by chiral glc.



SCHEME: i) CH_2=CH_2 / hv / acetone; ii) MeLi / THF; iii) TsCl / pyridine; iv) a: 4-fluorophenylchlorothionoformate / C_6H_6, b: TCDI / THF; v) Bu_3SnH, AIBN / toluene / Δ; vi) lit.[6]

To summarize, the radical deoxygenation described here leads to both optically pure enantiomers of 1 with overall yields higher than previously described.[3b,4] Since both have been already converted to (+) and (-)-grandisol, our work is a formal synthesis of the pheromone component of Boll weevil (*Anthonomous grandis*), and its enantiomer, with an equivalent overall yield of 33% for (+)-grandisol and 19% for (-)-grandisol.

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