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A STEREOSPECIFIC SYNTHESIS OF (±)-GRANDISOL VIA AN INTRAMOLECULAR LACTONE ENOLATE ALKYLATION: A REMARKABLE REGIODIVERGENCE IN C- VS O-ALKYLATION

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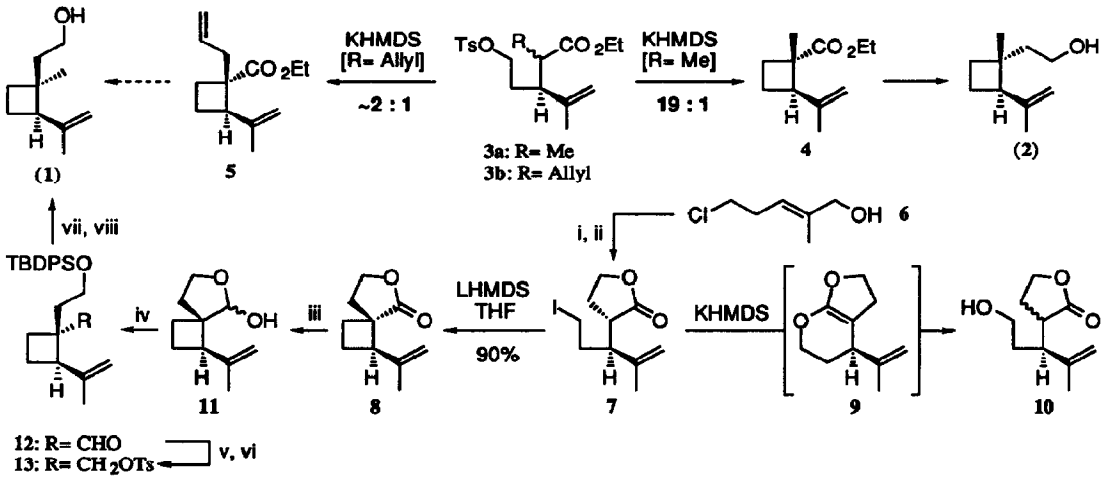
Abstract: (±)-Grandisol (**1**) has been synthesized in a stereospecific manner by an intramolecular lactone enolate alkylation route featuring remarkable control over C- vs O-alkylation.

(+)-Grandisol (**1**), a pheromone component of the male cotton boll weevil (*Anthonomus grandis*), has long been an attractive synthetic target owing to its remarkable biological activity coupled with an interesting molecular structure.[1] Described herein is a stereospecific approach to (±)-grandisol (**1**) based on our 'allylic strain-controlled'[2] and 'folding strain-controlled'[3] intramolecular lactone enolate alkylation methodology, highlighted by a remarkable regioselective C-alkylation.



Reagents: i) diethyl ortho-γ-butyrolactone, $CH_3CH_2CO_2H$ (cat.), 170 °C, 15 h (57%); ii) NaI, MEK, reflux, 24 h (94%); iii) DIBALH (1 eq), toluene, -78 °C, 1 h (75%); iv) TBDPSCl (2 eq), imidazole (2 eq), DBU (cat.), DMF, rt, overnight (90%); v) $NaBH_4$ (1.5 eq), EtOH, rt, 15 min (70%); vi) TsCl (2 eq), DMAP (2.5 eq), CH_2Cl_2, 4 °C, 12 h (100%); vii) $LiEt_3BH$ (3 eq), THF, reflux, 16 h (80%); viii) TBAF (1 eq), THF, rt, 1 h (100%).

In our previous synthesis of (±)-fragranol (**2**), a diastereomeric monoterpene isolated from *Artemesia fragranas*, intramolecular ester enolate alkylation of ω-tosyl ester **3a** with KHMDS afforded cyclobutanecarboxylate **4** with 19 to 1 stereoselectivity in 85% yield.[4] However, cyclization of the corresponding allyl ester **3b** under comparable conditions furnished allyl ester **5**, a potential synthetic

intermediate for (±)-grandisol (**1**), in only 2 : 1 stereoselectivity.[5] Envisioning that the stereoselectivity might be enhanced in the case of cyclic enolates, cyclization behavior of ω-iodo lactone **7**, prepared from chloro allylic alcohol **6** in two steps by ortholactone Claisen rearrangement followed by a Finkelstein reaction, was investigated. Unfortunately, subjection of iodo lactone **7** to our usual cyclization condition (i.e., KHMDS in THF) did not produce any desired spiro lactone **8**, but careful analysis of reaction mixture revealed the presence of hydroxyl lactone **10** in 50% yield.[6,7] Formation of hydroxy lactone **10** could be rationalized by internal O-alkylation of the potassium enolate of lactone **7** to form unstable cyclic ketene acetal **9**, followed by hydrolysis. After a considerable amount of experimentation, our attention was drawn to using the more tightly associated lithium enolate, which is known to favor C-alkylation compared to its potassium counterpart.[8] To our delight, iodo lactone **7** underwent smooth cyclization upon treatment with LHMDS in THF at -78 to -50 °C for 4 h to furnish the desired product **8** as a single stereoisomer in 90% yield.[6] This result constitutes a unique example of regiodivergence in C- vs O-alkylation during an intramolecular ester enolate alkylation. Finally, transformation of spiro lactone **8** into (±)-grandisol (**1**) was successfully executed by proper adjustment of oxidation state. Thus, DIBALH reduction of lactone **8**, followed by treatment of the resulting lactol **11** with TBDPSCl in the presence of DBU, afforded aldehyde **12** in 68% overall yield for the two steps. $NaBH_4$ reduction of aldehyde **12** and tosylation of the alcohol gave tosylate **13**. $LiEt_3BH$ reduction of tosylate **13** proceeded with minimal sulfur-oxygen bond cleavage leading to the desired (±)-grandisol (**1**) after removal of the TBDPS protecting group with TBAF (56% overall yield for four steps).[9,10] The synthetic (±)-grandisol had ^1H and ^{13}C NMR data identical to those reported in the literature.[1,11]

In summary, a stereospecific synthesis of (±)-grandisol (**1**), a cyclobutanoid monoterpene, was accomplished by an intramolecular lactone enolate alkylation featuring control of C- vs O-alkylation by judicious choice of leaving group and cation.

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5. Unpublished results with Y. K. Lee.
6. All new compounds exhibited satisfactory spectroscopic data. The ratio of stereoisomers was determined by capillary g. c. analysis (0.25 mm i.d. x 30 m length DBWAX, 100 to 200 °C) and/or rigorous analysis of 400 and 500 MHz ^1H NMR spectra.
7. Cyclization of the tosylate corresponding to **7**, which was prepared via a different route, with KHMDS and LHMDS led to the formation of hydroxy lactone **10** and a complex mixture, respectively.
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10. More direct conversion of lactol **11** to (±)-grandisol (**1**) by a Wolff-Kishner reduction was unsuccessful.
11. We thank Professor Kenji Mori (University of Tokyo) for copies of reference spectra of grandisol.

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