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Synthesis of Sex Pheromone 3,5-cis-Dimethyl-6-trans-isopropyl-3,4,5,6-tetrahydropyran-2-one

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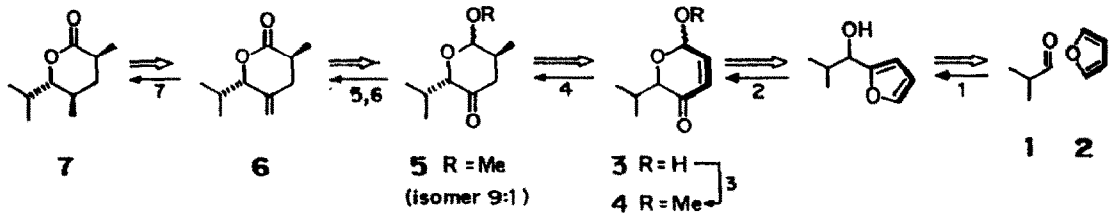
Abstract: *An expeditious stereoselective synthesis of sex pheromone (±)3,5-cis-dimethyl-6-trans-isopropyl -3,4,5,6-tetrahydropyran-2-one of larval parasitoid M. grandii, from readily available isobutyraldehyde and furan is described.*

Pheromones, allomones and kairomones are chemical substances that trigger inter-and intraspecific communication in a variety of bioorganisms eg. flies, moths, cockroaches, beetles, weevils, rootworms, ants and bees etc.[1] Much of their application involves control of behavior of these species and their developmental processes. Recently, a new and interesting aspect of the sex pheromone, secreted by the larval parasitoid *Macrocentrus grandii*, has been uncovered.[2,3] Thus, *M. grandii* have been shown to be effective in controlling the population of European corn borer *(Ostrimia nubilalis)*.[4,5] Naturally, a stable and increasing population of *M. grandii* will be highly valuable to control European corn borer, in an environmentally friendly way, to solve agricultural problems. Since the population of *M. grandii* is dependent on parasitoid courtship behavior, which in turn is related to the sex pheromone 3,5-cis-dimethyl-6-trans isopropyl-3,4,5,6-tetrahydropyran-2-one (7), an expeditious synthesis of 7 is highly desirable.[2,3] Here, we report an efficient, stereoselective, seven step strategy to assemble the desired pheromone from readily available isobutyraldehyde and furan.



Reagents: 1. Furan 2, n-BuLi (1.2:1eq), THF, 0° C, 20min., r.t. 5h (96%); 2. MCPBA (1.35eq), CH_2Cl_2, 5-7° C, 15min, r.t. 6h (85%, 3:1 ratio); 3. MeI (2.5eq), Ag_2O (1.15eq), acetone, r.t. 24h (92%, 3:1 ratio); 4. MeLi (3eq), CuI (1eq), Ether, 0°C, 1h (96%); 5. $Ph_3P^+CH_3Br^-$, n-BuLi (1.1eq), benzene, r.t. 2h (94%); 6. Jone's oxidation, 0° C, 20min. (96%); 7. H_2 (65parr), 10% Pd-C, Ethyl acetate, r.t. 10h, (85%).

The retrosynthesis and synthesis of the target pheromone is shown above. The essential features of our retro-analysis was the presumption that regioselective cuprate addition to protected 5,6-dihydropyran-2-one (4) would occur predominantly trans to isopropyl group, and catalytic reduction of the olefin 6 would be stereoselctive,

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Dedicated to Prof. S. Ranganathan on the occasion of his 60th birthday.

where isopropyl and regenerated methyl would be trans to each other. The only suspicion for this strategy was the Wittig step from **5**, where considerable steric interaction due to isopropyl group was anticipated. The anomeric stereoisomer distribution at 2 position throughout the synthetic scheme (**3-5**) was not a problem, as ultimately an oxidized ketone was required.

The detailed information regarding the reagents, molar ratio, solvent, and reaction conditions, followed by usual work up, is provided in Scheme-1. The synthesis of the main skeleton **3** was quantitative, starting from isobutyraldehyde and furan, followed by MCPBA oxidation. Similar transformation have been efficiently employed by Martin's group.[6] After, protection of anomeric hydroxyl with methyl iodide and silver oxide, cuprate addition in THF gave regio- and stereoselective introduction of methyl group in a quantitative yield.[7,8] The ratio of stereoisomers was 9:1 (major isomer depicted as **5**), and both could be separated by column chromatography (app. Rf of minor and major isomers in 4% acetone:pet.ether was 0.8 and 0.9 respectively). Indeed, the major isomer was the desired **5** which is expected as per lit. precedence[7] and by the coupling constant of cis methine protons adjacent to methyl and methoxy.[9] Contrary to our suspicion, the Wittig olefination of major isomer **5** was efficient (94%). Subsequently, oxidative deprotection of anomeric hydroxyl with Jone's reagent, followed by catalytic reduction in ethylacetate with 10% Pd-C gave, once again, a quantitative yield of the desired pheromone **6**.[10,11]

The above strategy is prone to modification for enantioselective manipulations. Currently, we are planning to synthesize Prelog-Djerassi lactone[12] and related natural products via this strategy.

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8. All new compounds gave satisfactory spectroscopic data. Selected spectral data for **5** and **6** are as follows: **5** (major isomer): IR (neat) : 1730cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 0.85 (3H, d, J=7Hz), 1.03 (3H, d, J=6Hz), 1.17 (3H, d, J=6Hz), 2.32 (1H, d, J=3Hz), 3.45 (3H, s), 3.88 (1H, d, J=4Hz), 4.55 (1H, d, J=3Hz); MS m/e (% abundance) 186 (M^+, 30), 170 (40), 155 (20), 144 (35), 139 (100).
6 IR (neat): 1735 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (3H, d, J=7Hz), 1.07 (3H, d, J=6Hz), 1.25 (3H, d, J=6Hz), 4.9 (1H, d, J=2Hz), 5.1 (1H, d, J=2Hz); MS m/e (% abundance) 168 (M^+, 40), 155 (45), 144 (15), 137 (15).
9. The coupling constant of two cis vicinal protons adjacent to methyl and methoxy in the major anomer **5** was 3Hz, indicating a trans relationship between methyl and isopropyl. The isopropyl and methoxy are trans to each other in the major anomers of **3** and **4**.
10. Identical ^{1}H-NMR, IR, ^{13}C-NMR and MS of the desired pheromone were obtained[11].
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