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A SHORT, STEREODIVERGENT SYNTHESIS OF THE RACEMIC ERYTHRO AND THREO DIASTEREOMERS OF 6-ACETOXY-5-HEXADECANOLIDE, A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE

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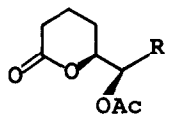
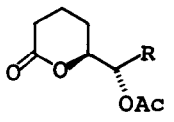
Summary. A versatile 3-step synthesis of the title lactones has been accomplished by the stereocontrolled addition of *n*-decylmetallic reagents to acrolein dimer.

erythro-6-Acetoxy-5-hexadecanolide (1) has been identified as the major component of the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*.[1] This species occurs worldwide, but particularly in tropical regions where it is believed to be a vector for potentially fatal diseases such as malaria and filariasis. Several syntheses of the enantiomers of 1 and its threo isomer 2 have been reported,[2] but they all suffer from various drawbacks. They either require uncommon reagents and intermediates or entail many steps giving low overall yields. Consequently, a need exists for a simple practical synthesis of 1 and 2 so that their potential utility for mosquito control can be evaluated by entomologists.[3] Moreover, optical purity is not necessary as the biological activity of the synthetic racemic mixture is similar to that of the natural product.[1]



erythro
1

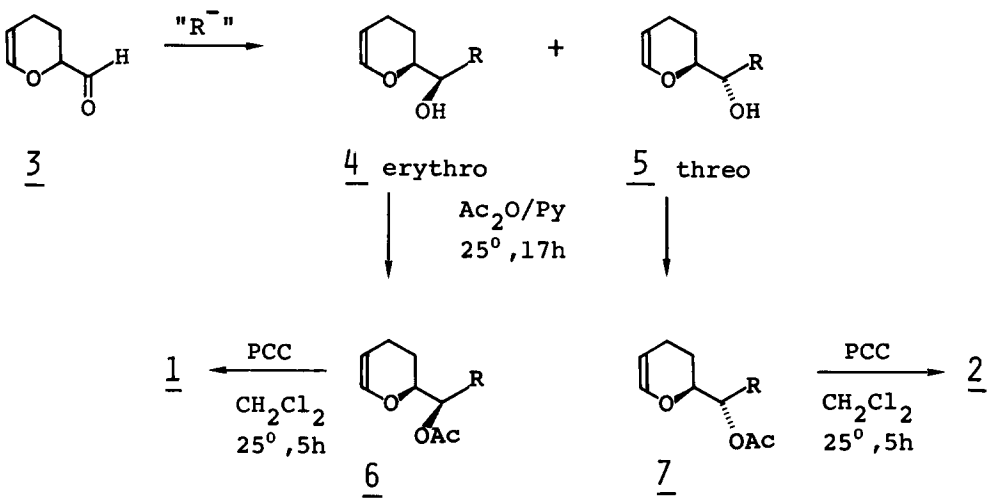


threo
2

R = n-decyl

We now describe a short stereodivergent synthesis of 1 and its threo isomer 2 which have the advantage of starting from a cheap, commercially available material, acrolein dimer (3).[4] The essence of the method consists of the diastereogenic addition of *n*-decylmagnesium bromide to 3. The general result is that the corresponding erythro 4 and threo 5 alcohols form in high yield depending on the temperature, but in roughly equal amounts (Table, entries 1 and 2). However, by appropriately choosing the conditions either one or other of the diastereomers (4 or 5) can be highly favored. The conditions are dictated by a consideration of the two limiting transition states which arise by nucleophilic attack on the diastereotopic faces of the carbonyl group. Cram's cyclic model[5] predicts predominant formation of the threo isomer 5, whereas the Cornforth dipolar[6] and the Felkin-Anh[7] models both favor the erythro isomer 4.

Scheme



Although the conformations preferred by 3 in the contiguous and opposed arrangements of oxygen atoms required by the cyclic and dipolar models are not known,[8] it can be assumed that steric differentiation towards a nucleophile (R^-) will be the same in both cases (Fig.). Therefore, the stereochemical outcome may be manipulated by suppressing or enhancing chelation.[9,10] In fact, when an excess of Grignard reagent was used (entry 3), a perceptible shift of the erythro-threo ratio (0.59) was observed, presumably owing to greater chelation caused by the magnesium derivative, thereby favoring Cram's model. This tendency was confirmed, when zinc bromide[11] was used in conjunction with excess Grignard reagent (entry 4). However, increased threo selectivity (0.18) was obtained at the expense of yield (20%). A more satisfactory result was provided by the *n*-decylcopper magnesium halide,[12] which furnished mainly the threo isomer (0.11) in high yield.

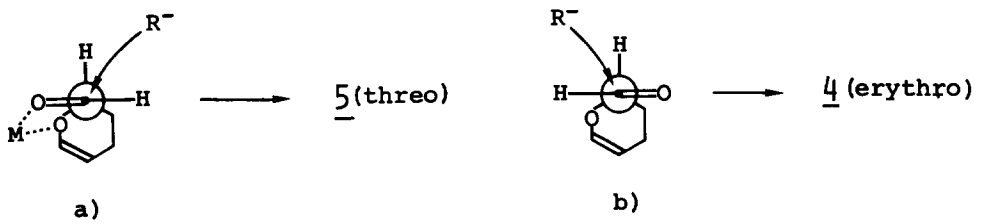


Fig. Contiguous (a) and opposed (b) arrangements of oxygen atoms in 3 favoring formation of threo 5 and erythro 4 alcohols

Table. Addition of *n*-Decylmetallic Reagents to Acrolein Dimer (3) to form alcohols 4 and 5.

Entry	Reagent[a]	No of equiv	Conditions	Yield[b] %	Erythro (4)/Threo (5) ratio[c]
1	RMgBr	1.1	THF, -50°	56	1.08
2	RMgBr	1.1	THF, 0°	81	0.79
3	RMgBr	3.0	THF, 15°	90	0.59
4	RMgBr	6.0	$ZnBr_2$ (1.1 eq) Et_2O, -10°	21	0.18
5	RCu•MgBrI[d]	1.0	THF, Me_2S, -78° → 0°	84	0.11
6	RMgBr	1.5	THF, HMPA (3.5 eq) -45°	71	3.76
7	RMgBr	3.0	THF, HMPA (6.0 eq) -20°	84	5.67
8	RMgBr	3.0	THF, HMPA (6.0 eq) +10°	91	4.56
9	RMgBr	3.0	THF, TMEDA (6.0 eq) 15°	83	0.49

[a] R=*n*-decyl. [b] Yield of isolated product. [c] Ratios were determined by GLC using a carbowax 20M high performance capillary column. [d] Prepared *in situ* from RMgBr and CuI (ref. 12).

The opposite effect, erythro selectivity, was caused by suppression of chelation. The addition of hexamethylphosphoramide (HMPA)[13] increased the amount of the erythro isomer 4 (entries 6-8). Yields remained high (70-90%), the best ratio (5.67) being obtained at -20° (entry 7). The replacement of HMPA by tetramethylenediamine (TMEDA) re-established the status quo (entry 9). The erythro/threo ratio was normal (0.49), thereby showing that TMEDA was without effect.

Using the above conditions, either diastereomer (4 or 5) could be produced at will from acrolein dimer. Separation by column chromatography was straightforward.[14] Acetylation (Ac_2O/pyridine) gave the corresponding acetates 6 and 7, which on oxidation with pyridinium chlorochromate (PCC) afforded the desired erythro lactone 1 and its threo isomer 2 in overall yields of 86 and 83% respectively from the alcohols[15] (Scheme). In this way, gram quantities of 1 and 2 were readily prepared.

Apart from the shortness and practicality of the present synthesis, the feature of interest is the stereocontrolled construction of the ε-hydroxy-δ-lactone skeleton. There has been surprisingly little exploitation of the acrolein dimer for the synthesis of δ-lactones. The few examples reported so far are confined to homologation.[16] Extension of the present strategy to the synthesis of related natural products is under way.[17]

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14. Preparative separation was effected on a silica gel column (Et_2O:hexane, 1:4). R_f values for 4 and 5 were 0.35 and 0.40 respectively.
15. All new compounds, 4, 5, 6, and 7 gave satisfactory analytical and spectral data. Selective ^{1}H-NMR (360 MHz) data ($CDCl_3$) δ: 4: 3.78 (m, 2H); 5: 3.58 (m, 1H), 3.67 (m, 1H); 6: 2.09 (s, 3H); 7: 2.11 (s, 3H). Relative configurations were assigned by conversion to the known lactones 1 and 2 (refs 1, 2b).
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