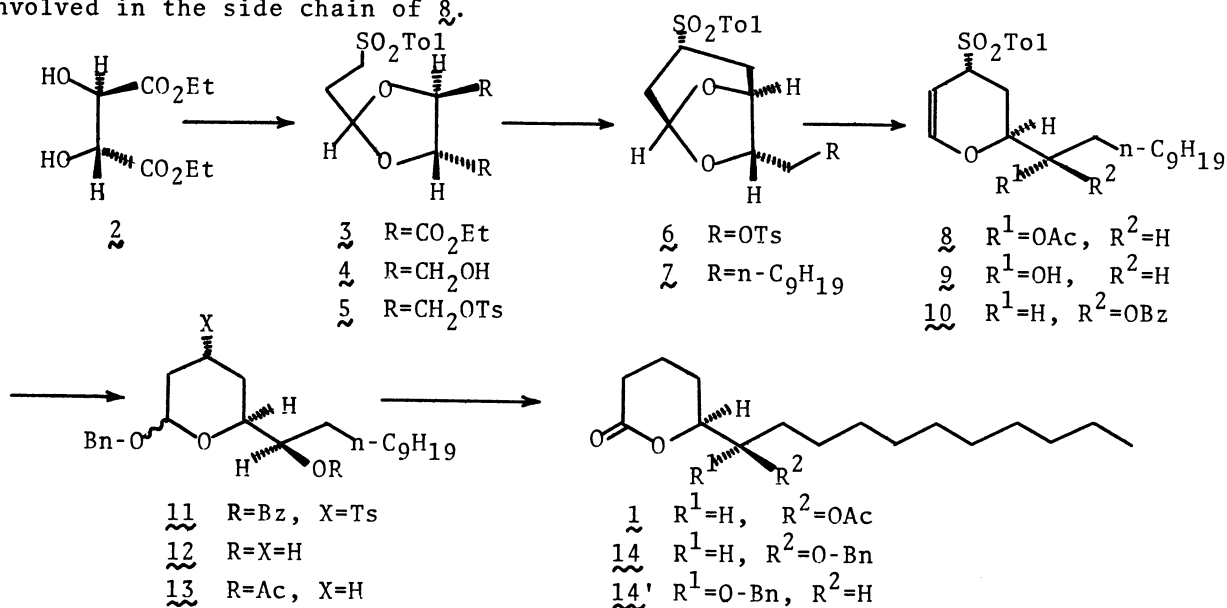


ENANTIOSPECIFIC SYNTHESIS OF (+)-ERYTHRO-(5S,6R)-6-ACETOXY-5-HEXADECANOLIDE, AN OPTICALLY ACTIVE FORM OF THE MAJOR COMPONENT OF A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE

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(+)-Erythro-(5S,6R)-6-acetoxy-5-hexadecanolide, an optically active form of the major component of an oviposition attractant pheromone of a mosquito *Culex pipiens fatigans*, was synthesized enantiospecifically from (+)-(R,R)-diethyl tartrate.

Laurence and Pickett¹⁾ reported the isolation of an oviposition attractant pheromone of a mosquito *Culex pipiens fatigans* and determination of the structure as erythro-6-acetoxy-5-hexadecanolide (**1**). The absolute configuration of two asymmetric centers in the pheromone structure, however, remains unsettled. Fuganti and coworkers²⁾ have reported recently the synthesis of both enantiomers of **1** from (2S,3S)-2,3-dihydroxybutanal acetonide in low overall yield via double diastereoselective alkylations and tedious separations of the diastereoisomers. We have recently developed a new method for the synthesis of optically active 6,8-dioxabicyclo[3.2.1]octanes by short-step elaborations of diethyl tartrate effectively utilizing the inherent C₂-symmetry.³⁾ In extension of the methodology to the natural product synthesis, we disclose here a short and enantiospecific synthesis of (+)-(5S,6R)-**1** from (+)-(R,R)-diethyl tartrate (**2**) by way of dioxolane ring fission of 6,8-dioxabicyclo[3.2.1]octane derivative (**7**) affording the functionalized 3,4-dihydro-2H-pyran (**8**), and stereospecific inversion of the asymmetric center involved in the side chain of **8**.



(+)-(R,R)-Diethyl tartrate (2) underwent acetalization with β -p-tosylpropanal diethyl acetal (p-TsOH/toluene/120 °C/4 h) as smoothly as with the corresponding 2-butanone acetal³⁾ to give the desired acetal 3 (mp 96-98 °C, $[\alpha]_D -21.0^\circ$ ⁴⁾) in 79% yield. A consecutive three-steps sequence of manipulations providing the optically active 6,8-dioxabicyclo[3.2.1]octane derivative (6) (mp 153-155 °C, $[\alpha]_D -36.7^\circ$) in 58% overall yield was carried out starting from 3 via diol 4 (mp 80-81 °C, $[\alpha]_D -8.8^\circ$) and ditosylate 5 as analogously as in the previous case.³⁾ Alkylation of the sulfonate terminus of 6 was carried out on treatment with (n-C₉H₁₉)₂CuLi in Et₂O-Me₂S (1:1) mixed solvent system (-20-15 °C/6 h/78% yield) to give 7-exo-decyl bicyclic compound (7) (mp 55-57 °C, $[\alpha]_D -45.5^\circ$). The dioxolane ring fission of 7 was achieved with Ac₂O (excess) and 1.2 equiv. of BF₃-Et₂O⁵⁾ (CH₂Cl₂/0 °C/1.5 h/72% yield) to furnish the functionalized 3,4-dihydro-2H-pyran derivative (8) as an oil ($[\alpha]_D +177.0^\circ$). Stereospecific inversion of the C(1')-asymmetric center in the side chain of 8 was performed on the alcohol 9 (mp 73-75 °C, $[\alpha]_D +198.0^\circ$) derived by hydrolysis of 8, by the application of the Mitsunobu method⁶⁾ (EtO₂CN=NCO₂Et/Ph₃P/benzoic acid/THF/20 °C/20 h) providing the benzoate 10 (mp 123-124 °C, $[\alpha]_D +169.5^\circ$) in 81% yield. Four-steps manipulation of the functional groups in 10 furnished optically pure 1 in 38% overall yield.⁷⁾ Thus, the benzoate 10 was converted on treatment with benzyl alcohol and bistrimethylsilyl sulfate [(Me₃SiO)₂SO₂]⁸⁾ (catalytic) in CH₂Cl₂ (20 °C/3 h/85% yield) into the benzyl acetal 11, which was desulfurized and debenzoylated in one operation with Na (10 equiv.) and EtOH (10 equiv.) in THF (-20-0 °C/3 h/75% yield) to give the hydroxy acetal 12. After acetylation of 12 (Ac₂O/pyridine/81% yield), transformation of the acetoxy acetal 13 into the final lactone acetate 1 was achieved in 73% yield by a sequential treatment with m-Cl-perbenzoic acid (1.2 equiv.) in the presence of catalytic amount of BF₃-Et₂O (CH₂Cl₂/15 °C/3 h)⁹⁾ and then with Et₃N (3 equiv.) (0 °C/2 h). The lactone acetate 1 was obtained as an oil ($[\alpha]_D +42.0^\circ$), whose structure and stereochemical homogeneity were confirmed by spectral identification with the authentic racemic compound¹⁾ and by HPLC comparison of the corresponding benzyl ether 14 prepared from 12 by benzylation and oxidation, with the threo-isomer 14' obtained from 9 without the Mitsunobu inversion.

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