AN ENANTIOSELECTIVE SYNTHESIS OF (R)- AND (S)-4,5-DIMETHYL-4-HEXANOLIDES——KEY INTERMEDIATES FOR 2,3-DIHYDRO-2-ISOPROPYL-2,5-DIMETHYLFURAN, A SEX SPECIFIC COMPOUND IN FEMALES OF THE BEETLE *HYLECOETUS DERMESTOIDES* L.+

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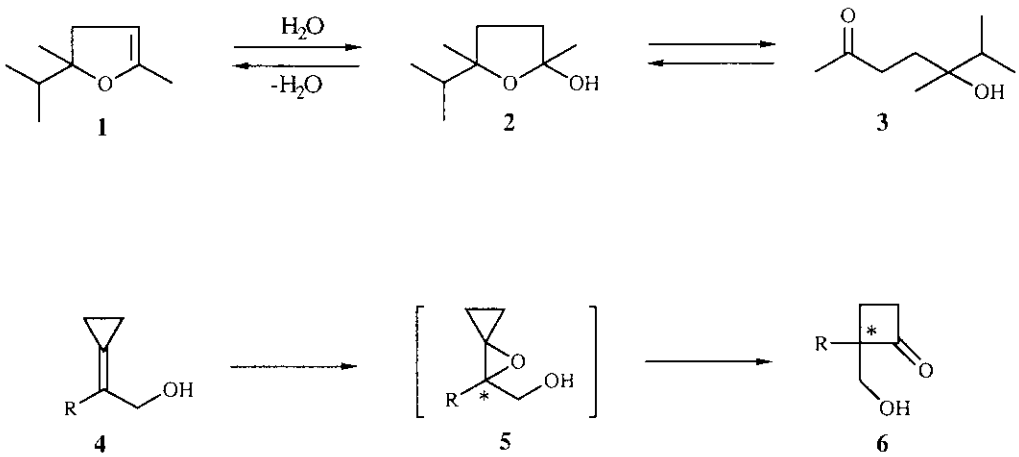
Abstract--Both the enantiomers, (R)- and (S)-4,5-dimethyl-4-hexanolides (**11**), were synthesized *via* tandem asymmetric epoxidation and enantiospecific 1,2-rearrangement of cyclopropylideneethanol (**7**) as a key reaction.

The cyclic enol ether, 2,3-dihydro-2-isopropyl-2,5-dimethylfuran (**1**), has been isolated as a sex specific compound from females of the beetle *Hylecoetus dermestoides* L.[1] The structure (**1**) was determined by comparison of its mass spectrum with that of its hydrogenation product and confirmed by a synthesis of its racemate.[1,2] But, some fundamental questions concerning the actual component and real enantiomer responsible for the biological activity of this insect specific compound have been remained to be answered, since the rapid and spontaneous conversion of **1** to **2** and **3** in the presence of adventitious moisture had been pointed out[3c] and the bioassay of optically active material had not been carried out. In this context, recently enantioselective syntheses of this compound (**1**) have been reported[3] in attempting to supply sufficient quantities for testing biological activity.

In the course of our studies[4] *aimed at enantioselective synthesis of chiral cyclobutanes, we have*

+ This paper is dedicated to Emeritus Professor M. Hamana on the occasion of his 75th birthday.

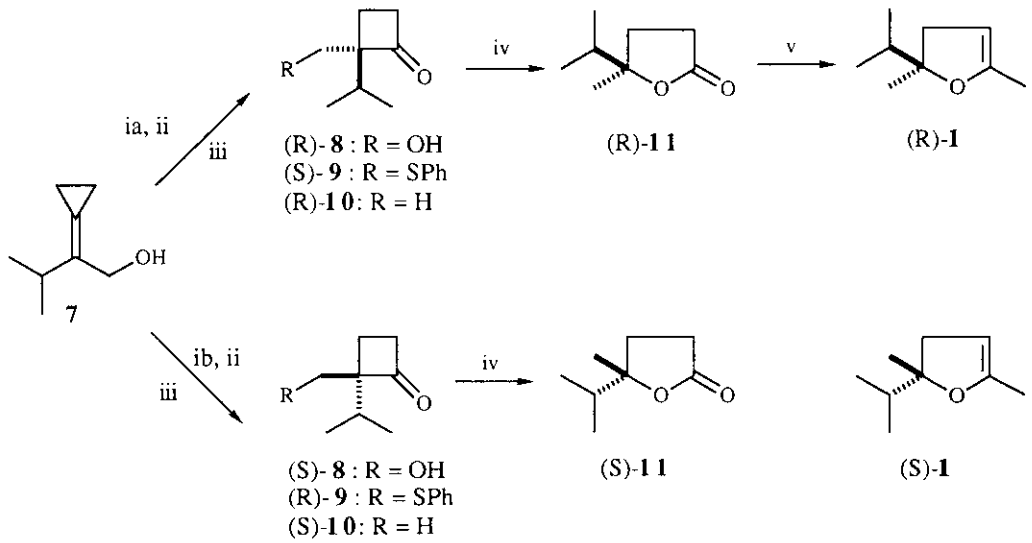
Scheme I



recently developed[5] an efficient method for the enantiocontrolled creation of α,α-disubstituted cyclobutanones(**6**) *via* the tandem asymmetric epoxidation of cyclopropylideneethanols(**4**) and enantiospecific 1,2-rearrangement of bicyclooxacyclopentanes(**5**). This finding enabled us to develop a convenient, concise, and enantioselective synthesis of chiral γ,γ-disubstituted γ-butyrolactones and here we wish to report an enantioselective synthesis of the both enantiomers (R)-**11** and (S)-**11**.[6]

The asymmetric epoxidation[7] of cyclopropylideneethanol[5] (**7**) with *t*-BuOOH in the presence of Ti(*i*-PrO)$_4$ and 3Å molecular sieves using diethyl D-(-)-tartrate and diethyl L-(+)-tartrate as the chiral auxiliary afforded the cyclobutanone alcohols (R)-**8** and (S)-**8** in 73% (89% ee[8]) and 80% (89% ee[8]) yields, respectively. The alcohols [(R)-**8** and (S)-**8**] were then subjected to Hata reaction[10] to give the sulfides (S)-**9** and (R)-**9** in 98 and 95% yields which were desulfurized to give (R)-**10** and (S)-**10** in 76 and 86% yields. Finally, Bacyer-Villiger oxidation of (R)-**10** and (S)-**10** furnished in 68 and 71% yields the our aimed γ,γ-disubstituted γ-butyrolactones (R)-**11** [$[\alpha]_D^{25}$ -9.56° (*c* 1.38, $CHCl_3$); lit.,[3b] $[\alpha]_D^{20}$ -10.2° (*c* 1.07, $CHCl_3$)] and (S)-**11** [$[\alpha]_D^{23}$ +8.80° (*c* 1.85, $CHCl_3$); lit.,[3d] $[\alpha]_D^{20}$ +10° (*c* 0.64, $CHCl_3$)]. Since (R)-**11** has been converted[3b] into (R)-**1**, this work constitutes the formal total synthesis of (R)-**1** and provides the key intermediate (S)-**11** for the synthesis of (S)-**1**.

Scheme II



Steps. ia) *t*-BuOOH, diethyl D-(-)-tartrate, Ti(*i*-PrO)$_4$, 3Å molecular sieves, CH_2Cl_2, -50 °C, 48 h; ib) *t*-BuOOH, diethyl L-(+)-tartrate, Ti(*i*-PrO)$_4$, 3Å molecular sieves, CH_2Cl_2, -50 °C, 48 h; ii) PhSSPh, *n*-Bu_3P, THF, ref., 10 h; iii) Raney Ni(W_2), acetone, room temperature, 10 min; iv) 70% *t*-BuOOH, 10% NaOH, THF, room temperature, 1.5 h; v) reference 3b.

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6. All new substances exhibited spectroscopic data [ir, ^{1}H nmr (500 MHz), and mass] in accord with the assigned structure and provided acceptable high resolution mass spectral data.

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8. The enantiomeric excess (ee) was estimated by ^{1}H nmr analysis (500 MHz) of α-methoxy-α-trifluoromethylphenylacetates prepared under the modified procedure of Mosher's original procedure.[9] [(S)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid, trifluoromethanesulfonyl chloride, triethylamine, dimethylaminopyridine, CH_2Cl_2, 0 °C, 10 min].

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