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Regioselective Synthesis Of Ceralure B_1 and A, Ethyl *cis*-(and *trans*-) 5-Iodo-*trans*-2-Methylcyclohexane-1-Carboxylate

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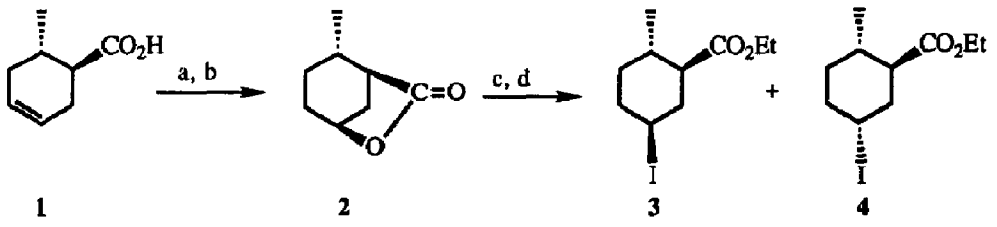
Abstract: Reaction of *trans*-2-methyl-6-oxabicyclo[3.2.1]octan-7-one with trimethylsilyl iodide, generated in situ, followed by refluxing with ethanol gives regioselectively ethyl *cis*-(and *trans*-) 5-iodo-2-methylcyclohexane-1-carboxylate, a persistent attractant for male Mediterranean fruit flies.

For more than 30 years, trimedlure (TML), a mixture of eight isomers of tert-butyl esters of 4 and 5-chloro-*trans*-2-methylcyclohexane-carboxylic acid (where the *trans* designation refers to the geometric relationship between the vacinal carboxylic ester group and the methyl group), has been widely used as the primary attractant in traps used to monitor and detect male Mediterranean fruit flies.[1,2,3] Recently, an analog of TML, ceralure (CER), a mixture of eight isomers of ethyl-4(and 5)-iodo-*trans*-2-methylcyclohexane-1-carboxylate, has been found to be a persistent and more active attractant for medflies.[4] Recent studies[5,6] have shown that only one of the CER isomers, CER B_1, ethyl-*cis*-5-iodo-*trans*-2-methylcyclohexane-1-carboxylate (**3**), is the most attractive isomer and it constitutes about 20-25% of commercially synthesized CER. We report here a regioselective synthetic procedure which yields only two CER isomers, CER B_1 and CER A, ethyl-*trans*-5-iodo-*trans*-2-methylcyclohexane-1-carboxylate (**4**).



1 **2** **3** **4**

Key: **a**, I_2/KI/$NaHCO_3$; **b**, H_2/Pd/EtOH or Bu_3SnH; **c**, NaI/TMS-Cl/CH_3CN; **d**, EtOH

The commercial preparation of CER,[6] adding hydroiodic acid across the olefinic bond of siglure acid, *trans*-2-methylcyclohex-2-ene carboxylic acid (**1**), followed by subsequent esterification, gives a mixture of eight isomers. Commercial samples of CER consist of a ≥81% mixture of the four *trans* isomers and with not less than 22% CER B_1. To our knowledge, this commercial synthesis of CER is the only preparative method found

in the literature. This research was aimed at development of a synthetic method that would improve the yield of the active CER B_1 isomer. A mixture of epimers of CER B_1 and CER A was prepared as follows: (a) Iodo lactonization[7] of siglure acid to afford the iodo lactone (*trans*-4-iodo-*trans*-2-methyl-6-oxabicyclo[3.2.1] octan-7-one) (81%), (b) Deiodoination of the iodo lactone with tributyltin hydride[8] or hydrogenolysis using hydrogen over platinum catalyst at 40 psi to give the lactone, *trans*-2-methyl-6-oxabicyclo[3.2.1]octan-7-one (**2**) (85%); (c) Opening of the lactone[9,10] by reacting with trimethylsilyl chloride and sodium iodide in acetonitrile, to generate trimethylsilyl iodide in situ, and; (d) Refluxing the intermediate trimethylsilyl ester with ethanol[11] to afford the regioselective ethyl *cis*-(and *trans*-) 5-iodo-2-methylcyclohexane-1-carboxylates (**3** and **4**) (78%, 60:40). The two isomers may be separated by flash chromatography (silica gel, EtOAc/hexane) or semi-preparative HPLC.[12]

A preliminary 2-week field test of the regioselective mixture on cotton wicks indicated competitive fly captures when compared with an equivalent amount of CER B_1 isomer in commercial CER. Because of the 2-fold difference in CER B_1 content, twice as much commercial CER as compared to the new attractant was required to give equal quantities of CER B_1 on the wicks.

In summary, the reaction of 2-methyl-6-oxabicyclo[3.2.1]octan-7-one with trimethylsilyl iodide, generated in situ, followed by refluxing with ethanol gives a 2-2.5 fold increase in the yield of active isomer, CER B1, than does commercial synthesis. Thus the increased efficacy per dose of material could result in the use of this new attractant as a replacement for TML which is now used at a rate of about 2000 kg per year in the United States.

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