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Synthesis of Optically Active Bisdifluorocyclopropanes through a Chemo-Enzymatic Reaction Strategy

Koichi Mitsukura, Satoshi Korekiyo, and Toshiyuki Itoh*

Department of Chemistry, Faculty of Education, Okayama University, Okayama 700-8530, Japan. E-mail: titoh@cc.okayama-u.ac.jp

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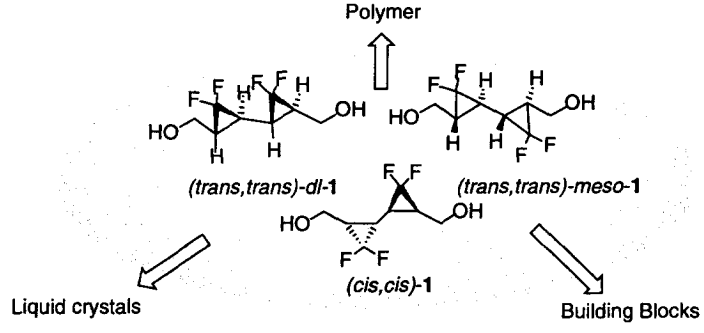
Abstract: The first synthesis of bisdifluorocyclopropane derivatives has been accomplished via a chemo-enzymatic reaction strategy; (*E*)- or (*Z*)-3-tributylstannyl-2-propenols were prepared and their conversion led to the (*trans,trans*)- and (*cis,cis*)-bisdifluorocyclopropanes. The subsequent lipase-catalyzed reaction efficiently afforded optically active (*trans,trans*)-2,2,5,5-tetrafluoro-1,6-bis(hydroxymethyl)bicyclopropane. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The substitution of two fluorine atoms on the cyclopropane ring is expected to alter both its chemical reactivity and biological activity due to the strong electron-withdrawing nature of the fluorine, and this makes it possible to create new molecules that would exhibit a unique biological activity or functionality. [1] We were attracted by the special properties of the difluorocyclopropanes, [2,3] and very recently accomplished the first synthesis of optically pure 1,1-difluoro-2,3-(bishydroxymethyl)cyclopropane.[4,5]



We postulated that the bisdifluorocyclopropanes (*trans,trans*)- and (*cis,cis*)-**1** would become unique sources of important organic compounds, such as a liquid crystal, monomer part for the synthesis of a unique polymer, and building blocks for the synthesis of difluoromethylene compounds. However, neither report concerning this idea or the synthesis of the bisdifluorocyclopropane derivatives have been reported so far, hence, we decided to attempt the synthesis of several types of bisdifluorocyclopropanes. In this communication, we report that the first synthesis of these bisdifluorocyclopropane derivatives, (*trans,trans*)-**1** and (*cis,cis*)-**1**, and the optically active bisdifluorocyclopropanes (+)-(*trans,trans*)-**1** and (-)-(*trans,trans*)-**1** has been accomplished through a enzymatic-chemical hybrid reaction methodology.

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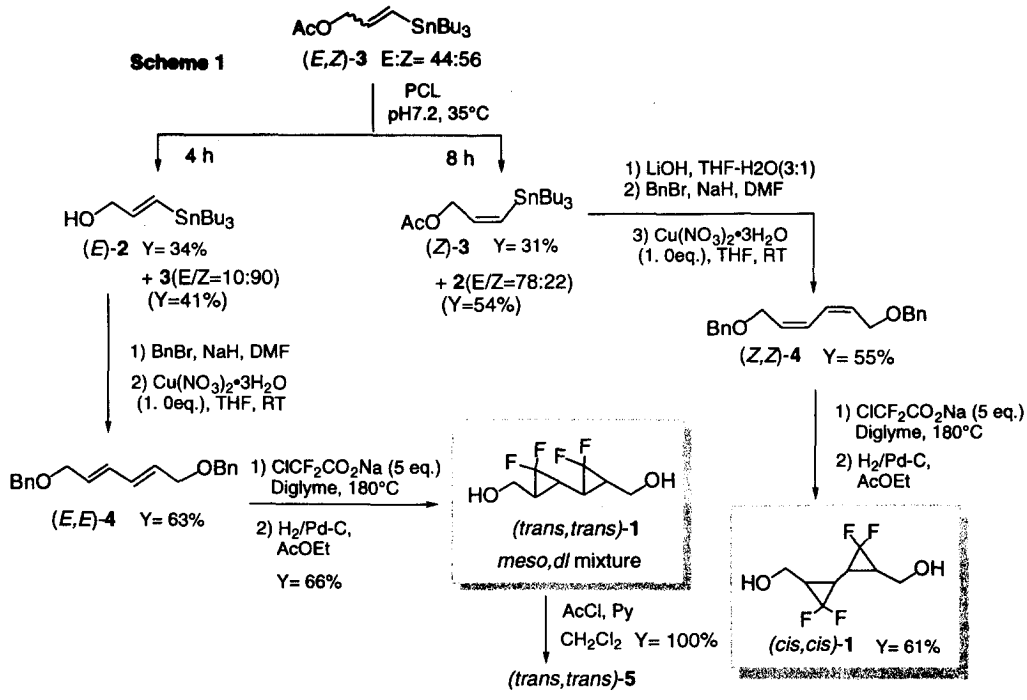
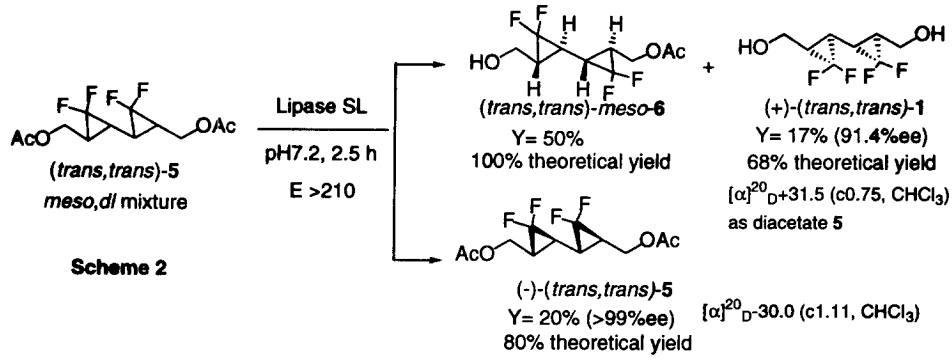


Our target bisdifluorocyclopropane derivatives, (*trans,trans*)-**1** and (*cis,cis*)-**1**, should be derived from the (*E*)- or (*Z*)-3-tributylstannyl-2-propene-1-ol (2). The value of an enzymatic reaction in organic synthesis is extensively increased by its environmentally friendly nature. [6] The lipase-catalyzed reaction was used for isolating the tributylstannyl alcohols, (*E*)-**2** and (*Z*)-**2**, from a stereomixture (Scheme 1).[7] Several lipases stereoselectively hydrolyzed acetate **3**, and *Pseudomonas cepacia* lipase (PCL) was found to be the best enzyme that smoothly hydrolyzed the acetate **3** to provide the (*E*)-olefin **2** with perfect selectivity. [8] The pure (*Z*)-isomer **2** was obtained as the unreacted acetate **3** by the PCL-catalyzed reaction when the reaction time was prolonged. This is a very convenient method to obtain the pure isomers of (*E*)-**2** and (*Z*)-**2** in the laboratory, though there exists several means to stetreoselectively prepare (*E*)-**2** using transition-metal chemistry.[9] The hydroxyl group of (*E*)-**2** was protected as the benzyl ether and treated with copper (II) nitrate trihydrate in THF at room temperature to produce the corresponding diene (*E,E*)-**4** in 63% yield.[10] Bisdifluorocyclopropanes (*trans,trans*)-**1** was directly synthesized in 66% yield from (*E,E*)-**4** using 5 eq. of difluorocarbene which was produced by the thermolysis of sodium chlorodifluoroacetate.[2] The benzyl protecting group was essential in achieving difluorocyclopropanation with sufficient yield. A significant drop in the chemical yield of the desired bisdifluorocyclopropane was observed when the reaction was carried out using the diacetate as a substrate. Bisdifluorocyclopropane (*cis,cis*)-**1** was also synthesized from (*Z*)-**2** using the same procedure (Scheme 1).

The diacetate of (*trans,trans*)-2,2,5,5-tetrafluoro-1,6-bis(hydroxymethyl)bicyclopropane (**5**) is a 1:1:2 mixture of (*1S,3R,4R,6S*)-**5**, (*1R,3S,4S,6R*)-**5**, and *meso*-(*1R,3S,4R,6S*)-**5**.[11] Optical resolution of (±)-



Scheme 2

(trans,trans)-**5** was very successfully achieved by the lipase SL-catalyzed reaction (Scheme 2). The lipase SL-catalyzed hydrolysis of the diacetate **5** gave the *meso* isomer as the monoacetate **6** in 50% yield, the diol (+)-*(trans,trans)*-**1** in 17% yield with 91.4% ee, and the unreacted diacetate (-)-*(trans,trans)*-**5** in 14% yield with >99% ee. E value [12] of the reaction was estimated to be >210. *The first synthesis of the optically active bis-difluorocyclopropane was accomplished very simply and efficiently.*

The stereochemistry of (+)-*(trans,trans)*-**1** was assigned as *(1S,3R,4R,6S)*, and (-)-*(trans,trans)*-**5** was *(1R,3S,4S,6R)*, based on the CD exciton chirality method using the 9-anthracenecarboxylate derivative **7** (Fig. 1).[13] The CD spectrum of the bis(9-anthracene)carbonyl ester **7**, which was derived from (+)-*(trans,trans)*-**1**, exhibited positive chirality on the Cotton effect [387.2 nm and 364.0 nm ($\Delta\varepsilon$+1.20), CH_3CN], while negative chirality on the Cotton effect [387.4 nm and 366.6nm ($\Delta\varepsilon$−3.05), CH_3CN] was observed by the 9-anthracene carboxylate derivative **7** derived from (-)-*(trans,trans)*-**5**. These observed Cotton effects were corresponded to E_2 absorption of the anthracene group (E_2 λ_{max}375 nm (ε= 28756). X-ray crystallographic analysis of the dibenzyl ether **8**, which was derived from *(trans,trans)*-*meso*-**6**, was successful and the stereochemistry of the lipase-catalyzed reaction was thus fully confirmed (Fig. 2).[14]

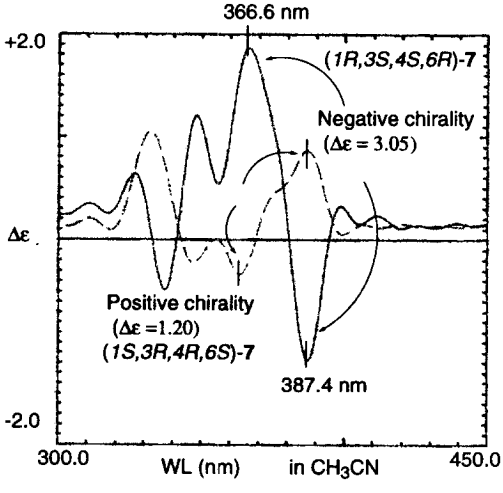


Fig. 1. CD spectrum of (-)-1,6-bis[(9-anthracene-carbonyl)methyl]-2,2,5,5-tetrafluorobiscyclopropane **7**

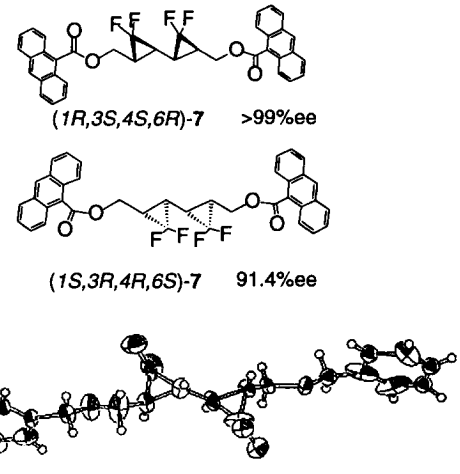


Fig. 2. ORTEP view of the dibenzyl ether **8** derived from *(trans,trans)*-*meso*-**6**

In conclusion, we have demonstrated the first synthesis of bisdifluorocyclopropane derivatives *via* a chemo-enzymatic reaction methodology. Results of the CD spectroscopic analysis showed that these bis-difluorocyclopropanes, (*trans,trans*)-**1**, exist with a helical shape configuration; this seems to suggest that a unique helical shape polymeric compound may be produced from (*trans,trans*)-**1** as a monomer unit. Further investigations into the preparation of the optically active (*cis,cis*)-biscyclopropanes and applications of these bisdifluorocyclopropanes **1** are ongoing.

Acknowledgment.

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7. 3-Tributylstanny-2-propene-1-ol was prepared as a mixture of (*E*)-**2** and (*Z*)-**2** (ca. 1:1) by the rapid addition of tributyltin hydride with propargyl alcohol in the presence of AIBN as a radical initiator.
8. Lipase SL (*Pseudomonas cepacia* SL-25), lipase PS (*Pseudomonas cepacia*), and AL (*Achromobacter* sp.) preferably gave *trans*-**2** with more than 80% selectivity and the best selectivity was recorded when the reaction was catalyzed by PCL.
9. For recent examples see. (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Medec, D.; Férézou, J-P. *Tetrahedron Lett.* **1997**, *38*, 6657. (c) Betzer, J-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768 and references cited therein.
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11. GC analysis for determination of % ee of **5** was carried out using a capillary column on a chiral phase; Chiraldex G-TA, ϕ0.25 mm x 20 m; Carrier gas: He 40 mL/min; Temp (°C); 100, Inlet pressure; 1.35 kg/cm^2; Amount; 400 ng; Detection; FID. The results of GC analyses of **5**: t_R of (+)-(*trans,trans*)-**5**; 26.2 min., (-)-(*trans,trans*)-**5**; 25.2 min., and (*trans,trans*)-*meso*-**5**; 38.6 min.
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14. Crystal and refinement data for **8**: $C_{22}H_{22}F_4O_2$, formula weight = 394.41, monoclinic, space group $P2_1$(#4), a= 8.6979 Å, b= 6.0163 , c= 19.3163 Å, V= 1005.5700Å^3, Z=2, dcalc= 1.30 g cm^{-3}, R(Rw)=0.082 for 1142 diffraction data with I>3.00σ (I) and 253 valiable.