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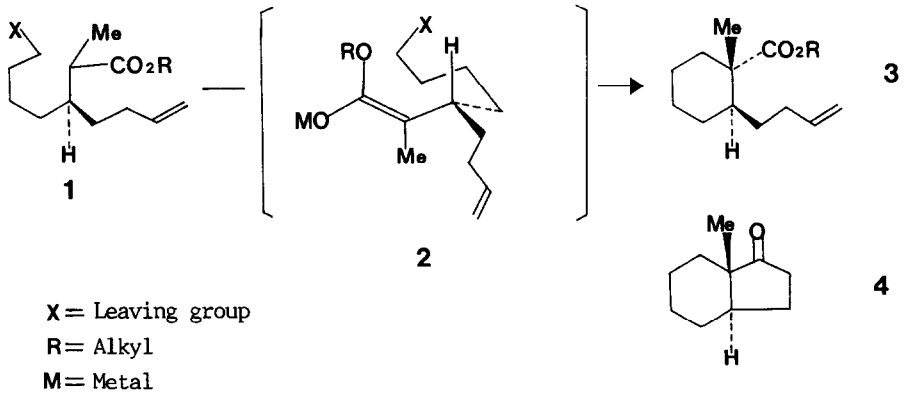
HIGHLY STEREOSELECTIVE INTRAMOLECULAR ALKYLATION OF ESTER ENOLATE: AN APPROACH TO TRANS-HYDRINDANE SYSTEM

Soon Hyuk Ahn, Deukjoon Kim*, Moon Woo Chun, Won-Keun Chung
College of Pharmacy, Seoul National University
San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151, Korea

Summary: Highly diastereoselective intramolecular alkylation of acyclic ester system was developed based upon allylic strain concept as an approach to trans-hydrindane system.

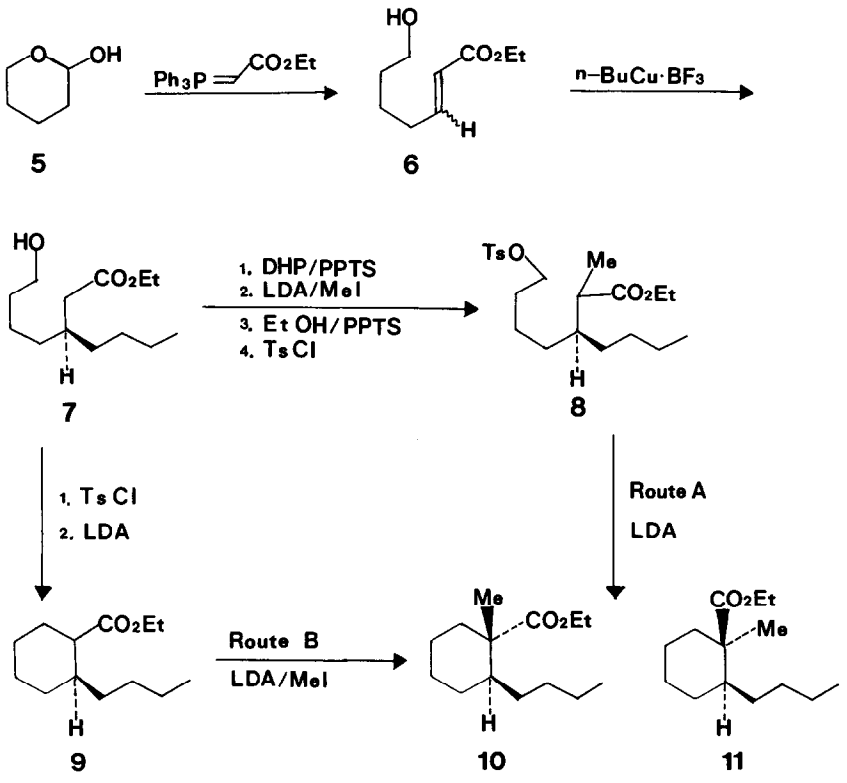
Stereoselective construction of trans-hydrindane nucleus has been a continuous challenge to synthetic organic chemists.[1] In connection with our studies on synthesis of optically active steroid CD ring, we have envisioned that intramolecular alkylation of ester such as **1** would provide cyclohexanecarboxylate **3** in a stereoselective manner through a conformation **2** where allylic hydrogen and OR (or OM) group are eclipsed.[11] Straightforward elaboration of functional groups in compound **3** would lead to trans-hydrindane **4** . Very recently Fleming, Koga, Yamamoto, and McGarvey reported successful cases of diastereoselective alkylation of acyclic esters with chirality at beta position during the course of our work.[2]



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

X = Leaving group
R = Alkyl
M = Metal

In this communication we wish to describe a highly diastereoselective intramolecular alkylation of acyclic ester **8** chosen as a model system which has the appropriate structural features present in compound **1** . (SCHEME I)



* Isomer ratio was determined by capillary GC analysis.

Route \ Compound	10	11
A	98	2
B	11	89

SCHEME I : Preparation of ester **8** and stereochemical outcome of intramolecular alkylation

Known aldehyde **5**[3] was condensed with ethyl (triphenylphosphoranylidene) acetate to give hydroxy ester **6** in 79% yield. Treatment of unsaturated ester **6** with excess amount of n-BuCu·BF_3 according to Yamamoto's procedure afforded ester **7** in 75% yield.[4] Key intermediate **8** was prepared from ester **7** in a four-step sequence in 40% overall yield.[5,6] (DHP/PPTS;[7] LDA/MeI;[8] EtOH/PPTS; TsCl/DMAP)

Upon treatment with LDA in THF at -78°C ester **8** underwent smooth intramolecular alkylation to give the desired cyclohexanecarboxylate **10** as a sole product to our delight. (Route A) In order to confirm the stereochemistry of cyclized product **10**, hydroxy ester **7** was converted to cyclohexanecarboxylate **9** by tosylation followed by cyclization with LDA. Alkylation of lithium enolate, generated from ester **9** and LDA, with MeI produced a 1 : 8 mixture of epimeric methylated cyclohexanecarboxylate **10** and **11**. (Route B)[9] This stereochemical result is consistent with Krapcho's observation in similar system.[10]

In conclusion we have demonstrated that intramolecular alkylation of acyclic system such as **8** proceeds with high degree of stereoselectivity which could be attributed to the well-documented allylic strain concept.[11] Application of this synthetic methodology to synthesis of steroids and other ring system is under active investigation in our laboratory.

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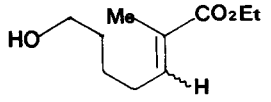

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   11 : 1.21 (s,-CH_3), 1.24 (t,J=7 Hz,-$COOCH_2\underline{CH_3}$), 4.12 (q,J=7 Hz,-$COO\underline{CH_2}CH_3$)
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