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NOVEL SYNTHESIS OF BREFELDIN A
AN APPLICATION OF THE OXIDATIVE FRAGMENTATION OF γ-HYDROXYALKYL STANNANES

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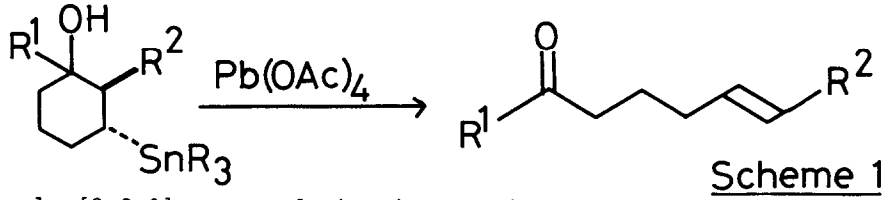
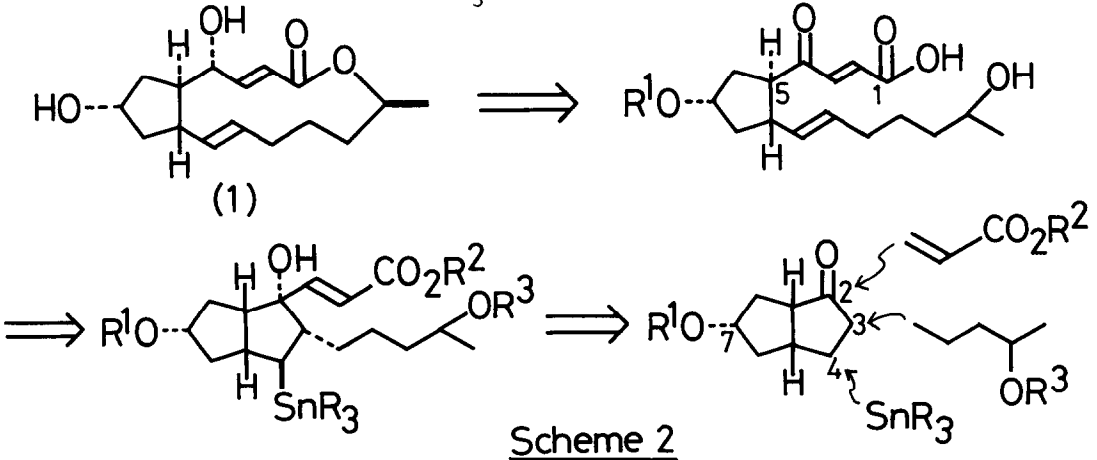
Summary: Synthesis of Brefeldin A seco acid (13) involving new oxidative fragmentation was reported.

Recently we have reported the stereospecific formation of (E) and (Z)-keto olefins by the oxidative fragmentation of γ-hydroxyalkyl stannane with lead tetraacetate[1] (Scheme 1). Now, this fragmentation was applied to the synthesis of Brefeldin A (1)[2] as a key step.



Scheme 1

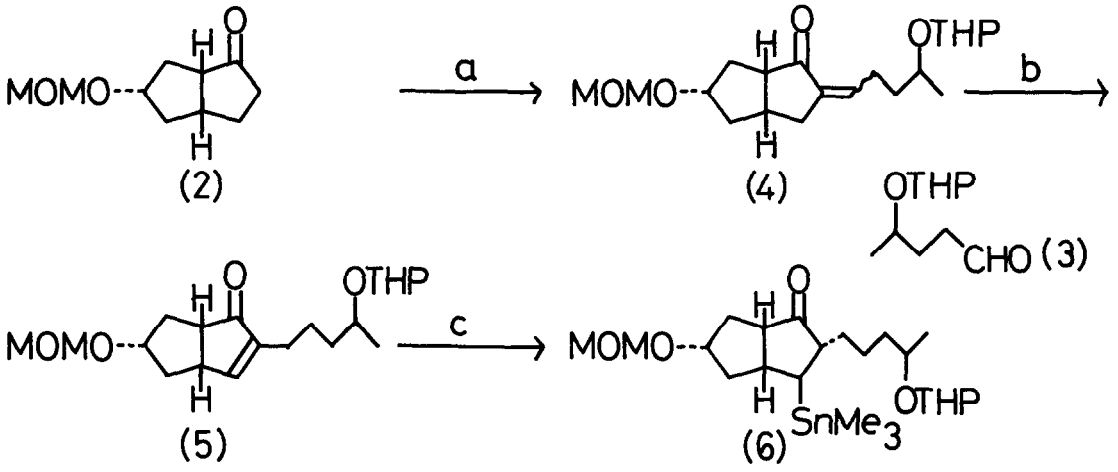
Bicyclo-[3,3,0]-octane derivatives, which are useful and versatile synthetic intermediates for cyclopentanoid natural products[3], were employed as a starting material. We considered that γ-hydroxyalkyl stannane derivative, a key intermediate, synthesized by successive introduction of C_5 unit into C3, trialkyl tin into C4 and then C_3 unit into C2 of bicyclic compound, was



Scheme 2

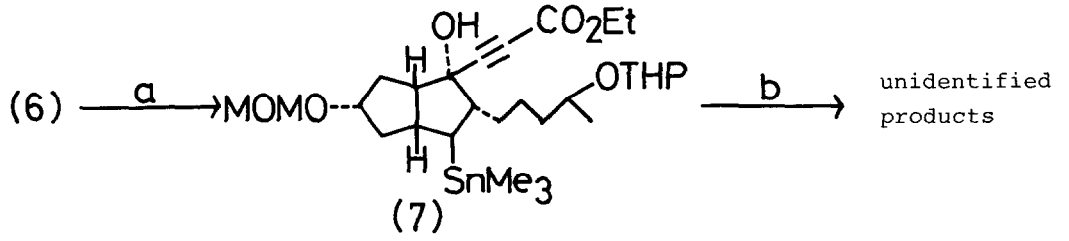
converted to Brefeldin A seco acid by fragmentation and isomerization at C5 to natural configuration[4] (Scheme 2).

First, C_5 unit was introduced into bicyclic ketone (2)[5], easily prepared from tricyclo-[3,3,0.0^{2,8}]-octan-3-one. Lithium enolate, generated by deprotonation of ketone (2) with lithium bistrimethylsilylamide(LBTMSA) in THF at -78°C, was reacted with aldehyde (3)[6] to afford aldol product, which was successively treated with MsCl,Et_3N and DBU to give exo-enone (4) in 61% yield. Rhodium chloride catalyzed olefin isomerization[7] proceeded smoothly to afford endo-enone (5) in 72% yield.[8] 1,4-Addition of Me_3SnLi,[9] generated by lithium-halogen exchange of Me_3SnCl with metal lithium, to (5) followed by kinetic protonation with aq.NH_4Cl at -78°C yielded ketostannane as a mixture at C3(ca. 1:1). Desired trans isomer (6) , however, was predominantly obtained by NaOMe catalyzed isomerization in 71% yield from (5) (Scheme 3).



Scheme 3. a) LBTMSA/THF/-78°C; (3); MsCl/Et_3N/DBU/Benzene. b) $RhCl_3 \cdot 3H_2O$/EtOH/K_2CO_3/70°C. c) Me_3SnLi/THF/-78°C; NH_4Cl; NaOMe/MeOH.

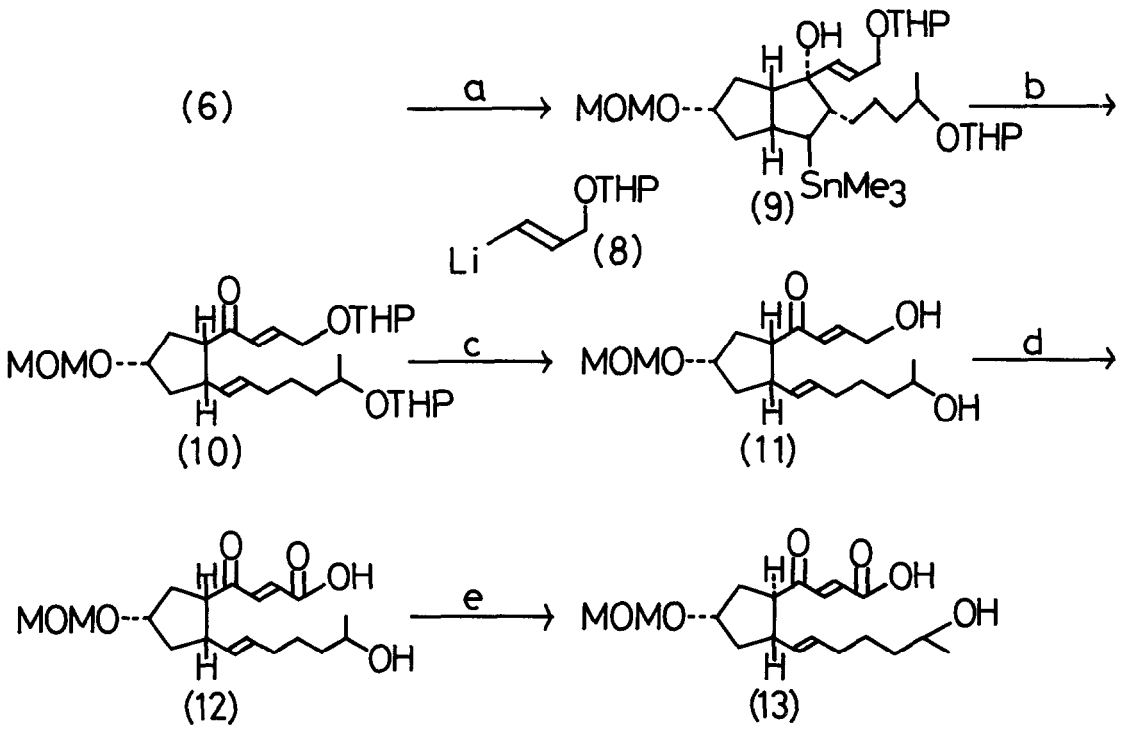
Next stage is the introduction of C_3 (E)-alkenoic acid unit into C2 ketone group of (6) to afford γ-hydroxyalkyl stannane derivative. First we considered that (E)-alkenoic acid would be obtained by reduction of alkynoic acid.[10] Addition of lithio propiolate,[11] generated by deprotonation of ethyl



Scheme 4. a) LiC≡CCO_2Et/THF/-78°C. b) $Pb(OAc)_4$/$CaCO_3$/Benzene/80°C.

propiolate with LDA in THF at -78°C, to (6) afforded alkynoic acid ester (7). In our surprise, the fragmentation of (7) with lead tetraacetate in refluxing benzene did not proceed and afforded unidentified products. The reason why this fragmentation did not occur is now under investigation[12] (Scheme 4).

Therefore we next considered the introduction of (E)-vinyl lithium reagent (8).[13] A large excess of (8) was reacted with (6) to afford the allyl alcohol (9) in 82% yield. In this case, the fragmentation proceeded smoothly in refluxing benzene in the presence of $CaCO_3$ to afford an α,β-unsaturated ketone (10) in 82% yield. Since the relative configuration between C3 and C4 is trans, the geometry of generated double bond should be E. Deprotection of (10) by PPTS in refluxing aq.acetone gave diol(11) in 87% yield. Next the allyl alcohol was selectively oxidized to (E)-alkenoic acid in two steps. Oxidation of (11) with activated MnO_2 in CH_2Cl_2 gave unsaturated aldehyde, which was oxidized to carboxylic acid (12) by $NaClO_2$ in ^tBuOH and acetate buffer in the presence of resorcinol as a chlorine scavenger.[14,15] At last the configuration of carbonyl side chain was corrected by base catalyzed isomerization to afford Brefeldin A seco acid (13). This seco acid was already synthesized by Bartlett



Scheme 5. a) (8)/THF/-78°C. b) $Pb(OAc)_4/CaCO_3$/Benzene/80°C. c) PPTS/aq. Acetone. d) MnO_2/CH_2Cl_2; $NaClO_2$/Resorcinol/Acetate Buffer/^tBuOH-H_2O. e) DBU/CH_2Cl_2.

group in their synthesis of Brefeldin A and identical to their compound in ^{1}H-NMR (Scheme 5).

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5. Prepared from tricyclo-[3,3,0,$0^{2,8}$]-octan-3-one in 60% overall yield by the following sequence:[3] (1) treatment with 99% HCOOH/70-80°C, (2) hydrolysis with K_2CO_3/MeOH, (3) acetylation with Ac_2O/pyr., (4) reduction with $NaBH_4$/EtOH, (5) reaction with CH_3OCH_2Cl/ iPr_2NEt/CH_2Cl_2, (6) reduction with $LiAlH_4/Et_2O$, (7) Jone's oxidation/acetone/0°C.
6. Aldehyde (3) was prepared from ethyl levulinate in four steps: $NaBH_4$/EtOH, DHP/PPTS/CH_2Cl_2, $LiAlH_4/Et_2O$, PDC/CH_2Cl_2. As this compound is a mixture of diastereomers double doublet signals for methyl in ^{1}H-NMR were observed.
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