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A Stereoselective Synthesis of Two Epimeric Polypropionate Fragments with Four Adjacent Chiral Centers from 7-Oxanorbornene Derivatives

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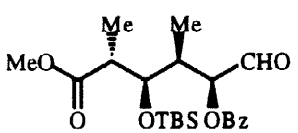
Abstract: The two epimeric stereotetrads **3** (*syn, anti, anti*) and **4** (*syn, anti, syn*) have been prepared from the Diels-Alder endo adduct of furan and acrylic acid, using as a key step a new epoxysulfone-enone transformation.

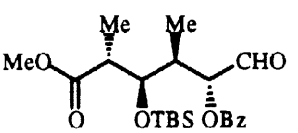
The chemistry of polypropionate-derived structures has attracted considerable attention due to their large range of biological properties,[1] and different synthetic approaches to polypropionate segments in a stereocontrolled fashion have been developed starting from both acyclic[2] and cyclic[3] precursors.

Recently we published a new route for the preparation of stereotetrads **1** (*anti, syn, syn*) and **2** (*anti, syn, anti*)[4] starting from 7-oxanorbornene derivatives.[5] In this report we wish to account for the synthesis of the stereotetrads **3** and **4** also from the same starting material but using complementary synthetic methodology (Figure).



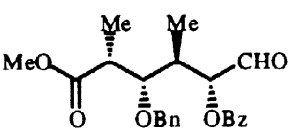
anti, syn, syn

1



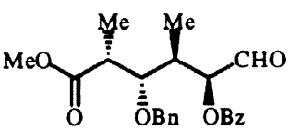
anti, syn, anti

2



syn, anti, anti

3



syn, anti, syn

4

Figure

In our retrosynthetic approach (Scheme 1) the enone **5** appears as a key intermediate. Stereocontrolled reduction of the carbonyl group followed by ozonolysis of the resulting allylic alcohol **6** should give **3**, whereas Mitsunobu inversion of the hydroxyl functionality of **6** followed by the same ozonolytic cleavage should afford **4**. In this way a divergent access of the two stereotetrads from the common intermediate **5** could be achieved.

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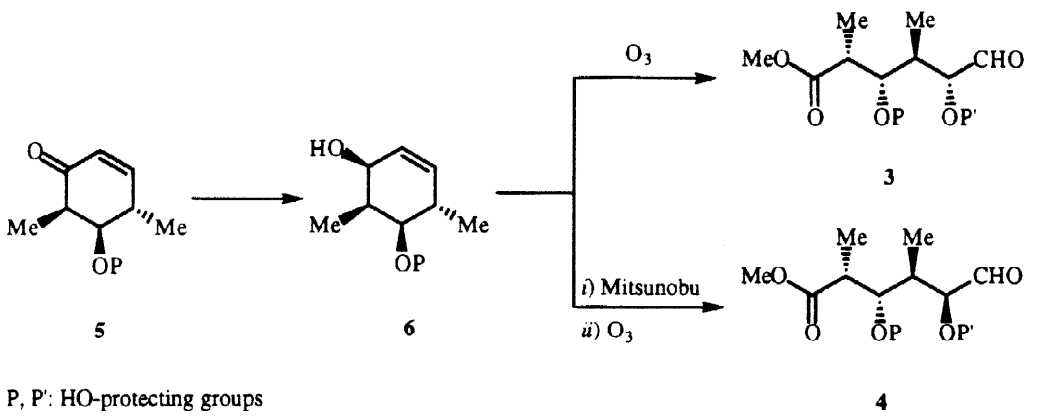
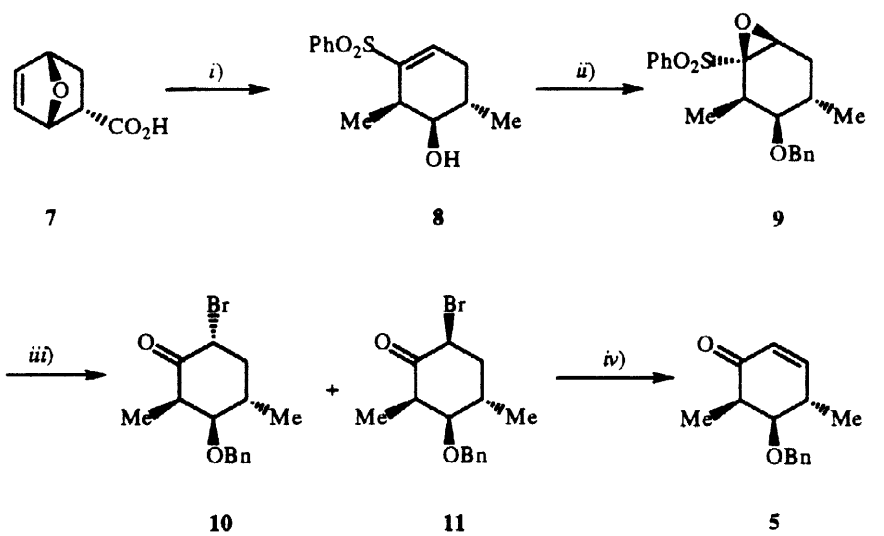


Scheme 1

The synthesis of the enone **5** was first performed from the vinylsulfone **8** previously prepared in six steps and 46% overall yield from oxabicyclic derivative **7**,[4a] the Diels-Alder endo adduct of furan and acrylic acid.[6] Thus, epoxidation of **8** with lithium *t*-butyl hydroperoxide[7] followed by protection of the free hydroxyl group and reaction with $MgBr_2$[8] gives bromoketones **10** and **11** in ratio **10**:**11**, 69:31 and 85% overall yield.[9] Transformation of this mixture into enone **5** was performed using $CaCO_3$ in DMF.[10] However, and after considerable experimentation, only a modest 31-32% isolated yield of **5** was obtained at most (Scheme 2).

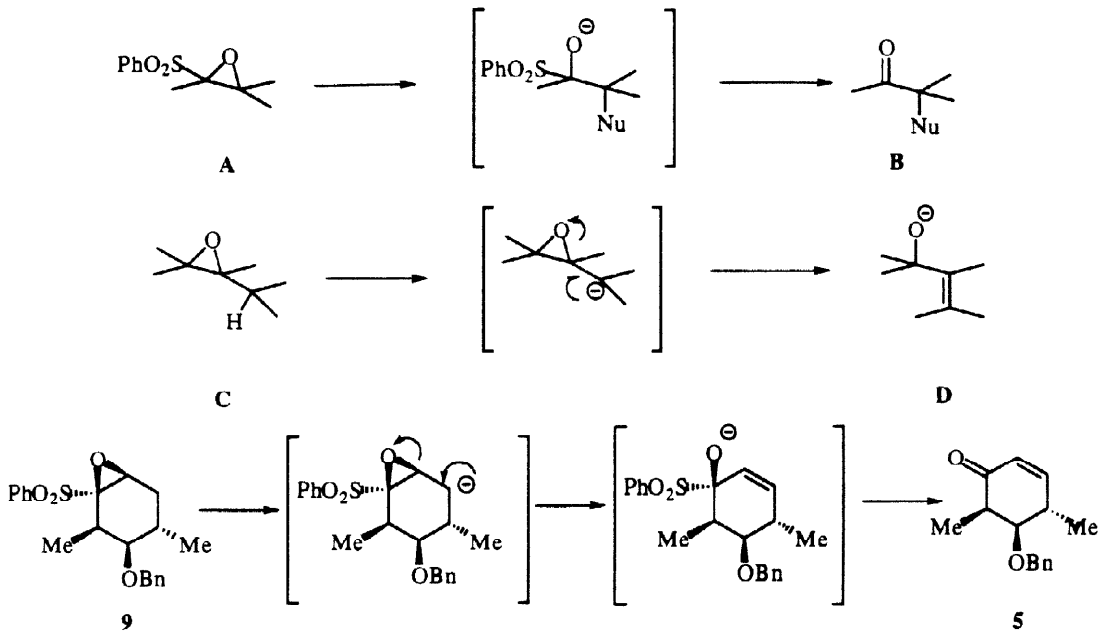


Reagents and conditions: i) Six steps; 46 % overall yield. See ref. 4a; ii) a) *t*-BuO_2Li, THF, -78°C, 12h. 92 %; b) BnBr, NaH, Me_4NI, THF, 0°C, 96 %; iii) $MgBr_2$, Et_2O, rt, 5h. 85 %; iv) $CaCO_3$, DMF, 150°C, 45 min. 31-32 %.

Scheme 2

At this point we speculated that the transformation of **9** into **5** would occur in one step combining two well-known transformations: the nucleophilic ring opening of α,β-epoxysulfones[11] (transformation A-B, Scheme 3) and the rearrangement of epoxides to allylic alcohols using lithium amides[12] (transformation C-D, Scheme 3).

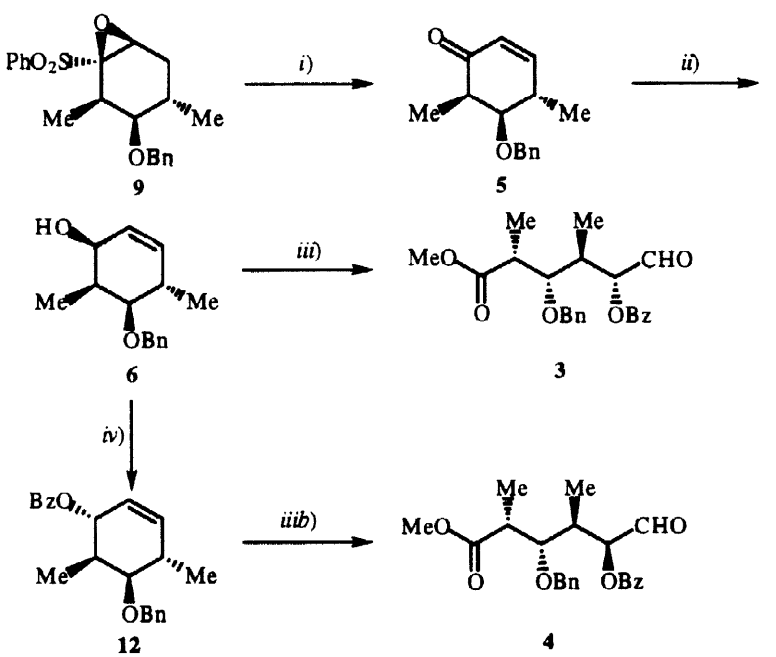
In this way, transformation of **9** into **5** by deprotonation followed by allylic displacement of the sulfone functionality appeared to be an interesting possibility.



Scheme 3

Confirmation of our speculation was obtained when the reaction of **9** with LDA in ether-hexane afforded **5** in 65% isolated yield. These reaction conditions are critical for the success of the transformation. For instance, using THF as solvent, the reaction does not work at all and with ether as the only solvent, only a 30% of **5** was isolated.

With enone **5** in hand, the reaction sequence was continued according to our previous strategy (Scheme 4).



Reagents and conditions: i) LDA, Et_2O-hexane, 35°C, 5 h. 65 %; ii) $NaBH_4$, $CeCl_3$, MeOH, -78°C, 3 h. 81 %; iii) a) BzCl, pyr-CH_2Cl_2, 0°C, 3 h. 100 %; b) O_3, $NaHCO_3$, CH_2Cl_2-MeOH, 4:1, -78°C; c) pyr, Ac_2O, CH_2Cl_2, rt, 24 h. 80 %; iv) DEAD, Ph_3P, benzoic acid, toluene, rt, 12 h. 71 %.

Scheme 4

Thus, reduction of **5** in Luche's conditions[13] gives **6** as sole product which, after benzoylation, was ozonolyzed using the Schreiber's method[14] to give **3**. On the other hand, Mitsunobu inversion[15] of allylic alcohol **6** affords **12** which, after ozonolysis under the same conditions as above gives rise to **4**.

In summary, an efficient synthesis of two epimeric stereotetrads (*syn, anti, anti*) and (*syn, anti, syn*) has been performed with total stereocontrol of their four chiral centers. Implicit in this strategy is the ready access to longer polypropionate segments (natural and unnatural) by the selective elongation at the different ends of the chain. In addition a new, direct transformation of an epoxysulfone into an enone has been described. The scope of this method is now under research in our laboratory.

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