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Polypropionates from 7-Oxanorbornene Derivatives. A Stereoselective and Divergent Synthesis of Fragments with Four Contiguous Chiral Centers

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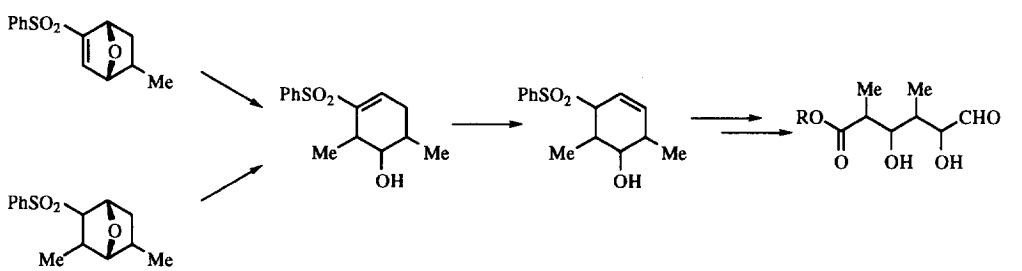
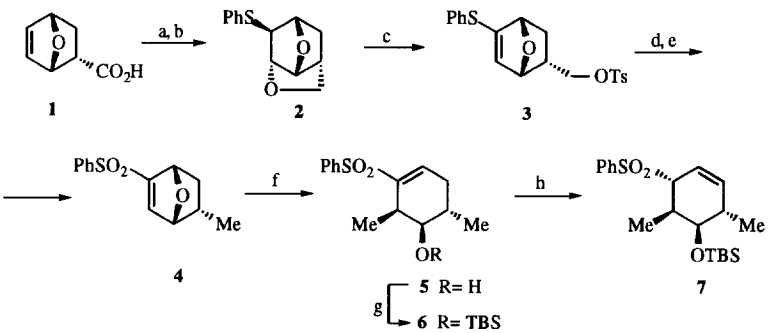
Abstract: The epimeric stereotetrads **12** and **14** have been prepared starting from the Diels-Alder *endo* adduct of furan and acrylic acid. The key steps of the route were the alkylative cleavage of the oxygen bridge and the transformation of the resulting cyclic vinyl sulfone into the allyl isomer.

Polypropionate-derived structures are present in several classes of natural products having a large range of biological properties.[1] Although the synthesis of these compounds usually rely on methods of acyclic stereocontrol,[2] rigid bicyclic precursors can also serve as building blocks for this purpose and, for instance, different approaches to polypropionate segments have been developed starting from oxabicyclic intermediates.[3] In this report we wish to account a new route for the preparation of acyclic chains with four adjacent stereocenters alternating hydroxyl and methyl substituents (stereotetrads[4]) from 7-oxanorbornene derivatives. In our synthetic scheme we envisaged two key steps, namely the oxygen bridge opening by means of sulfone-directed methodologies[5] and the base-mediated vinyl-allyl isomerization of the resulting cyclohexenyl sulfones (Scheme 1). The latter is a well-known process which can be achieved under kinetic or thermodynamic control conditions, usually leading to the allylic isomer.[6] The versatility of our plan would allow the preparation of all the possible stereotetrads, by fixing the orientation of the substituents on the bicyclic precursors and controlling the stereochemistry of the reactions involved in the route. As an example of this idea we have prepared two epimeric stereotetrads starting from the acid **1** (Scheme 2), the Diels-Alder *endo* adduct of furan and acrylic acid which is also available in optically pure form.[7]



Scheme 1

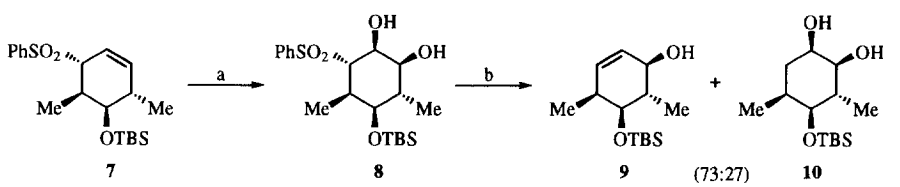
Tricyclic sulfide **2**[8] was obtained in two steps from acid **1**. Its treatment with *n*-BuLi led to the cleavage of the more strained tetrahydrofuran ring and *in situ* addition of TsCl yielded tosylate **3**.[9] Chemoselective reduction of the tosylate function and sulfide oxidation gave vinyl sulfone **4**. The alkylative oxa-bridge opening[5b] by addition of MeLi produced regio- and stereoselectively the cyclohexenyl sulfone **5**. The crucial isomerization step was achieved on the silyl protected sulfone **6** by reaction with LDA in THF at -78 °C, affording the allyl isomer **7** as a single product. The pseudoaxial orientation of the phenylsulfonyl group in **7** was determined by the further transformations described below.



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 8 h, 90%. b) PhSH, NCS, $CHCl_3$, 0 °C to rt, 12 h, 95%. c) *n*-BuLi, THF, -78 °C, 1 h, then TsCl, -78 °C to rt, 1 h, 83%. d) $LiAlH_4$, Et_2O, 0 °C, 5 h, 81%. e) MMPP, MeOH, 0 °C to rt, 12 h, 86%. f) MeLi, THF, -78 °C, 1 h, 94%. g) TBSOTf, Et_3N, THF, -78 °C, 1 h, 91%. h) *i*-Pr_2NH, *n*-BuLi, THF, -78 °C, 15 min, then **6**, THF, -78 °C, 1 h, 87%.

Scheme 2

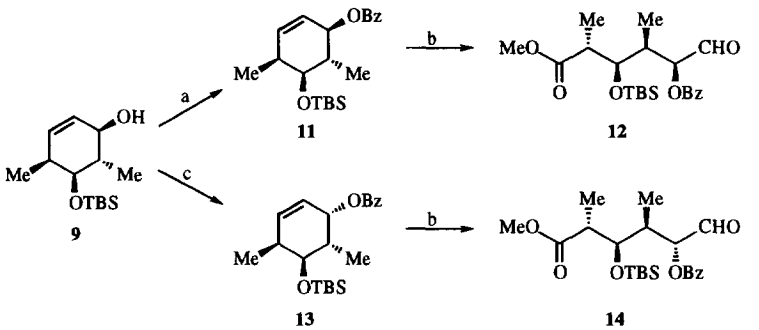
The OsO_4-catalyzed dihydroxylation of **7** gave a 91:9 mixture of diols, from which the major diastereoisomer **8** was separated by column chromatography[10] (Scheme 3). In this product, proton H-1 showed an axial-equatorial coupling constant (6.2 Hz) with H-2 and an equatorial-equatorial one (3.4 Hz) with H-6, thus indicating that the dihydroxylation took place predominantly *anti* with regard to the pseudoaxial phenylsulfonyl group (Figure 1). Julia olefination[11] of this compound by treatment with Na-Hg afforded the expected allylic alcohol **9** along with the simple desulfonylation product **10** in a 73:27 ratio (89% overall yield).



Reagents and conditions: a) OsO_4, $Me_3NO{\cdot}H_2O$, Me_2CO:H_2O 8:1, rt, 48 h, 88% overall (de: 91:1). b) Na-Hg, Na_2HPO_4, MeOH:THF 1:1, -20 °C to rt, 12 h, 89% overall.

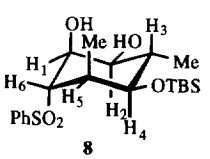
Scheme 3

In order to avoid undesired cyclizations in the further ozonolysis step, alcohol **9** was protected as its benzoyl derivative **11** or transformed into its epimer **13** by a Mitsunobu process[12] (Scheme 4). Their different stereochemical arrangements were confirmed by coupling constants determinations.[13]

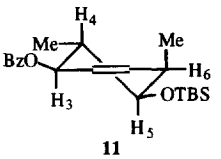


Reagents and conditions: a) BzCl, pyr, CH_2Cl_2, 0 °C, 2 h, 81%. b) O_3, $NaHCO_3$, CH_2Cl_2:MeOH 4:1, -78 °C, 30 min; then Ac_2O, pyr, CH_2Cl_2, rt, 24 h, 85%. c) BzOH, PPh_3, DEAD, PhMe, rt, 12 h, 82%.

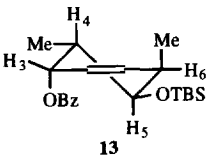
Scheme 4



$J_{1,2}$= 6.2 Hz
$J_{1,6}$= 3.4 Hz
$J_{3,4}$= 8.3 Hz



$J_{3,4}$= 9.2 Hz
$J_{4,5}$= 11.0 Hz
$J_{5,6}$= 5.5 Hz



$J_{3,4}$< 4-5 Hz
$J_{4,5}$= 8.8 Hz
$J_{5,6}$= 4.8 Hz

Figure 1

Finally, unsymmetrical ozonolysis of benzoates **11** and **13** under the conditions described by Schreiber[14] produced the oxoesters **12** and **14** respectively. In these compounds four chiral centers have been constructed with a high level of stereocontrol. The change of orientation of the substituents on the cyclic intermediates would supply the remaining isomers of **12** and **14**. Implicit in this strategy is the ready access to longer polypropionate segments by the selective elongation at the different ends of the chain. Work aimed in both senses is the focus of current investigation in our laboratory.

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9. All new compounds showed spectroscopic and analytical data consistent with the assigned structures.
10. Epoxidation of **7** with *m*-CPBA yielded a 69:31 mixture of diastereomeric oxiranes. The major product was also converted into allylic alcohol **9** by reaction with Na-Hg.
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13. The coupling constant between H-3 and H-4 in benzoate **13** could not be measured, although the width of their signals did not contain a constant value higher than 4-5 Hz, thus indicating the seudoaxial orientation of the benzoyl group.
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