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# Building Blocks for Skipped Polyols: *syn*-1,3-Acetonides by Chemoenzymatic Synthesis from Cycloheptatriene

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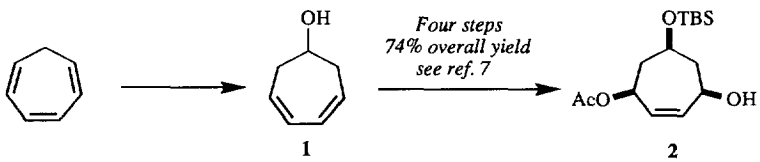
***Abstract:*** Enantiopure enones obtained via lipase asymmetrization of *meso*-diols derived from cycloheptatriene underwent tin-directed ring-openings to give *syn*-1,3-bis(silyloxy) olefins which were converted to their acetonides in a one-pot sequence.

*syn*-1,3-Acetonides have been useful intermediates in the construction of polyene macrolides[1] and other natural products that contain "skipped" 1,3-polyhydroxy units.[2] Enantiopure *syn*-1,3-acetonides have been obtained from carbohydrate-derived precursors[3] and asymmetric epoxidation products.[4] The latter methodology was exploited in the reiterative two-directional chain extension of a skipped 1,3-polyol chain.[5]

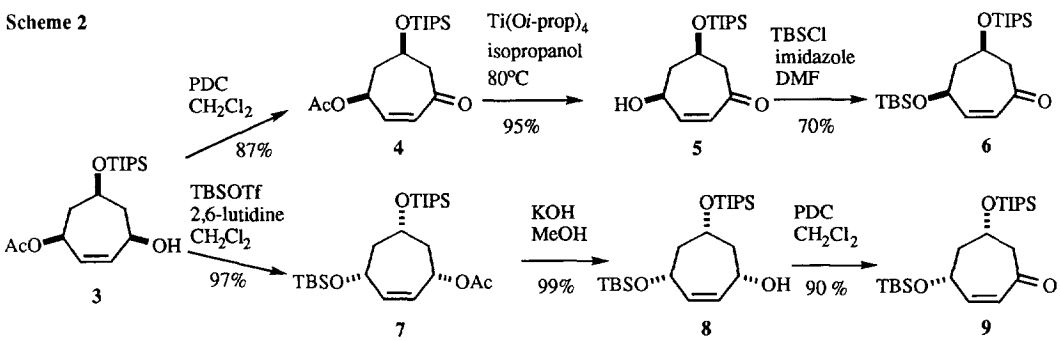
Recent reports from this laboratory have described the use of lipase-derived cycloheptene monoacetate **2** as a convenient precursor for the synthesis of carbohydrates.[6] This can be prepared in optically pure form (> 95% ee) on a multi-gram scale from dienol **1** (Scheme 1).[7]

**Scheme 1**




Herein we describe the transformation of the related monoacetate **3**, prepared by treatment of the corresponding diol with isopropenyl acetate in the presence of *Pseudomonas cepacia* lipase, into enantiomerically pure, end-differentiated, *syn*-1,3-acetonides.[8] The monoacetate **3** was easily transformed into enantiomeric enones **6** and **9** by protecting group manipulations and oxidation of the allylic alcohol (Scheme 2).[9] Enones of this type have been employed in the preparation of enantiomeric compactin analogs.[10]

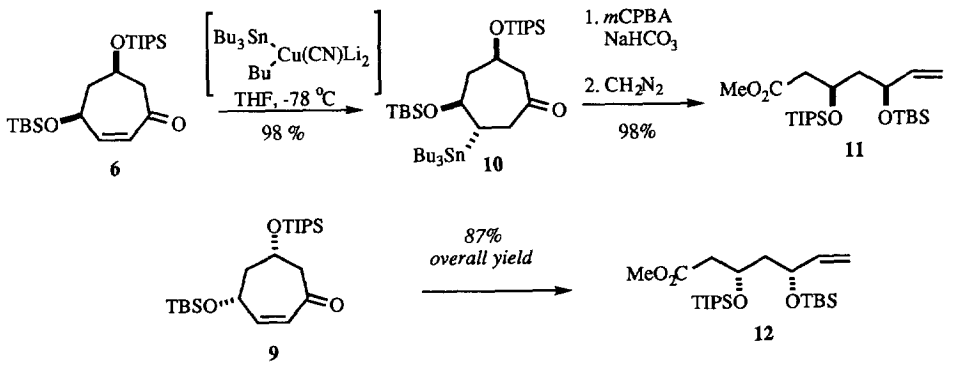
**Scheme 2**




Recently, we reported the use of tin-directed Baeyer-Villiger oxidations and Beckmann fragmentations as regioselective methods for the ring-opening of enones.[11,12] Conjugate addition of the tributylstannyl

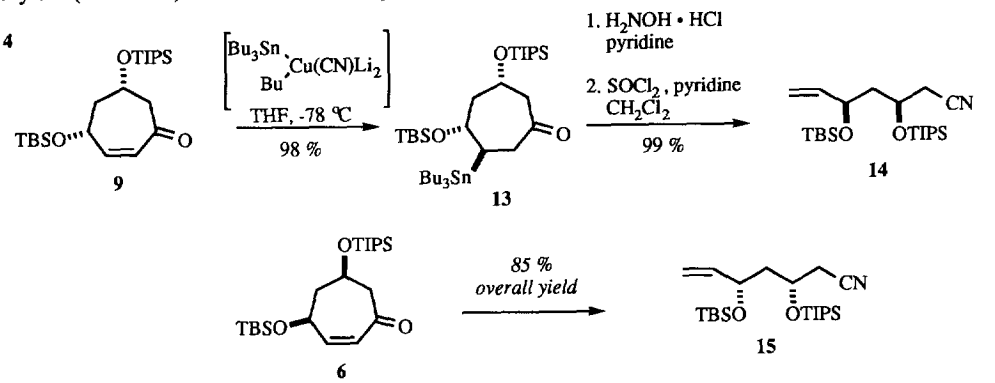
group[13] to enone **6** gave the corresponding β-stannylketone **10**, which under tin-directed Baeyer-Villiger conditions, afforded *syn*-1,3-bis(silyloxy) olefinic ester **11** in excellent yield (Scheme 3).

**Scheme 3**

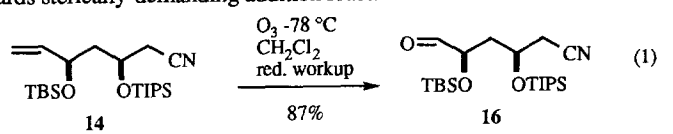



Enone **9** gave the enantiomeric, *syn*-1,3-bis(silyloxy) olefinic ester **12.** The tin-directed Beckmann fragmentation of the β-stannylketoxime derived from enone **9** gave *syn*-1,3-bis(silyloxy) olefinic nitrile **14** in excellent yield (Scheme 4). The enantiomeric *syn*-1,3-bis(silyloxy) olefinic nitrile **15** was obtained from **6.**

**Scheme 4**




We found *syn*-1,3-bis(silyloxy) fragmentation products **11**, **12**, **14** and **15** to be somewhat unreactive at the terminal functionalities. Attempts to reduce either the ester or nitrile with diisobutylaluminum hydride proved to be unsuccessful under a variety of conditions. However, the terminal olefin of nitrile **14** could be cleaved with ozone to furnish, after reductive workup, the corresponding aldehyde **16** (eq 1). This aldehyde, however, was surprisingly unreactive to a variety of carbon nucleophiles including enolates. These results led us to believe that the bulky silyl protecting groups, repelled by each other, were flanking the termini rendering them unreactive towards sterically-demanding addition reactions.

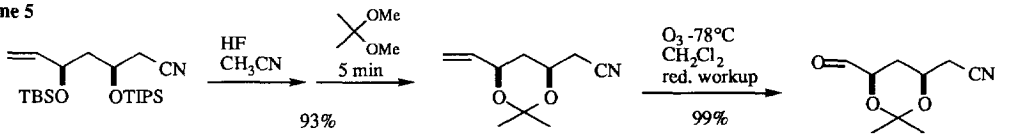



(1)

For this reason we decided to investigate a deprotection/protection procedure for the *syn*-1,3-bis(silyloxy) fragmentation products. Removal of the silyl groups under acidic conditions followed by acid-catalyzed reprotection of the *syn*-1,3-diol intermediate as its acetonide, was carried out in a one-pot sequence in

excellent yield (Scheme 5).[14] Ozonolytic cleavage of the terminal olefin followed by reductive workup gave the corresponding aldehyde **18** in nearly quantitative yield. Since the bulk of the acetonide, namely the geminal-dimethyl group, is held out of the plane of the termini, the usual reactivity displayed by aldehydes (reduction, addition) was now observed.

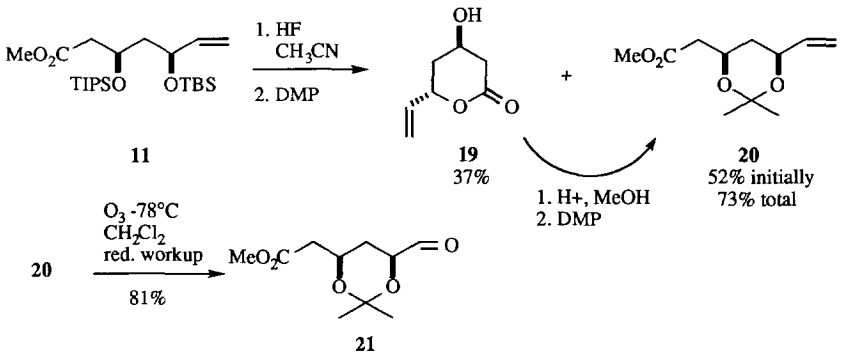
**Scheme 5**




**14** **17** **18**

Treatment of methyl ester **11** under the same conditions gave the desired acetonide **20** in modest yield due to the lactonization of the intermediate dihydroxy ester to give the hydroxylactone **19** (Scheme 6). Aldehyde **21** is a key building block in mevalonate-based HMG-CoA reductase inhibitors.[15]

**Scheme 6**

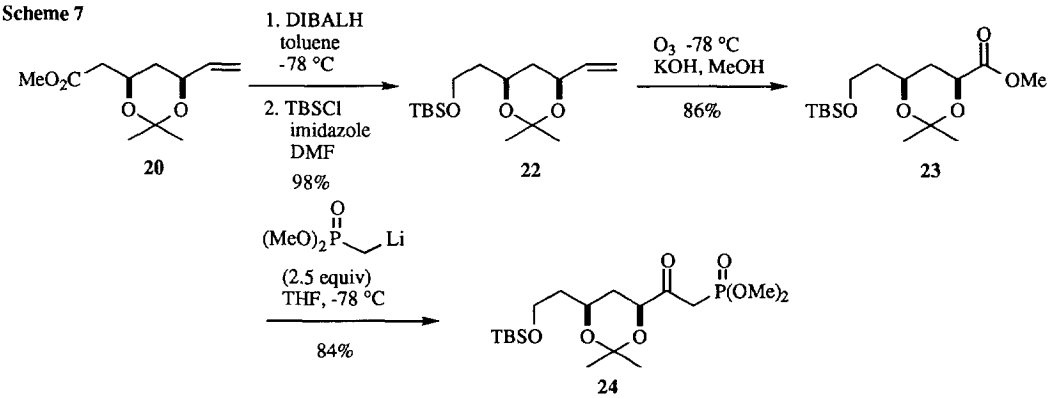



**11** **19** 37% **20** 52% initially 73% total

**20** **21**

*syn*-1,3-Acetonides **22** - **24** were prepared in excellent yields using standard methodology from methyl ester **20** (Scheme 7).[16] β-Ketophosphonate **24** is the enantiomer of a key building block used in Nicolaou's total synthesis of amphoteronolide B.[1,3a]

**Scheme 7**




**20** **22** **23** **24**

In summary, we have demonstrated that optically active monoacetate **3** is a precursor for end-differentiated *syn*-1,3-acetonides. The tin-directed fragmentations of enones **6** and **9** gave *syn*-1,3-bis(silyloxy) olefins that were desilylated and reprotected as their acetonides in a clean, one-pot reaction. These enantiopure *syn*-1,3-acetonides are attractive building blocks for the synthesis of more complex polyhydroxy products.[17]

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8 With the more bulky triisopropylsilyl (TIPS) protecting group at the apex oxygen, better endo selectivity (8 : 1) was observed in the singlet oxygen 4 + 2 cycloaddition than with the *tert*-butyldimethylsilyl (TBS) group (5 : 1). Furthermore the peroxide products were easier to separate by silica gel chromatography, which increased the overall efficiency of the preparation.

9 All new compounds displayed spectroscopic data consistent with their structural assignments.

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14 Upon treatment of the *syn*-1,3-bis(silyloxy) olefinic nitrile **14** ($R_f$ = 0.95 in 20% EtOAc/ pet. ether) with 5% hydrofluoric acid in $CH_3CN$, a new spot ($R_f$ = 0.50) on the TLC plate corresponding to the monodeprotected alcohol, visualized within 1 h. After 16 h, a baseline "smear" corresponding to the diol was the only spot observed. Dimethoxypropane (DMP) was then added in excess and a new spot ($R_f$ = 0.80) visualized instantly that corresponded to acetonide **17**. It was very important to quench the excess acid with aqueous bicarbonate immediately to keep formation of acid-catalyzed aldol products of dimethoxypropane to a minimum. These highly-colored by-products were often difficult to separate from the desired acetonide product.

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17 Selected $[\alpha]_D 20$ (*c* ca. 1, $CHCl_3$): **3**: +33.7; **6**; -56.7; **9**: +57.5; **11**: -10.7; **12**: +10.9; **14**: -14.7; **15**: +13.7; ent-**17**: -3.2; ent-**18**: -3.5; **20**: -3.1; **21**: -14.9; **22**: -24.1; **23**: -23.6 (Lit. 3a ent-**23**: +20.4); **24**: -52.1 (Lit. 3a ent-**24**: +48.1).

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