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A FORMAL TOTAL SYNTHESIS OF PGA_2 USING THE DIRECTED PAUSON-KHAND REACTION

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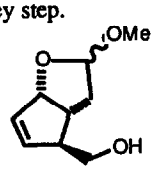
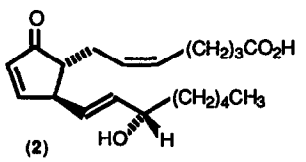
Summary: 3,3a,4,6a-Tetrahydro-2-methoxy-2H-cyclopenta[b]furan-4-methanol **1**, a key intermediate in the synthesis of PGA_2 **2**, was prepared via the first example of the use of the directed Pauson-Khand reaction in a natural product synthesis.

The Pauson-Khand reaction was first reported in 1973.[1] Although it has been widely utilized in synthetic chemistry its scope has been limited almost entirely to the intramolecular version due to the generally poor yields and low regioselectivity in the intermolecular case.[2] Our reports[3] on the ligand-directed Pauson-Khand reaction have, we feel, substantially broadened the potential applications of this cycloaddition in synthetic organic chemistry. In order to illustrate this we carried out a formal total synthesis of PGA_2 **2** using the directed Pauson-Khand reaction as a key step.



(1)



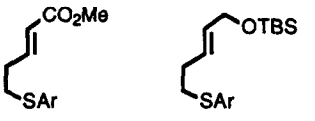
(2) PGA_2

We have previously shown that 1,2-disubstituted alkenes give rise to *trans*-4,5-disubstituted-2-cyclopentenones in a directed Pauson-Khand reaction[3]. Thus, acetal **1**, a key intermediate in Corey's synthesis[4] of PGA_2 **2**, seemed like an appropriate target molecule for a Pauson-Khand based approach as it contained a cyclopentenol skeleton and side chains bearing a *trans*-relationship.

Radical addition of 4-methoxybenzenethiol to acrolein (AIBN, toluene, 55 °C, 30 min, 0.06 M in 4-methoxybenzenethiol) gave a β-thioarylaldehyde. Immediate *in situ* treatment of the unstable aldehyde with methyl (triphenylphosphoranylidene)acetate ($MeO_2CCH_2PPh_3Br$, *t*-BuOK, CH_2Cl_2, 0 °C, 2 h) yielded the α,β-unsaturated ester **3** (90%, 8:1 E:Z; separated by column chromatography). Reduction of **3** to a primary alcohol (DIBAL-H, THF, -78 °C, 1 h, 97%) followed by formation of the *t*-butyldimethylsilyl ether (TBSCl, imidazole, THF, ambient temperature, 5 h, 99%) gave the Pauson-Khand precursor **4**.

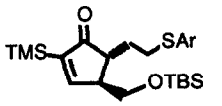
The key cycloaddition step was carried out by reaction of thio-olefin **4** and two equivalents of [(trimethylsilyl)acetylene]hexacarbonyldicobalt complex[5] (toluene, 95 °C, 30 h) yielding the *trans*-4,5-disubstituted-2-cyclopentenone **5** as the sole product (79%). No stereoisomeric products were observed. In the absence of the sulfide directing ligand a mixture of 4,5-disubstituted regioisomers would be expected,[2] thus illustrating the regiocontrol the directing group exerts over the cycloaddition reaction. The steric bulk of the TBS group also plays a role in enhancing the selectivity of the reaction. When 2-(trimethylsilyl)ethoxymethyl (SEM) or 2-methoxyethoxymethyl (MEM) ethers were used in place of the TBS ether the reaction was slower (48 h) and lower yielding (40-55%) and, in the case of the MEM group, 20% of the regioisomer was obtained.

Stereoselective reduction of **5** gave alcohol **6** (inverse addition of **5** to 2.5 equivalents of 1-pyrrolylborane-THF complex,[6] THF, 0 °C, 30 min, 75%). Cleavage of the vinyl TMS moiety with concomitant loss of the TBS protecting group to give **7** (*t*-BuOK, H_2O/DMSO, 80 °C, 30 min, 81%)[7] was followed by diol protection



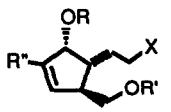
(3)

(4)

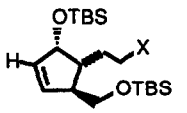


(5)

Ar=4-methoxyphenyl



(6) R =H, R'=TBS, R"=TMS, X=SAr
(7) R=R'=R"=H, X=SAr



(8) X=SAr
(9) X=S(O)Ar

(TBSCl, imidazole, THF, ambient temperature, 6 h, 99% of **8**) and oxidation (*m*-CPBA, CH_2Cl_2, -78 °C, 20 min, 98%) to afford sulfoxide **9**. Conversion to the required acetal **1** was then effected in one pot by Pummerer rearrangement (trifluoroacetic anhydride, 2,6-lutidine, MeCN, 0 °C, 30 min)[8] followed by *in situ* acetal formation ($HgCl_2$, H_2SO_4, MeOH, H_2O, 79 °C, 10 min, 51% of acetal **1** as a 2:1 mixture of acetal isomers).[9,10]

In conclusion, we have illustrated the usefulness of the directed Pauson-Khand reaction in organic synthesis by using it to form a functionalized cyclic intermediate, *trans*-4,5-disubstituted-2-cyclopentenone **5**, stereoselectively from simple acyclic precursors, thus effecting a short and efficient preparation of **1**.

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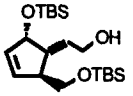
10. Acetal **1** underwent some decomposition during attempted rigorous purification and, as a result, satisfactory elemental analysis was obtained for bisether **10**, generated by $NaBH_4$ reduction (89%) of the Pummerer intermediate.

(10)



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