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DIASTEREOTOPIC GROUP SELECTIVITY AT A PROSTEREOGENIC CARBON CENTER: SYNTHESIS OF (±)-SYN-4,8-DIMETHYLDECANAL

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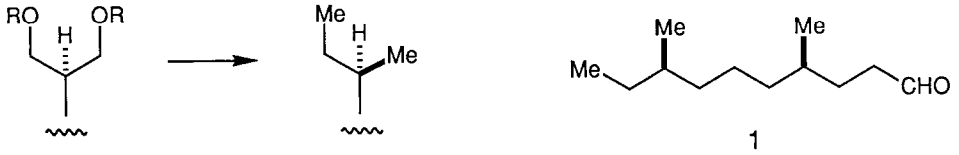
Abstract A group selective dealkylation reaction of a bridged ketal with trimethylsilyl iodide serves to control stereochemistry at carbon centers that are separated by five atoms. In combination with the iron/copper promoted fragmentation reaction of a hydroperoxide, a new synthesis of (±)-syn-4,8-dimethyldecanal has been achieved.

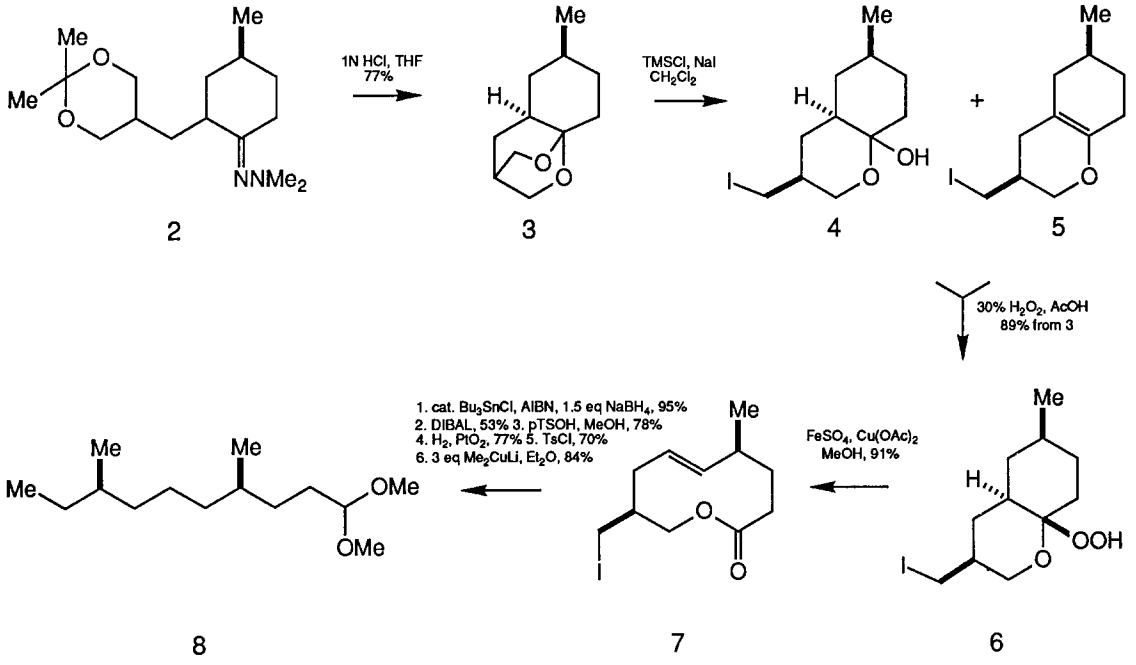
Group and/or face selective transformations constitute the means by which the process of asymmetric synthesis can be achieved.[1,2] We have been interested in developing group selective reactions in the context of natural products synthesis. Several spiroketalization reactions that proceed with diastereotopic group selectivity have been developed and applied to the synthesis of talaromycin B[3], talaromycin A[4], invictolide, and an ionophore subunit.[5] Several diastereotopic group selective peroxyketalization reactions were found to be useful in the context of a synthesis of an unsaturated macrolide.[6,7] In these latter studies we found that cis-4,8-disubstituted-$\Delta^{5,6}$-nonenolides could be prepared from the resultant peroxyketals *via* the iron/copper promoted fragmentation reaction.



1

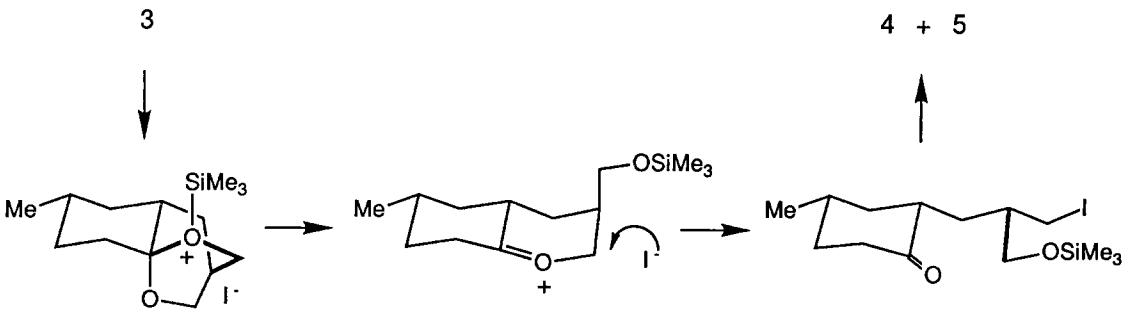
Since the macrolide is readily transformed into an acyclic chain, this process serves to control acyclic stereochemistry of alkyl groups in a 1,5-relationship. To demonstrate this point we have carried out further studies that (a) employ a group selective dealkylation reaction on route to the requisite hydroperoxyketal that proceeds with improved stereoselectivity relative to the previous methods[6] and (b) result in a synthesis of (±)-syn-4,8-dimethyldecanal **1**, the aggregation pheromone of the red flour beetle and the confused flour beetle.[8]

The tricyclic ketal **3** contains a prostereogenic carbon that is equipped with diastereotopic alkoxymethyl groups and serves as the substrate for the dealkylation reaction. Compound **3** was prepared by the alkylation of the dimethylhydrazone of 4-methylcyclohexanone[9] with 5-iodomethyl-2,2-dimethyl-1,3-dioxane.[10] The mixture of hydrazones was deprotected and cyclized in acid with concomitant equilibration of the alkyl group α to the ketal moiety.[12] Attempts to form the α-



2 3 4 5 6 7 8

alkoxyhydroperoxide directly with acetic acid and hydrogen peroxide[13] led to modest group selectivity. An alternative procedure was sought that might exploit the different locations of the alkoxymethyl groups in **3**. Thus, the reaction of **3** with iodotrimethysilane[14] proceeded with greater than 25:1 group selectivity to afford a mixture of iodides **4** and **5**. The formation of **4** and **5** can be explained by the initial silylation of the equatorial oxygen of the ketal in **3** to provide **9** followed by opening of the ketal to the oxenium ion **10** and displacement of the carbon-oxygen bond by iodide to afford **11**.[15] After workup and SiO_2 chromatography, the desilylated products **4** and **5** are obtained.



9 10 11

The equivalency of the compounds **4** and **5** with respect to the synthetic scheme was demonstrated by their transformation to the same alkoxyhydroperoxide **6** upon treatment with hydrogen peroxide in acetic acid. Fragmentation of hydroperoxide **6** with $Cu(OAc)_2/FeSO_4$ [6,13,16] gave rise to the macrolide iodide **7** with 10:1 selectivity in the position of the olefin. The mechanism of and selectivity in related reactions has been discussed elsewhere.[6b]

With the syn-1,5-dialkyl stereochemistry along the single carbon chain now established, the final conversion to **1** could be achieved in a straightforward manner. Reduction of the iodomethyl group[17] and the lactone,[18] protection of the aldehyde, hydrogenation of the double bond and homologation of the alcohol through displacement of the tosylate[19] afforded the acetal **8** which has been converted to **1** by Professor K. Mori.[8d,e] The stereochemistry of **8** was confirmed by comparison to an authentic sample of **8** prepared through Mori's unambiguous synthesis[8d,e] and the diastereomeric mixture (1:1) of syn and anti **8**.[20] The 125.8 MHz ^{13}C NMR of the diastereomeric mixture showed doubling of 6 of the 14 resonances.[21] The peaks belonging to the syn isomer could be identified by comparison to the "authentic" sample of **8**.[22] The chemical shifts of our synthetic material were in turn compared to these assigned values and were found to be identical to within 0.01 ppm. This ^{13}C NMR comparison[23] allows us to identify **8** as the syn isomer and to conclude that a synthesis of (±)-syn-4,8-dimethyldecanal has been achieved.

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21. ^{13}C NMR of the syn/anti mixture (125.77MHz, $CDCl_3$) δ 11.39, 19.20, 19.25, 19.57, 19.63, 24.44, 29.47, 29.56, 30.07, 31.62, 31.70, 32.67, 34.41, 36.89, 36.93, 37.22, 37.26, 52.54, 52.62, 104.97.

22. ^{13}C NMR of **8** (125.77MHz, $CDCl_3$) δ 11.38, 19.25, 19.63, 24.44, 29.47, 30.07, 31.62, 32.70, 34.42, 36.93, 37.26, 52.54, 52.62, 104.97.

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