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Stereoselective Production of β-Amino Alcohols and β-Thioacyl Alcohols via an Application of the non-Aldol Aldol Process

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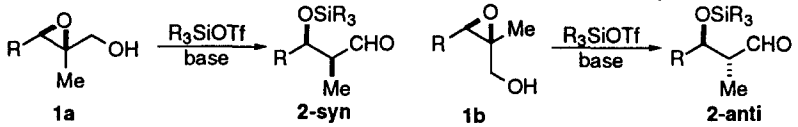
Abstract: The mesylates used as protecting groups to permit the formation of bis(polypropionates) via the non-aldol aldol process can be easily displaced with good nucleophiles, e.g., azide, thioacetate, acetate, to generate β-azido (and β-amino) alcohols, β-thioacyl alcohols, and aldols of the opposite chirality, e.g., syn isomers afford anti products. Thus the anti mesylate **15** affords the all-anti mzido aldol system **16** in good yield.

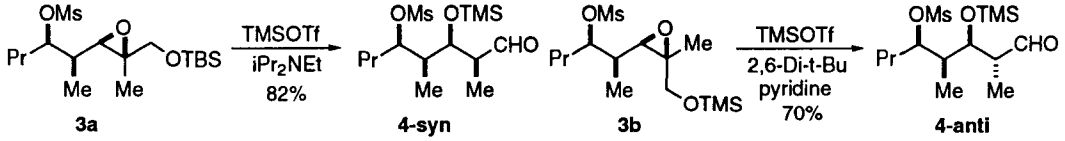
Keywords: Non-aldol aldol process, anti-aldol products, β-amino and β-thioacyl alcohols

Over the last several years, we have reported the stereospecific rearrangement of several classes of epoxides, e.g., various tertiary allylic epoxides and β-hydroxy tertiary epoxides.[2-7] We have described the efficient preparation of both the syn and anti aldol diastereomers via the rearrangement of *E* and *Z*-epoxy alcohols on treatment with mild Lewis acids, e.g., trialkylsilyl triflates.[3] For example, treatment of the homochiral epoxide **1a** formed from the *E* allylic alcohol with a silyl triflate affords the syn aldol diastereomer **2-syn** in good yield and purity. The anti aldol diastereomer **2-anti** is available from the homochiral epoxide **1b** prepared from the *Z*-allylic alcohol. We have extended this process to the preparation of polypropionates[7] and intermediates for the synthesis of the tedanolides.[6, 8-9]



1a **2-syn** **1b** **2-anti**

In order to prepare the bis(propionates) **4** from the substituted epoxy alcohol derivatives, we needed to protect the β-hydroxyl group with a non-participating group to prevent cyclization to give tetrahydrofurans.[5] It turned out that the best protecting group we have examined was the mesylate. Thus treatment of the silyl ethers **3ab** with trimethylsilyl triflate and base afforded the syn and anti bis(propionates) **4** in good yields.[7] We have shown that the mesylate can



3a **4-syn** **3b** **4-anti**

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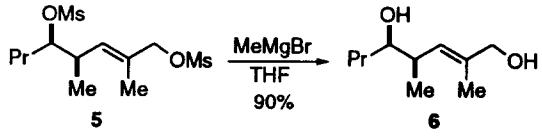
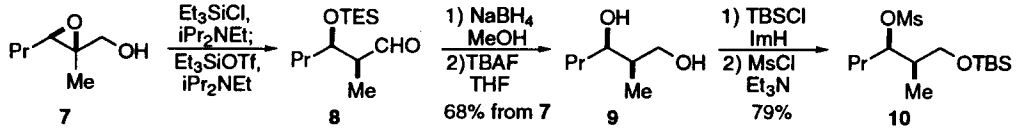
be removed by treatment with methylmagnesium bromide,[7,10] regenerating the alcohol and thereby serving as a protecting group, e.g., **5** → **6**. However, we argued that the mesylate could serve not only as an unusual protecting



5 **6**

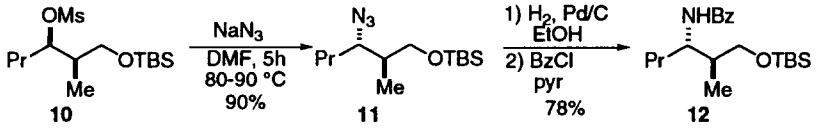
group but also in its normal role as an activator of alcohols for S_N2 attack. Nucleophilic displacement of the mesylate from syn aldol diastereomers with nitrogen or sulfur nucleophiles would extend the non-aldol aldol process to the formation of β-amino and β-thioacyl alcohols. Also the use of oxygen nucleophiles might generate the anti aldol diastereomers by a route that might be superior in certain cases to the direct route. We now report the successful implementation of this strategy.

We first decided to look at a simple mono-aldol system. The required substrate **10** was prepared as follows. The alcohol **7**, prepared in >95% ee by a Sharpless asymmetric epoxidation, was converted into the syn aldol product **8** which was reduced and deprotected to give the diol **9** in 68% yield. Selective silylation of the primary alcohol

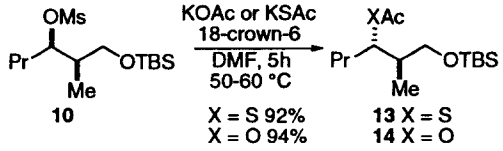


7 **8** **9** **10**

and mesylation afforded **10** in 79% yield. Displacement of the mesylate of **10** with sodium azide in dimethylformamide (DMF) at (80-90 °C) gave the azide **11** which was then catalytically hydrogenated to give the amine, which was benzoylated to aid in isolation and structure determination to give **12** in 70% overall yield. Also treatment of the mesylate **10** under somewhat milder conditions, e.g., with potassium thioacetate and 18-crown-6 in DMF at 50-60 °C for 5h gave the thioacetate **13** in 92% yield as a 20 : 1 mixture with elimination products. Thus both anti β-amino alcohols and anti β-thio-alkyl alcohols are readily available from the syn aldol products. The simple anti aldol product can also be prepared by this route, e.g., displacement of the mesylate with potassium acetate and 18-crown-6 in DMF at 50-60 °C for 5h gave a 94% yield of a 12 : 1 mixture of the desired acetate **14** and elimination products.



10 **11** **12**



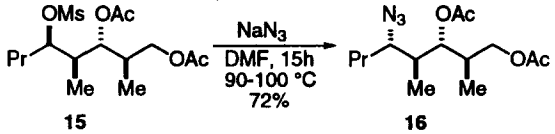
10

X = S 92%
X = O 94%

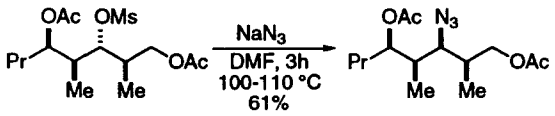
13 X = S
14 X = O

Thus displacement of the mesylate protecting group allows one to prepare the anti compounds **11-14** starting with the syn aldol product **8** in several steps. These compounds are precursors to important anti β-amino acids and anti β-thio acids.

We next examined analogous displacements with the more hindered bis(propionate) products. The anti mesyloxy diacetate **15** (prepared as described before)[7] was treated with sodium azide in DMF at 90-100 °C for 15 h



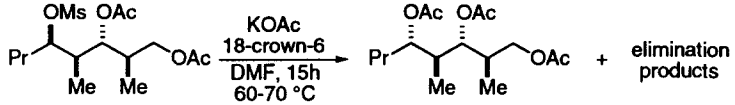
15 **16**



17 **18**

to give the product of displacement, the azide **16**, in 72% yield. Thus one can prepare all-anti amino aldol systems such as **16** by an adaptation of the non-aldol aldol route. Also the much more hindered mesylate of the isomeric mesyloxy diacetate **17** could also be displaced by sodium azide similar conditions to give the all-syn amino aldol system **18** in good yield.

Finally the all-anti aldol system **20** could also be prepared, along with significant amounts of elimination products, by displacement of the mesylate **19** with potassium acetate.



19 88% **20**

Further work on the use of this chemistry to produce amino and thio derivatives of syn and anti polypropionates is currently under way in our laboratories.

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References and Notes

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