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Reductive Lithiation of Alkyl 2-Thiopyridyl Ethers to Generate Optically Pure α-Alkoxylithium Reagents

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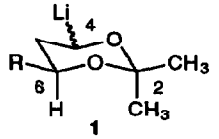
Abstract.: Enantiomerically pure 4-lithio-2-alkyl-1,3-dioxanes, **11** and **13**, were prepared by reductive lithiation of alkyl 2-thiopyridyl ether **10**, which was in turn prepared by Barton radical decarboxylation of the homologous acid. The optical activity was introduced by chirality transfer to and from the stereogenic acetal center.

Many methods have been developed to prepare optically pure, configurationally stable α-alkoxy organolithium reagents, including classic resolution[1] of and enantioselective preparation[2] of the corresponding α-alkoxystannanes, diastereoselective reductive lithiations,[3] and enantioselective deprotonations.[4] We have previously shown that diastereoselective reduction of 6-alkyl-2,2-dimethyl-4-thiophenyl-1,3-dioxanes give optically pure α-alkoxylithium reagents that can be useful synthons in the preparation of 1,3-diols.[5] The initially formed axial (trans) alkyllithium reagents can be equilibrated to the thermodynamically more stable equatorial (cis) alkyllithium reagents with high diastereoselectivity, extending the utility of these reagents.[5,6] The initial work was carried out using acetonides **1**, where the 6-alkyl substituent controls the conformation of the dioxane ring and thus the configuration at the alkyllithium center.[5] Subsequently, the more readily available acetals **2** have been developed as 1,3-diol synthons, where both the 6-alkyl substituent and the acetal stereogenic center reinforce the preferred chair conformation.[7] We now report the preparation of the non-racemic acetals **3**, where the acetal stereogenic center locks the dioxane ring into a single chair conformation and thus controls the configuration at the alkyllithium center. The conformational anchor is part of a removable protecting group, thus the diastereomeric trans and cis alkyllithium reagents lead to enantiomeric products after addition and deprotection.



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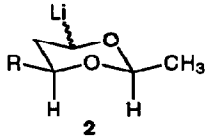

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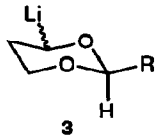
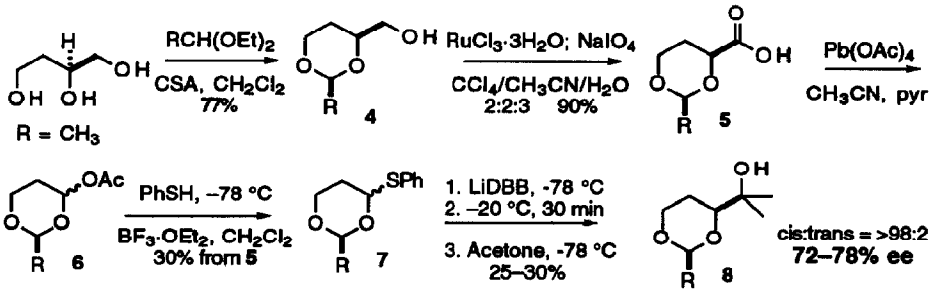


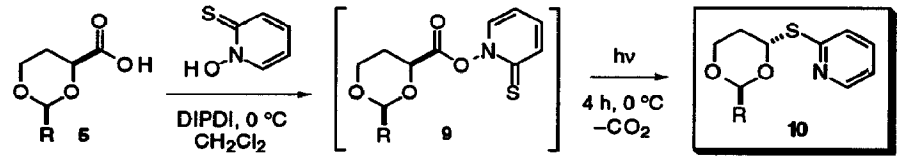
3

The chiral alkyllithium reagent **3** was initially prepared as described in Scheme I. Diastereoselective protection of (*S*)-(–)-1,2,4-butanetriol[8] with 1,1-diethoxyethane and CSA gave the cis 1,3-dioxane **4** in 77% yield along with dioxolanes and ethoxyethyl protected products that could be

Scheme I

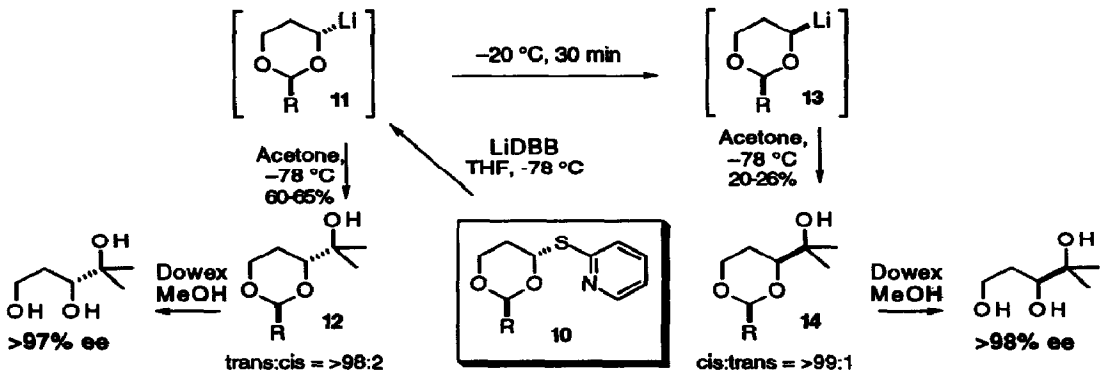


recycled. The chirality of the starting material was relayed to the stereogenic acetal center in the product. In order to replace the 4-hydroxymethyl subsitituent with a 4-thiophenyl group, the alcohol **4** was oxidized to carboxylic acid **5**,[9] which was then oxidatively decarboxylated by treatment with $Pb(OAc)_4$ to give the acetates **6** as a mixture of diastereomers. Treatment of **6** with $BF_3{\cdot}OEt_2$ and PhSH gave the 2-methyl-4-thiophenyl-1,3-dioxanes, **7**, as a mixture of diastereomers. Reductive lithiation of **7** by treatment with 2 equiv LiDBB in THF at -78 °C gave the axial lithium reagent, which was warmed to –20 °C for 30 min to equilibrate to the more stable (cis) equatorial lithium reagent.[3a,6] Trapping with acetone at -78 °C gave a modest yield of the cis adduct **8** with >98:2 diastereoselectivity. To evaluate the optical purity of **8**, the acetal was removed (Dowex/MeOH) and the resulting triol was derivatized with (*S*)-MTPA-Cl to give the bis (*R*)-MTPA ester. To our surprise, ^1H NMR analysis showed that the optical purity of the product had eroded to 72-78% ee. Direct trapping of the axial alkyllithium reagent gave products of comparable enantiomeric excess. Where was the stereochemical integrity being lost? The acid **5** was determined to be >98% ee by converting it to alcohol **8** (*i.* CH_2N_2, *ii.* MeLi) and evaluating the optical purity as described above. Somewhere in the sequence from **5** to **8** via **7** the acetal configuration was partially scrambled.



Of the several intermediates along the way from **5** to **8**, an oxonium ion appeared to be the most likely culprit in the acetal epimerization. To avoid the intermediacy of an oxonium ion, we developed a preparation of alkyllithium reagent **3** based on Barton's radical decarboxylation.[10] Although we developed this procedure to answer a mechanistic question, it has potential as a synthetic method in its own right. Acid **5** (R = n-C_6H_{13}) was coupled with *N*-hydroxypyridine-2-thione using diiospropylcarbodiimide (DIPDI) in CH_2Cl_2 in the dark. Irradiation of the reaction mixture containing the ester **9** lead to radical decarboxylation and trapping to give the trans 4-(2-thiopyridyl)-1,3-dioxane **10**

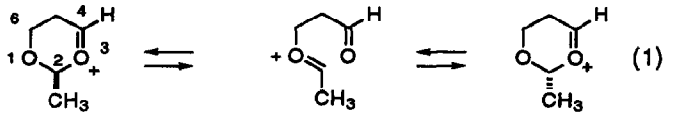
Scheme II



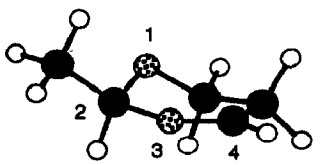
in 65–73% yield.[10] This sequence was initially carried out on the acetaldehyde acetal **5** (R = CH_3), but later work was performed using the heptanal acetal **5** (R = n-C_6H_{13}) to avoid losses attributed to volatility. By analogy with the thiophenyl group, the 2-thiopyridyl group was expected to generate an alkyllithium reagent on reductive lithiation. We were pleased to find that reduction worked well when 2-thiopyridyl ether **10** was added to excess LiDBB in THF at -78 °C, Scheme II. The initially formed axial alkyllithium reagent **11** coupled with acetone in good yield to give the trans adduct **12** with >98:2 diastereomeric purity. Hydrolysis gave (*R*)-4-methyl-1,3,4-pentanetriol, which was shown by Mosher ester analysis to be >97% ee. In a complementary sequence, reduction of **10** followed by equilibration of the axial alkyllithium reagent **11** to an equatorial alkyllithium reagent **13** and trapping with acetone gave cis adduct **14** in modest yield but with >99:1 selectivity. Protonation of **11** during the equilibration step accounted for the balance of the material. Hydrolysis gave (*S*)-4-methyl-1,3,4-pentanetriol with >98% ee by Mosher ester analysis. Either enantiomer of the product was prepared from one enantiomer of **10** by reaction of the diastereomeric alkyllithium reagents **11** or **13**, and subsequent removal of the stereogenic acetal protecting group.[11] Both products were isolated with high enantiomeric excess, demonstrating that the acetal configuration was maintained in the Barton decarboxylation, reductive lithiation, and alkyllithium epimerization.

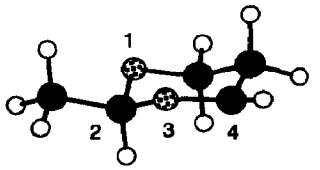
Acetal epimerization was observed in Scheme I but not in Scheme II, so the epimerization could have occurred in either the $Pb(OAc)_4$ oxidation or the thiophenol/BF_3·OEt_2 treatment. Both reactions are expected to proceed via oxonium ion **15**. Epimerization of **15** could occur by ring opening to the acyclic oxonium ion **16** followed by reclosure to **15** or **15'**, eq 1. Calculations were carried out to clarify the structure and reactivity of **15**. The RHF 6-31G*//6-31G* minimized structure for cation **15** is shown in Figure 1, along with selected bond lengths and Lowdin bond orders.[12] Also shown in Figure 1 is the structure for the corresponding radical, **17**, at the UHF 6-31G*//6-31G* minimum. The O3-C4 bond in **15** shows significant double bond character, while the C2-O3 bond is both longer and has a lower bond order than a normal C-O single bond. The proposed epimerization of **15** via intermediate **16** involves

breaking the C2-O3 bond, and it is clear from the calculation that this bond is already quite weak in **15**. In contrast, the C2-O3 bond in the radical **17** shows only a slight weakening, consistent with the lack of epimerization observed in the Barton decarboxylation.



15 **16** **15'** (1)





2-Methyl-1,3-dioxane-4-carbenium ion (15)
E(HF) = -344.0437136
Bond Order and Length
O_1–C_2 = 1.270, 1.34 Å
C_2–O_3 = 0.757, 1.55 Å
O_3–C_4 = 1.884, 1.23 Å
C_6–O_1 = 1.069, 1.41 Å

2-Methyl-1,3-dioxan-4-yl (17)
E(UHF) = -344.2525586
Bond Order and Length
O_1–C_2 = 1.144, 1.39 Å
C_2–O_3 = 1.091, 1.40 Å
O_3–C_4 = 1.197, 1.36 Å
C_6–O_1 = 1.105, 1.40 Å

The acetal stereogenic center can be used as a conformational anchor to control the alkyllithium configuration of 4-lithio-2-methyl-1,3-dioxanes **11** and **13**. Alkyllithium reagents **11** and **13** are both prepared from 2-thiopyridyl ether **10**, and lead to enantiomeric adducts once the stereogenic acetal protecting groups have been removed. Oxonium ion intermediate **15** leads to partial epimerization in the preparation of thiophenyl ether **7**, but epimerization is avoided in the Barton radical decarboxylation route to 2-thiopyridyl ether **10**. Reductive lithiation of 2-thiopyridyl ethers provides an unusual entry to complex alkyllithium reagents that should be of general utility.[13]

References and Footnotes

1 Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.
2 Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5586.
3 a) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. b) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
4 Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1457.
5 Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982.
6 Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011.
7 Rychnovsky, S. D.; Skalitzky, D. *J. Org. Chem.* **1992**, *57*, 4336.
8 The triol is available commercially, or it can be prepared by the reduction of (*S*)-(–)-malic acid.
9 Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
10 Barton, D. H. R.; Crich, D.; Motherwell, W. B.; *Tetrahedron*. **1985**, *41*, 3901.
11 Reagents **11** and **13** (R = CH_3) also coupled stereoselectively with PhCHO and Bu_3SnCl.
12 SPARTAN 3.0, Wavefunction Inc., 18401 Von Karman, #210, Irvine, CA 92715.

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