

Construction of a Chiral Quaternary Carbon Center via 1,2-Acyl Migration of
an Optically Active α,β -Epoxy Ketone

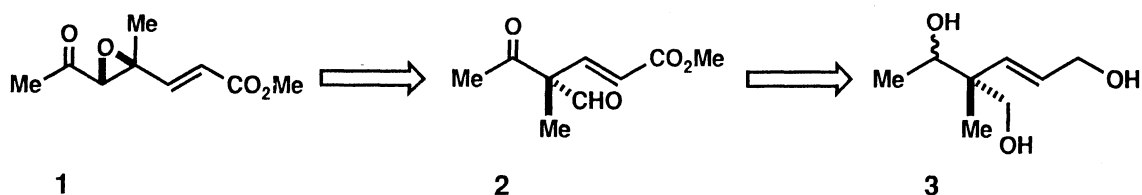
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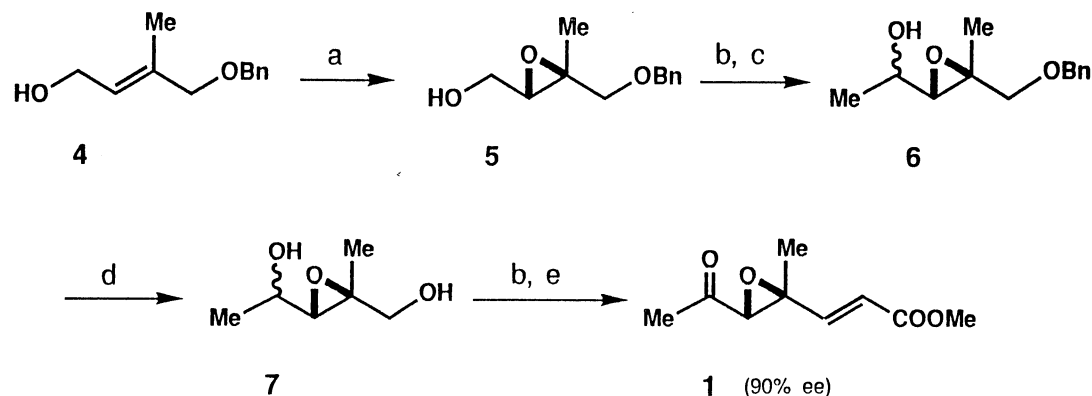
The construction of a chiral building block with a quaternary carbon center is described, based on the Lewis acid-catalyzed acyl migration of α,β -epoxy ketone with alkyl and alkenyl substituents.

Recent stereochemical studies on Lewis acid catalyzed acyl migration in optically active α,β -epoxy ketones, such as 1,3-diphenyl-2-butene-1-one oxide leading to 1,2-diphenyl-2-methyl-1,3-propanedione indicate 1,2-shifts of carbonyl groups to be a concerted process with inversion of configuration at the migration terminus and without loss of optical purity.¹⁾ However, application of this transformation²⁾ to the synthesis of useful chiral synthons has not been developed. Thus, study was made to examine whether isomerization of an optically active acyclic α,β -epoxy ketone with appropriate alkyl and alkenyl substituents in place of a phenyl group can serve as a method for constructing a chiral quaternary carbon center.

This paper reports the results of the BF_3 -catalyzed rearrangement of the simple optically active epoxy ketone **1** which leads to the optically active building block **2** or **3**. The Chiral epoxy ketone **1** was used as a substrate, since Sharpless asymmetric epoxidation³⁾ of allylic alcohols is applicable to the synthesis of **5**, a key precursor of **1**, in high optical purity. The structural feature of **1** is the α,β -unsaturated ester moiety which may promote selective ring opening of the oxirane and stabilize a resulting carbenium ion intermediate.⁴⁾



The synthesis of chiral epoxy ketone **1**⁵⁾ through optically active epoxy alcohol **5** (90% ee, estimated by Mosher's method⁶⁾) was achieved conventionally as summarized in Scheme 1.



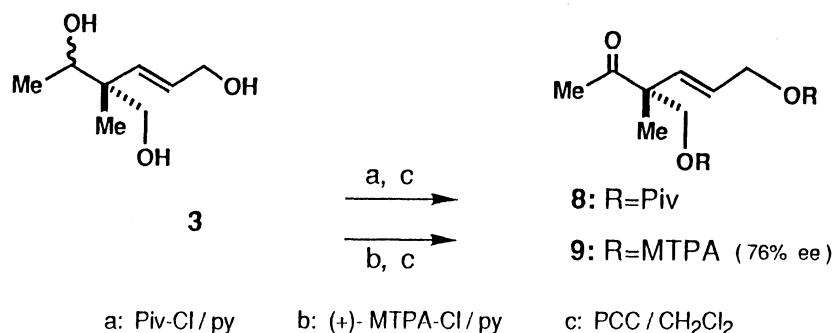
a: $\text{Ti}(\text{OiPr})_4$ -TBHP-(+)-DET / CH_2Cl_2 / -20°C b: Swern oxidn. c: MeMgI d: H_2 / Pd - C / EtOAc
 e: $\text{Ph}_3\text{P}=\text{CHCOOMe}$

Scheme 1.

When optically active epoxy ketone **1** ($[\alpha]_{\text{D}}^{25} -9.97^\circ$ (c 0.56, CHCl_3)) was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv) in CH_2Cl_2 at -20°C for 1 h followed by the addition of anhydrous NaHCO_3 (10 equiv) and extractive work up with CH_2Cl_2 , 1,2-acyl migration product **2** was detected in the reaction mixture by ^1H -NMR spectroscopy in ca. 80% yield.⁷⁾ However, the product **2** could not be isolated from the reaction mixture by silica gel TLC.⁸⁾ After several trials, we concluded that the transformation of **1** into **2** could be achieved under the above mentioned conditions, but **2** was too unstable to be isolated. Indeed, the product **2** gradually decomposed even in CH_2Cl_2 and rapidly in MeOH.

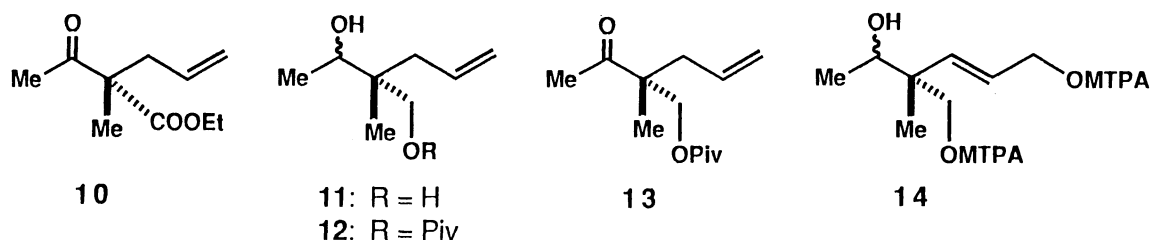
We have established a procedure for the transformation of **1** into triol **3** in one pot: the direct reduction of the migration product with diisobutylaluminum hydride (DIBAL-H, 5.0 mol equiv) in CH_2Cl_2 at -20°C in the presence of powdered anhydrous NaHCO_3 followed by careful decomposition of an excess DIBAL-H with 1N HCl in MeOH. Concentration of the reaction mixture gave a residual solid which was then poured into a silica gel column using a mixture of CH_2Cl_2 -MeOH (100:7) and eluted with the same solvent to give the desired triol **3** in 75% overall yield from **1**: The triol **3** was apparently a mixture of diastereoisomers (1:1) which was then treated successively with pivaloyl chloride (Piv-Cl, 3.0 equiv) in pyridine and with pyridinium chlorochromate (PCC) in CH_2Cl_2 to give an optically active ketone **8**⁹⁾ (85%, $[\alpha]_{\text{D}}^{25} +14.6^\circ$ (c 0.37, CHCl_3)) as an oil. The triol **3** was transformed into **9**¹⁰⁾ by treatment with (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride ((+)-MTPA-Cl, 3.0 equiv) in pyridine in the usual way (Scheme 2).⁶⁾

The optical purity of **9** was conventionally determined by an NMR to be 84% ee based on two singlets appeared at 2.00 and 2.02 ppm with an integral ratio of 88:12.



Scheme 2.

The absolute configuration of **9** was established by comparison with an authentic sample derived from Koga's chiral keto-ester (S)-**10**¹¹) ($[\alpha]_D^{25}$ -26.8° (c 0.53, CHCl₃), 90% ee; lit. $[\alpha]_D^{22}$ -27.9°, 94% ee). Reduction of **10** with DIBAL-H in CH₂Cl₂ at 0 °C produced the diol **11** in 82% yield. Esterification of **11** with Piv-Cl in pyridine afforded **12** in 92% yield, which was then oxidized with PCC in CH₂Cl₂ to give **13** (85%). Treatment of **13** with mercuric acetate (1.05 equiv) in AcOH (140 °C, 4 h) followed by demercuration mediated by NaBH₄-O₂ in N,N-dimethylformamide and alkaline hydrolysis produced a triol (80%) which was successively treated with 2 equivalent of (+)-MTPA-Cl in pyridine, giving rise to **14** (74%). The Oxidation of **14** with PCC in CH₂Cl₂ afforded the desired ketone, whose ¹H-NMR spectrum was in complete agreement with that of **9** above.



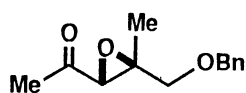
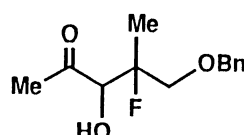
Acyl migration in optically active **1** occurs in the presence of BF₃-Et₂O at -20 °C with inversion of configuration at the migration terminus with a high degree of concertedness. Product **3** obtained from **1** has a chiral quaternary carbon center with the four differently functionalized substituents. Application of this method to the synthesis of various chiral synthons bearing a quaternary carbon center is now in progress.

References

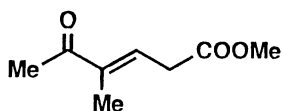
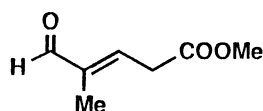
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- 2) R. D. Bach and R. C. Klix, *Tetrahedron Lett.*, **26**, 985 (1985); F. Kunisch, K. Hobert, and P. Welzel, *ibid.*, **26**, 6039 (1985); R. D. Bach and R. C. Klix, *J. Org. Chem.*, **50**, 5438 (1985); R. D. Bach, M. W. Tubergen, and R. C. Klix, *Tetrahedron Lett.*, **27**, 3565 (1986); R. C. Klix and R. D. Bach, *J. Org. Chem.*, **52**, 580 (1987); V. St. Enev and E. T. Tsankova, *Tetrahedron*, **47**, 6399 (1991).
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- 4) Treatment of the epoxide **A** resulted in the formation of fluorohydrin **B** (41%). No other desirable products related to the rearrangement were detected.

**A****B**

- 5) ¹H-NMR (CDCl₃) δ: 1.45 (3H, s), 2.27 (3H, s), 3.54 (1H, s), 3.77 (3H, s), 6.10 (1H, d, J=15.5 Hz), 6.74 (1H, d, J=15.5 Hz).
- 6) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
- 7) ¹H-NMR (CDCl₃) δ: 1.53 (3H, s), 2.21 (3H, s), 3.78 (3H, s), 5.99 (1H, d, J=16.2 Hz), 7.24 (1H, d, J=16.2 Hz), 9.61 (1H, s).
- 8) Purification of the crude product **2** on a silica gel TLC gave **C** (42%) and **D** (13%) as an oil, respectively.

**C****D**

- C**: ¹H-NMR (CDCl₃) δ: 1.78 (3H, s), 2.36 (3H, s), 3.30 (2H, d, J=7.1 Hz), 3.75 (3H, s), 6.81 (1H, t, J=7.1 Hz). **D**: ¹H-NMR (CDCl₃) δ: 1.74 (3H, s), 3.40 (2H, d, J=7.1 Hz), 3.78 (3H, s), 6.69 (1H, t, J=7.1 Hz), 9.49 (1H, s).
- 9) ¹H-NMR (CDCl₃) δ: 1.17 (9H, s), 1.20 (9H, s), 1.31 (3H, s), 2.15 (3H, s), 4.18 (1H, d, J=11.1 Hz), 4.24 (1H, d, J=11.1 Hz), 4.57 (2H, d, J=5.4 Hz), 5.72 (1H, m), 5.82 (1H, d, J=16.1 Hz).
 - 10) ¹H-NMR (CDCl₃) δ: 1.28 (3H, s), 2.02 (3H, s), 3.48 (3H, s), 3.53 (3H, s), 4.33 (1H, d, J=11.1 Hz), 4.40 (1H, d, J=11.1 Hz), 4.73 (1H, dd, J=13.4, 5.4 Hz), 4.81 (1H, dd, J=13.4, 5.4 Hz), 5.72 (1H, dt, J=15.8, 5.4 Hz), 5.79 (1H, d, J=15.8 Hz), 7.38-7.51 (10H, m).
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