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

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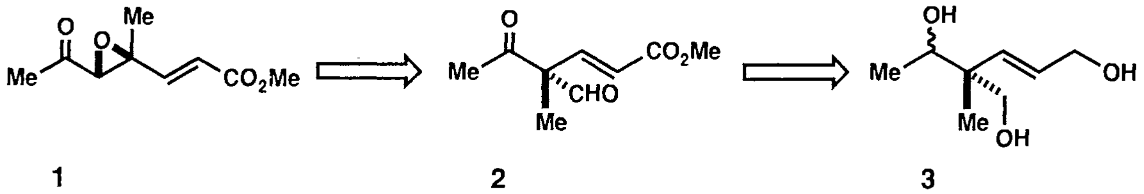
The construction of a chiral building block with a quaternary carbon center is described, based on the Lewis acid-catalyzed acyl migration of α,β-epoxy ketone with alkyl and alkenyl substituents.

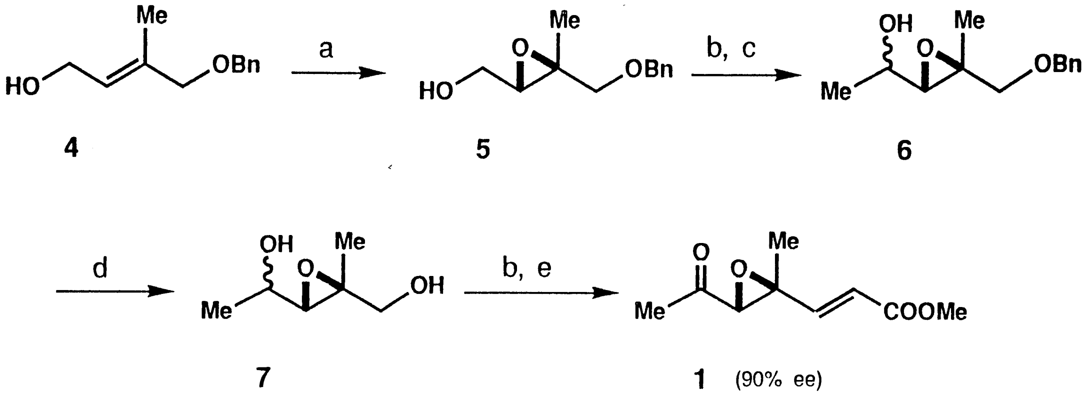
Recent stereochemical studies on Lewis acid catalyzed acyl migration in optically active α,β-epoxy ketones, such as 1,3-diphenyl-2-butene-1-one oxide leading to 1,2-diphenyl-2-methyl-1,3-propanedione indicate 1,2-shifts of carbonyl groups to be a concerted process with inversion of configuration at the 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 quarternary 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)



1 **2** **3**

The synthesis of chiral epoxy ketone **1**[5] through optically active epoxy alcohol **5** (90% ee, estimated by Mosher's method[6]) was achieved conventionally as summerized in Scheme 1.



a: Ti $(OiPr)_4$-TBHP-(+)-DET / CH_2Cl_2 / -20 °C b: Swern oxidn. c: MeMgI d: H_2 / Pd - C / EtOAc

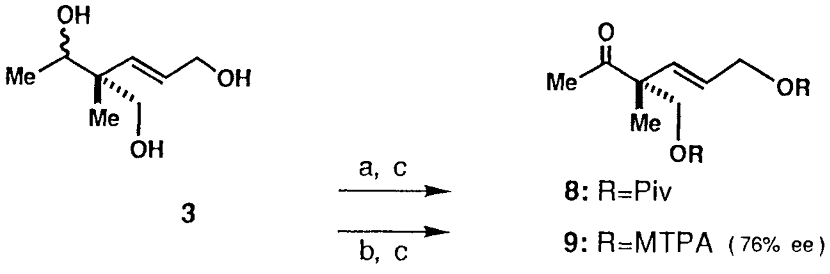
e: $Ph_3P{=}CHCOOMe$

Scheme 1.

When optically active epoxy ketone **1** ($[\alpha]_D^{25}$ -9.97° (c 0.56, $CHCl_3$)) was treated with BF_3-Et_2O (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 ^{1}H-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%, $[\alpha]_D^{25}$ +14.6° (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]

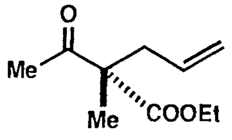
The optical purity of **9** was conventionaly determined by an NMR to be 84% ee based on two singlets appeared at 2.00 and 2.02 ppm with an integral ratio of 88:12.



a: Piv-Cl / py b: (+)- MTPA-Cl / py c: PCC / CH_2Cl_2

Scheme 2.

The absolute configuration of **9** was establised by comparison with an authentic sample derived from Koga's chiral keto-ester (S)-**10**[11] ($[\alpha]_D^{25}$ -26.8° (c 0.53, $CHCl_3$), 90% ee; lit. $[\alpha]_D^{22}$ -27.9°, 94% ee). Reduction of **10** with DIBAL-H in CH_2Cl_2 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 CH_2Cl_2 to give **13** (85%). Treatment of **13** with mercuric acetate (1.05 equiv) in AcOH (140 °C, 4 h) followed by demercuriation mediated by $NaBH_4$-O_2 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 CH_2Cl_2 afforded the desired ketone, whose ^1H-NMR spectrum was in complete agreement with that of **9** above.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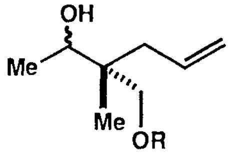
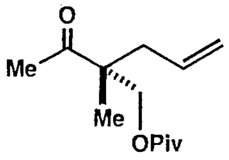

11: R = H
12: R = Piv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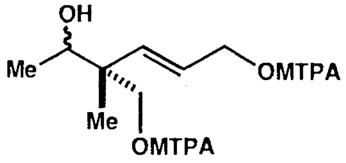
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Acyl migration in optically active **1** occurs in the presence of BF_3-Et_2O at -20 °C with inversion of configuration at the migration terminus with a high degree of concertedness. Product **3** obtained from **1** has a chiral quaternary carbon 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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J. Am. Chem. Soc., **100**, 1605 (1978) and references cited therein.

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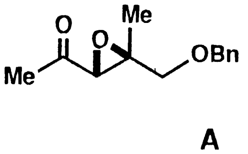
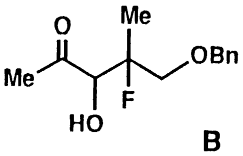
4) Treatment of the epoxide **A** resulted in the formation of fluorohydrin **B** (41%). No other desirable products related to the rearrangement were detected.



A



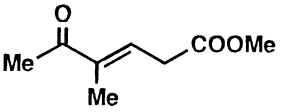
B

5) ^{1}H-NMR (CDCl$_3$) 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).

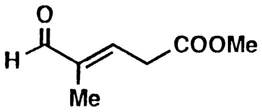
6) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

7) ^{1}H-NMR (CDCl$_3$) 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: ^{1}H-NMR (CDCl$_3$) 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**: ^{1}H-NMR (CDCl$_3$) 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) ^{1}H-NMR (CDCl$_3$) 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) ^{1}H-NMR (CDCl$_3$) 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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