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Nonracemic 2-Diazo-1-oxiranyl-ethanone, a Versatile Chiral Epoxide Educt in Diazocarbonyl Reactions

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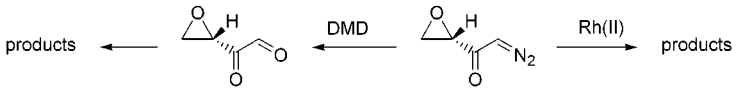
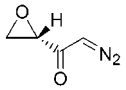
ABSTRACT

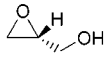


(*S*)-(−)-2-Diazo-1-oxiranyl-ethanone, prepared in two steps from (*R*)-(+)-glycidol, has been employed as an intermediate in several characteristic diazocarbonyl reactions to yield novel, nonracemic products including an epoxy quinoxaline and epoxy thiazoles and oxazoles.

Although several substituted epoxy diazoketones are known, some in enantiomerically pure form,[1] the simplest member of the series, 2-diazo-1-oxiranyl-ethanone (epoxy diazomethyl ketone) **1** has not been reported. The availability of glycidol **2** in single enantiomer form[2] prompted us to explore the possibility of preparing epoxy diazomethyl ketone **1** from glycidol and studying its potential as a chiral educt for a monosubstituted epoxide in diazocarbonyl reactions. Many



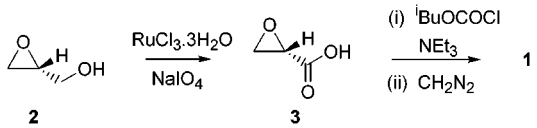
1



2

diazocarbonyl reactions[3] occur under mild, neutral conditions, suggesting that it might be feasible to transfer the epoxide moiety from a diazoketone to a variety of substrates without competition from ring opening reactions. The experiments that were subsequently undertaken to explore this idea were conducted with a sample of (*R*)-(+)-glycidol **2** of ca. 86% enantiomeric purity.[4]

Oxidation of (*R*)-(+)-glycidol using the ruthenium chloride−sodium periodate procedure modified by Genet and co-workers[5] for water-soluble epoxy alcohols furnished acid **3**[6] in 95% yield. Purification was unnecessary prior to activation



2 **3**

of the crude acid via in situ mixed anhydride formation with isobutyl chloroformate. Exposure of the anhydride to ethereal diazomethane yielded diazoketone **1** (93% yield) as a low melting solid (mp ca. 20 °C).

Our main objective in exploring the chemistry of **1** was to identify reactions, both catalytic and noncatalytic, in which the epoxide ring remains intact. In earlier work with diazoketones derived from amino acids we found that oxidation with dimethyldioxirane (DMD) proceeds under mild conditions to furnish glyoxals that could be used in situ in various condensation reactions.[7,8] Oxidation of **1** with

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(1) Van Haard, P. M. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1979**, 803.

(2) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(3) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds;* Wiley-Interscience: New York, 1998.

(4) Supplied by PPG-SIPSY, France.

(5) Pons, D.; Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 5023.

(6) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.

(7) Darkins, P.; McCarthy, N.; McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1993**, *15*, 1222.

(8) For other recent examples of condensations of chiral glyoxals with amines, see: Darkins, P.; Groarke, M.; McKervey, M. A.; Moncrieff, H.; McCarthy, N.; Nieuwenhuyzen, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 381.

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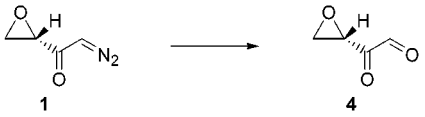
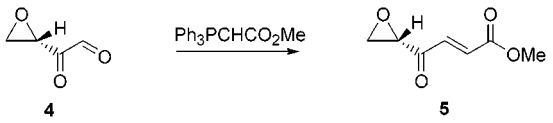
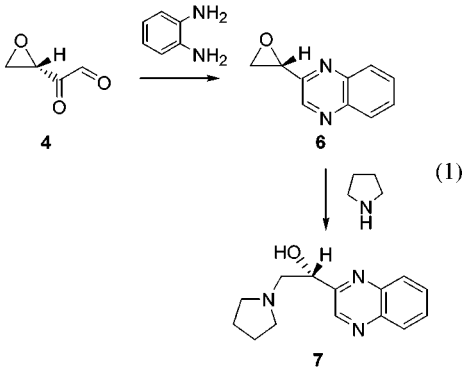


distilled DMD in acetone was similarly effective, affording epoxy glyoxal **4** in quantitative yield. Although the product **4** is represented for convenience here as a glyoxal, this is certainly an oversimplification. Removal of the acetone solvent produced a waxy solid whose IR spectrum showed a strong OH absorption with only a very weak carbonyl absorption, indicating that both carbonyl groups were largely hydrated. The ^{1}H and ^{13}C NMR spectra (D_2O) were much more complex than those expected for a simple monomeric bishydrate, suggesting that the species in water was at least a dimeric hydrate. There are a small number of natural products that contain an epoxy glyoxal as a side chain, e.g., clerocidin and terpentecin;[9] these compounds exhibit antibiotic and antitumor activity that may well be associated with the presence of this side chain. Without isolation or purification, **4** was treated with the Wittig reagent Ph_3PCHCO_2Me to yield the epoxy *trans*-alkene derivative **5** (82% yield).

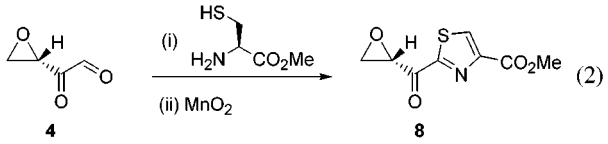


The structure of this product, which could be purified by flash chromatography, was readily confirmed by its spectroscopic data. HPLC analysis revealed that **5** had an ee of 86%. Two additional condensation reactions of epoxy glyoxal **4** are summarized in eqs 1 and 2. In the former, reaction



(1)

with 1,2-diaminobenzene furnished 2-oxiranyl-quinoxaline **6**, $[\alpha]^{20}_D$ −30.8 (*c* 1.52, $CHCl_3$), in 77% yield.[8] Epoxide ring opening of **6** occurred readily on heating with pyrrolidine to afford amino alcohol **7** in 96% yield. The condensation reaction in eq 2 illustrates the formation of a thiazole from glyoxal **4**. The reaction with L-cysteine methyl ester was conducted in aqueous ethanol containing potassium bicarbonate. The intermediate thiazolidine was isolated and



(2)

subsequently oxidized with MnO_2 in benzene to yield (28% from the diazoketone) the epoxy thiazole **8**, $[\alpha]^{20}_D$ −44 (*c* 1.28, $CHCl_3$), as a crystalline solid, mp 108−111 °C, the structure of which was confirmed by X-ray diffraction analysis (Figure 1).[10]

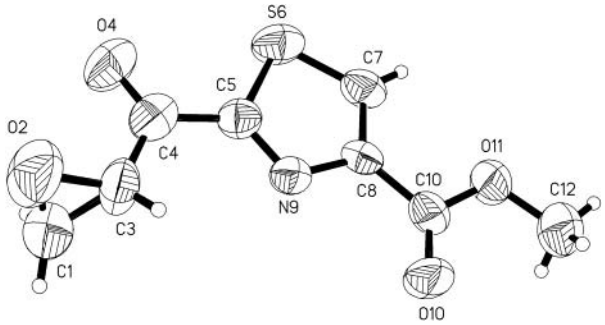
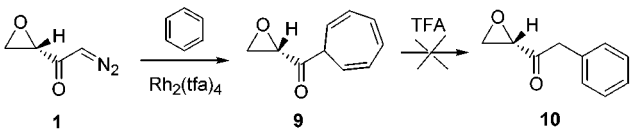


Figure 1. A view of 2-(2′-(*S*)-oxiranyl-1′-*oxo*-ethyl)-4-methylcarboxylate-thiazole (**8**) showing the atom-labeling scheme for all nonhydrogen atoms. Thermal ellipsoids at 50% level.

Of the many catalyzed reactions of diazocarbonyl compounds,[3] we selected aromatic cycloaddition and 1,3-dipolar addition with which to explore the reactivity of **1**. Both of these processes are very efficiently catalyzed by rhodium(II) carboxylates. The process of aromatic cycloaddition, which also encompasses heteroaromatic substrates, is essentially one of cyclopropanation,[11] though in most cases, the cyclopropane adduct undergoes spontaneous ring opening. This is the situation with benzene itself, which reacted with **1** at room temperature in the presence of rhodium(II) trifluoroacetate to form the cycloheptatrienyl epoxyketone **9** in quantitative yield (eq 3). Attempts to isomerize **9** to benzyl



(3)

epoxyketone **10** using trifluoroacetic acid, a process known with related cycloheptatrienyl alkyl ketones,[12] were unsuc-

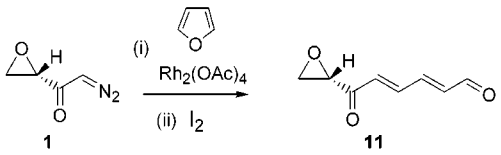
(9) Bailey, M.; Marko, I. E.; Ollis, D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509.

(10) Crystallographic data for the compound **8** in this paper have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 143897). Copies of the available material can be obtained free of charge on application to the CCDC, 12, Union Rd., Cambridge, CB2 1EZ, U.K. Fax: +44 -(0) 1223-336033. Email: deposit@ccdc.cam.ac.uk.

(11) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssié, P. *J. Org. Chem.* **1981**, *46*, 873.

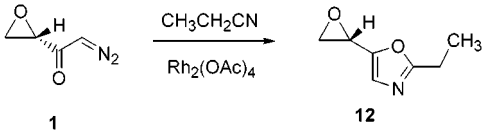
(12) McKervey, M. A.; Russell, D. N.; Twohig, M. F. *J. Chem. Soc., Chem. Commun*. **1985**, 491.

cessful; NMR analysis indicated a complex mixture of products of both epoxide ring opening and aromatization. Cycloaddition was also observed between **1** and furan, and although stable cyclopropane adducts have been obtained from reaction of furan[13] and diazoesters, the product was a mixture of geometrical isomers of ring-opened dienes.



Exposure of the mixture to a catalytic amount of iodine in dichloromethane produced the all-*trans* epoxy dienal **11** in 61% yield.

1,3-Dipolar addition between diazocarbonyl compounds and aryl and alkyl nitriles has been applied extensively by Helquist[14] and Moody[15] to the synthesis of oxazoles. We



selected the combination of propionitrile and diazoketone **1** under rhodium(II) acetate catalysis and found that epoxy oxazole **12** could be obtained in 95% yield. This product slowly decomposed on standing at room temperature, though it could be stored for long periods at −15 °C.[16]

In conclusion, epoxy diazomethyl ketone **1** is now readily available from glycidol, and its chemistry has been exploited in several ways to exemplify its potential as a nonracemic epoxy transfer agent.

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(13) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J. H. *J. Org. Chem.* **1990**, *55*, 6203.

(14) Gangloff, A. R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797.

(15) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761.

(16) All compounds were characterized by ^{1}H NMR, ^{13}C NMR, accurate MS, and/or elemental analysis.