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NOTE

Isotopic Labeling as a Probe in the Study of a Degenerate Payne Rearrangement in a Tertiary Epoxide System

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Summary

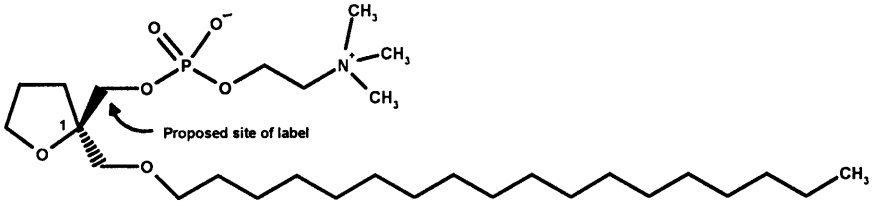
Through the use of isotopic labeling, it has been shown that epoxide **6** undergoes Payne Rearrangement under basic protic conditions ($NaOD/D_2O$/rt). However, no rearrangement took place when epoxide **6** was exposed to basic aprotic conditions (NaH/THF/reflux).

Key Words: Degenerate Payne Rearrangement, Epoxide, Isotopic Labeling.

Introduction

SDZ MLS 337 zi, **1**, (Scheme 1) is currently in the clinical phase of drug development for the treatment of multiple sclerosis. In order to support pharmacokinetic as well a ADME (absorption, distribution, metabolism and excretion) studies, a variety of radio- and stable-label isotopomers of this material were required.

Scheme 1



1 **Absolute configuration as shown : SDZ MLS 337 zi**

2 **Racemate : [^{14}C] SDZ 62-834 zi, labelled at C-1**

Although a synthesis of the *racemic* [^{14}C]-labeled analog, [^{14}C] SDZ 62-834 zi, **2**, was recently published (1), it was obvious that a different tactic was required for the preparation of this particular enantiomer. Furthermore, since the site of carbon-14 labeling in the racemic product had proven to cause unusual

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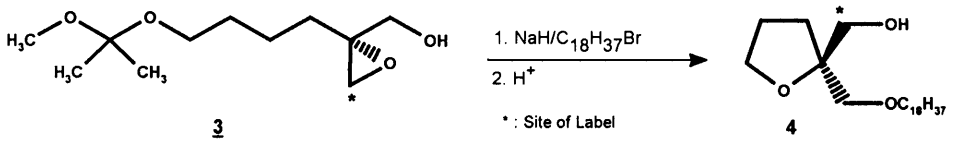
instability (2), we contemplated moving the label site to the methylene proximal to the phosphate functionality as shown above.

Discussion

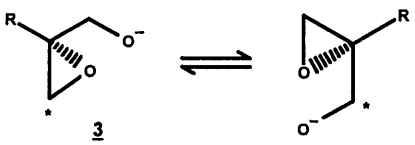
For the synthesis of compound 1, we wished to utilize the methodology developed for the construction of the unlabelled drug (3). In this approach, the chiral epoxide 3 is alkylated with 1-octadecylbromide and then cyclized to the tetrahydrofuran 4 (Scheme 2). The carbon-14 label would then be required in the position shown in structure 3.



3 4

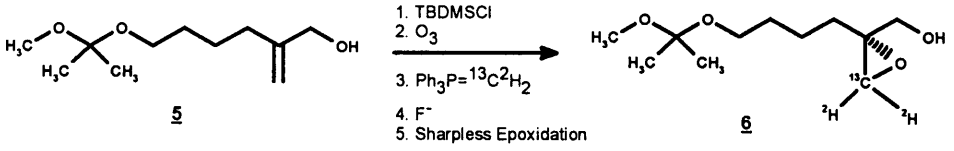
Scheme 2

One concern that arose in this protocol, however, was the possibility (4,5) of a Payne Rearrangement taking place during the alkylation procedure (6) and thus scrambling the label site between the two "external" methylenic positions (Scheme 3). This event could not be detected in the unlabelled series via measurement of the optical rotation of the epoxide after generation and quenching of the intermediate alkoxide, or of the resultant ether because in this particular molecular array, *the Payne Rearrangement is degenerate and thus there is no loss of optical purity!* Therefore, before the investment with carbon-14 was made, a stable-labeled system was synthesized (Scheme 4) in order to study the behavior of this tertiary epoxide architecture under the anticipated alkylation conditions.



3

Scheme 3



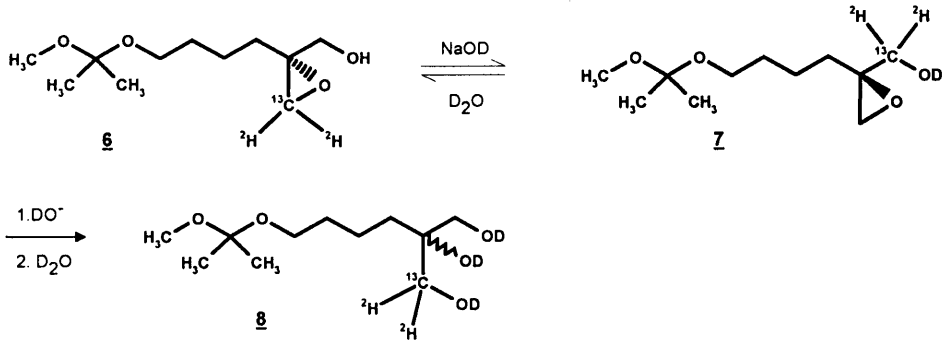
5 6

Scheme 4

The intermediate of interest, 6, was prepared from the allylic alcohol 5 (3) by way of protection with *tert*-butyldimethylsilyl chloride, ozonolysis of the alkene to the ketone, Wittig reaction of this material with $Ph_3P=^{13}C^2H_2$ (7) followed by deprotection with fluoride anion and finally epoxidation *via* the Sharpless procedure (8), although for the purposes of this study a chiral epoxide was not needed. When this epoxy alcohol 6 was subjected to similar aprotic alkylation conditions as was employed for the unlabelled series (NaH, THF, reflux, 2 hours), ^{1}H- and ^{13}C-NMR indicated *no discernible scrambling of the label.* This

result was gratifying from the point of view of our plans for radioisotopic labeling. The intermediate **6** was further processed (3) to give the M+3 molecular weight analog of the drug substance, which was used as an internal standard in mass spectrometry studies.

While the above conditions proved ineffective in promoting the Payne Rearrangement, we were interested to see if the prescribed conditions for this transformation (4) would trigger such a reaction in this tertiary system (9). Exposure of compound **6** to a 0.5 N solution of NaOD in D_2O at room temperature indeed resulted in loss of regiochemical integrity of the label within ten minutes to give a mixture of epoxides **6** and **7**, (Scheme 5) as evidenced by the appearance of peaks at δ = 2.85 ppm corresponding to the epoxy methylene group of **7** in the ^{1}H-NMR spectrum (Figs. 1 and 2). After 1h, the two isomers were found to be in a ratio of 1:1. This ratio is not surprising, since the equilibrium amounts of reactants involved in the Payne Rearrangement are dependent upon the thermodynamic stability of the partners (10), and in this case, with the exception of negligible contributions from the isotopes, the intermediates are equivalent. Extended reaction times (24 h) led exclusively to the triol **8**, where evidence of rearrangement was lost.



Scheme 5

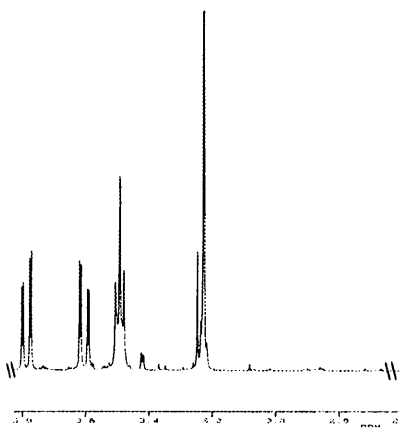


Fig. 1 ^{1}H-NMR spectrum of **6** in D_2O

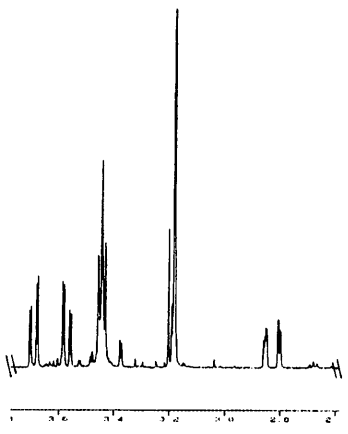


Fig. 2 ^{1}H-NMR spectrum of **6** in D_2O/NaOD, 10 minutes after sample preparation

In summary, through the use of isotopic labeling techniques, we have been able to unequivocally demonstrate the operation of a Payne rearrangement or its absence in a system where such information would have been difficult, if not impossible, to gather.

References

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