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# PAYNE REARRANGEMENT ROUTE TO THE OPTICALLY ACTIVE OXIRANE PRECURSOR FOR THE PREPARATION OF TRIAZOLE ANTIFUNGALS

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Optically active epoxide **1**, an important intermediate for the preparation of antifungal triazole-amides **2**, was synthesized starting from the (*S*)-lactic acid-derived ketone **9** and taking advantage of the Payne rearrangement of the epoxyalcohol **8**.

**KEYWORDS** triazole antifungal; Payne rearrangement; (*S*)-lactic acid; oxirane; stereocontrol

In a previous paper,[1] synthesis of the optically active (2*R*,3*S*)[2] triazole-epoxide **1**, an important intermediate for the preparation of the potent antifungal compounds **2**[3] and their cyclic analog oxazolidines,[4] was described. Synthesis of **1** was achieved in a stereocontrolled manner using an inexpensive starting material, (*S*)-lactic acid acetate (**3**). However, the synthetic route was somewhat roundabout (Chart 1); it involves the two-step conversion of the alcohol (*S*)-**4** to its enantiomer (*R*)-**4** using the alkaline displacement reaction of the (*S*)-**4**-derived tosylate (*S*)-**5**, or the Mitsunobu reaction in transformation of the epoxyalcohol **6** to its 3*R* epimer **7**. In order to eliminate these steps, a simpler synthetic route that takes advantage of the Payne rearrangement[5] was planned. In this paper we will describe this new route leading to the epoxide **1**.

Behrens and Sharpless[6] have demonstrated the usefulness of the "Payne rearrangement-opening sequence" for regio- and stereoselective introduction of functional groups into epoxyalcohols. Based on their study, the epoxyalcohol **7** of our interest was analyzed

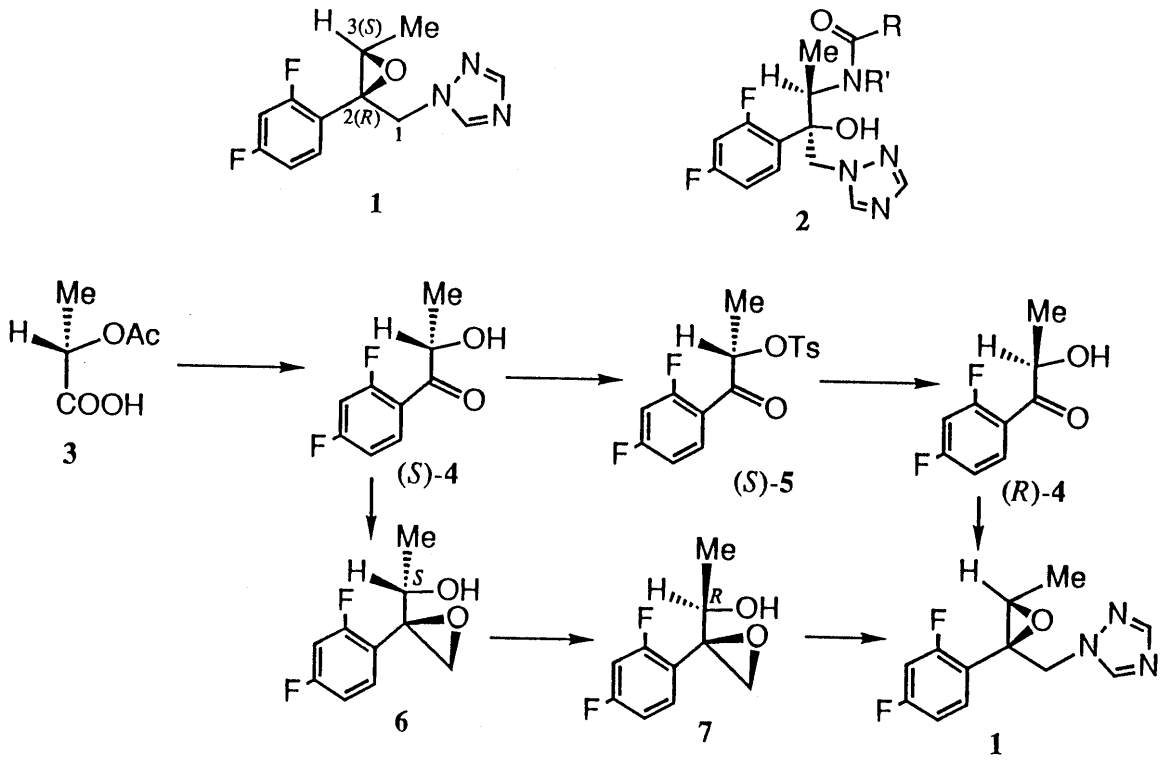


Chart 1

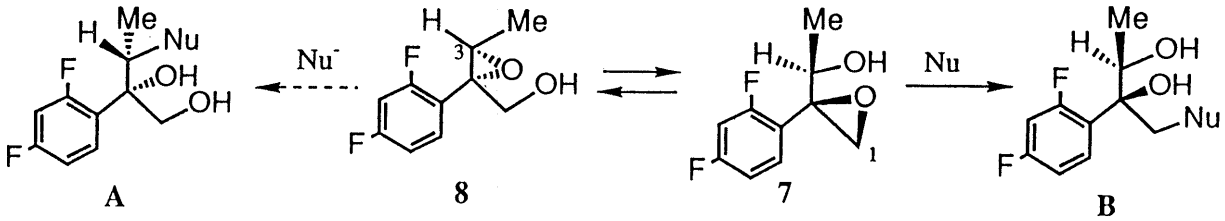


Chart 2

as follows (Chart 2). The epoxyalcohol **7** is expected, under a basic condition, to be in equilibrium with the more accessible, isomeric epoxyalcohol **8** *via* Payne rearrangement. In the presence of a suitable nucleophile ($Nu^-$), the isomer **7** is predicted to be selectively captured by attack of the nucleophile on the oxirane carbon C1, which is less hindered than the carbon C3 in **8**, to give the adduct **B**. On the other hand, direct attack of the nucleophile on **8** would result in the formation of another conceivable adduct **A**, which is the enantiomer of **B** if one supposes Nu=OH. If the selective formation of the adduct **B** from **8** were possible, the Payne rearrangement involved here would then function as an inversion step of the absolute configuration of the oxirane carbons, and therefore it would be presumed to be successfully utilized in substitution for the above-mentioned, roundabout inversion steps. With this prospect in mind, the Payne rearrangement precursor, the epoxyalcohol **8**, was prepared in the following straightforward steps (Chart 3).

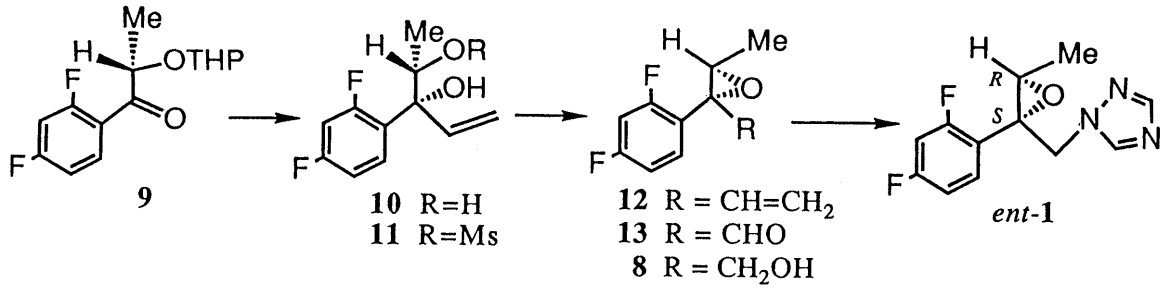


Chart 3

The THP ether **9**,[1] which was derived from (*S*)-**4**, was treated with vinylmagnesium bromide in THF, followed by acid treatment, to give the diol **10** $[[\alpha]_D^{25}$ +54.3° (*c*=0.96, $CHCl_3$)] in 99% yield. In parallel with the result obtained in a similar Grignard reaction of **9**,[1] no diastereomeric diol was formed. The diol **10** was mesylated in a usual manner, giving the monomesylate **11**, and the latter was treated with NaH in DMF to give the epoxide **12** $[[\alpha]_D^{25}$ +76.3° (*c*=0.95, $CHCl_3$)] in 83% overall yield from **10**. The olefinic bond in **12** was cleaved using a catalytic amount of $OsO_4$ and excess $NaIO_4$ in MeOH-$H_2O$ to give the aldehyde **13**, which was treated with $NaBH_4$ in MeOH, affording the desired epoxyalcohol **8** $[[\alpha]_D^{25}$ -21.8° (*c*=1.10, $CHCl_3$)] in 70% yield from **12**.

Following a procedure similar to that described for the conversion of the enantiomer of **8** into the triazole-epoxide **1**,[7] mesylation of the epoxyalcohol **8** by treatment with MsCl and triethylamine in $CH_2Cl_2$, followed by reaction of the resulting mesylate with sodium triazolide in DMF at 85 °C, gave *ent*-**1**,[1] the enantiomer of the desired triazole-epoxide.

Accordingly, the use of the Payne rearrangement was examined at the stage of the epoxyalcohol **8** in order to invert its absolute configuration; the behavior of **8** in an alcoholic solvent under basic conditions was investigated first. Treatment of **8** with a catalytic amount of MeONa in MeOH under reflux for 4 h gave a 7:3 equilibrium mixture of the isomeric epoxyalcohols **8** and **7**. Thus, Payne rearrangement of **8** was indeed shown to take place, although the desired epoxyalcohol **7** turned out to exist as the minor isomer.

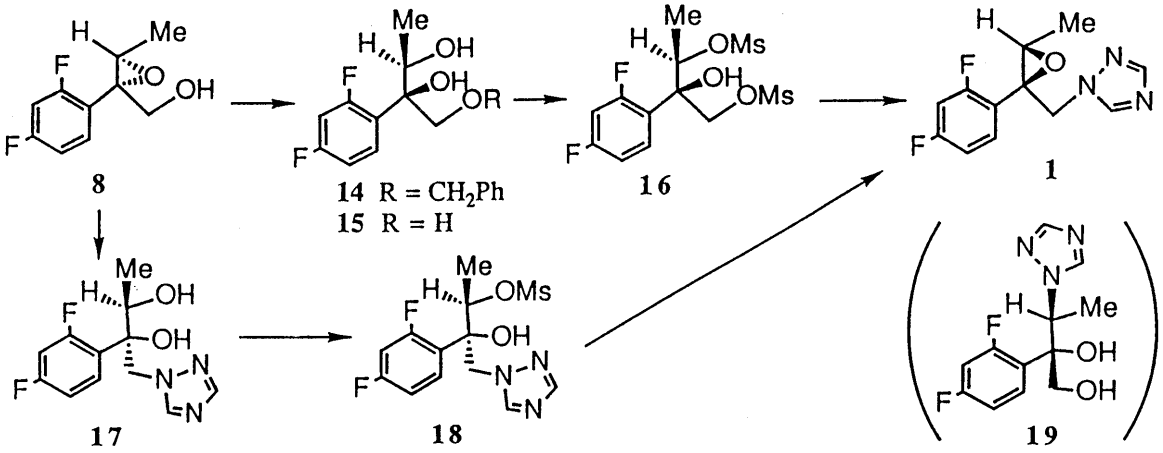


Chart 4

Consequently, selective capture of the minor isomer **7** was investigated using benzyl alcohol as the nucleophile (Chart 4). Treatment of **8** with 0.5 equiv. of sodium benzyloxide in benzyl alcohol at 100 °C for 4 h gave the benzyl ether **14**; this benzyl ether, without purification, was hydrogenolyzed by treatment with 10% Pd/C in EtOH under $H_2$ (1 atm) to give, after separation by chromatography, the known triol **15**[1] [$[\alpha]_D^{25}$ +11.5° (*c*=1.05, $CHCl_3$)] as a solid in 83% overall yield from **8**. The optical purity of this triol was determined to be 97.3% ee (>99% ee after recrystallization from acetone—cyclohexane) by HPLC using a chiral stationary phase column. The two-step transformation of **15** into the epoxide **1** *via* the dimesylate **16** has already been described.[1] Thus, synthesis of the optically pure triazole-epoxide **1** was achieved starting from (*S*)-lactic acid acetate (**3**) without resorting to the forced inversion steps shown in Chart 1.

Our attention was next paid to examination of the ring-opening reaction of the epoxyalcohol **8** with triazole, an unprecedented example of the nucleophile in the Payne rearrangement-opening sequence, and this was successfully carried out as follows. Treatment of **8** with 3.3 equiv. of *t*-BuOK and 3.0 equiv. of triazole in *t*-BuOH at 70 °C for 15 h afforded, after separation by chromatography, the triazole-diol **17** [$[\alpha]_D^{25}$ -101° (*c*=0.95, $CHCl_3$); mp 116—118 °C, $[\alpha]_D^{25}$ -108° (*c*=0.79, $CHCl_3$) after recrystallization from acetone-benzene] as a solid in 59% yield. There was no formation of the possible regioisomer **19** under these conditions.[8] The triazole-diol **17** was mesylated by treatment with MsCl in pyridine to give the monomesylate **18**, which was cyclized using NaH in THF—DMF into the optically pure epoxide **1** in 87% overall yield from **17**. Thus, the epoxide **1** was shown to be prepared in an even fewer number of steps and in a more direct manner.

The study described here demonstrated the usefulness and the applicability of the Payne rearrangement for the introduction of functional groups into three contiguous carbons. The new routes are now being conveniently utilized for the preparation of the optically active triazole antifungals **2** and related compounds.

REFERENCES AND NOTES

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2) For covenience, numbering hereinafter in this text corresponds to that indicated in **1**.
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8) Treatment of **8** with sodium triazolide in DMF resulted in the formation of the regioisomer **19**.

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