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Total Chiral Synthesis of Azole Antifungals via α-Hydroxylation of Ketones:

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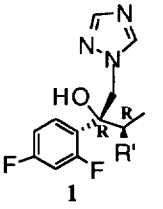
Abstract: The use of camphorsulfonyl oxaziridines for the preparation of 2',4'-difluoro-(R)-2-hydroxypropiophenone, (**2**), a key intermediate for the synthesis of azole antifungals Sch 42427 and ER-30346 (**1**) in excellent enantiomeric excess and high chemical yield is described.

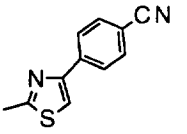
The emergence of drug resistant forms of fungi resulting from AIDS has intensified the search for novel antifungal agents that could combat these forms. Research in this area has led to a new class of potent azole antifungals, e. g. Sch 42427/SM 9164 and ER-30346 (**1**). [1,2]



1

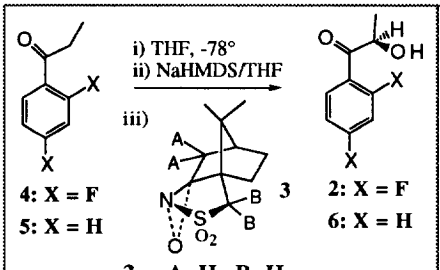
Sch 42427/SM 9164 : R' = -SO_2CH_3

ER-30346: R'=



Methods that allow for their total chiral syntheses on a mole scale without chromatographic or chemical resolutions are needed. This article describes one such new synthesis.

Publications towards the syntheses of these compounds indicate that chiral hydroxyketone **2** is a key intermediate that has been used to prepare antifungals such as **1**.[1-3] In our pursuit of a synthesis which would lead to a yield and *ee* of ~ 95 of **2**, recently published[4] chiral hydroxylations of ketones with camphorsulfonyl oxaziridines **3(a, b)** were examined. **Table 1** summarizes the best results[5] obtained when the literature procedures were applied to the hydroxylation of 2,4-difluoropropiophenone **4**. Although the synthesis[6] of **4** as well as its hydroxylation were accomplished in good chemical yields, the *ees* of **2** were moderate. In the control



4: X = F
5: X = H

3

3a : A=H, B=H
3b : A=Cl, B=H

2: X = F
6: X = H

Table 1: Comparison of hydroxylation of ketones **4** and **5**.

Ketone	Oxaziridine	Yield[1]	R:S (*ee*)[1]	Literature yield, (*ee*)
4	**3a**	80%	72:28(44)	--
4	**3b**	85%	90:10(80)	--
5	**3a**	88%	78:12(66)	77 (68)[4a]
5	**3b**	80%	96:04(92)	61 (95)[4b]

Notes: (1) These are isolated yields. (2) The % enantiomeric excesses were determined by HPLC. [7]

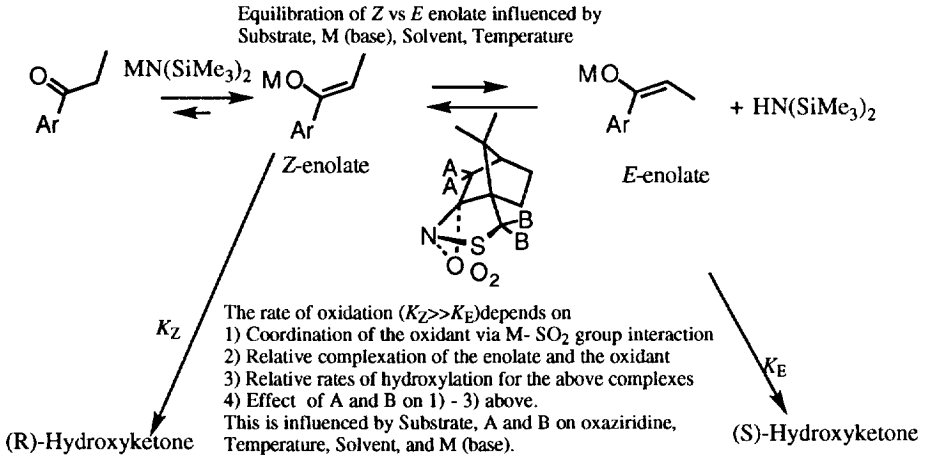
study the hydroxylation of commercially available propiophenone **5** to **6** resulted in expected *ees*[7] with higher than reported yields. [8] Thus the moderate *ees* of **2** were neither due to inferior quality of oxaziridines[9] nor due to variation in the experimental techniques.

To improve the *ees* of **2** while maintaining yields, a two prong approach, one involving a mechanistic

study, and the other involving evaluation of new oxaziridines was undertaken. Mechanistically, the reported[10] work using TMS trapped enolates suggests that upon treatment of **5** with the base, essentially only the *Z* enolate is formed which reacts with the oxaziridines to produce the hydroxyketone of the dominant chirality. Independently synthesized TMS trapped *E* enolate leads to the product of the opposite chirality. As was seen with **5**, the treatment of **4** with NaHMDS followed by the addition of either TMS-triflate or TBDMS-triflate resulted in the isolation of essentially only the *Z*-silylated enolate. To complement the above experiments we undertook an NMR study[11] to monitor the 'in solution' dynamics of this reactions. This study revealed that i) both the *Z* and the *E* enolates are formed for **4**, and **5**; ii)the *Z* enolates are formed in larger amount than *E* enolates for both **4**, and **5**; iii) the ratio of *Z* vs. *E* enolates for **4** (and **5**) are temperature dependent, iv) between the temperature of -40° to -90° the lower the temperature, the better the *Z/E* ratio, v) at the same temperature (e. g. -78°C) the *Z/E* ratio for **4** (2. 1:1) is inferior compared to *Z/E* ratio of **5** (2. 6:1), and vi) for practical purposes, the reaction of these enolates with the oxaziridines is completed within minutes as judged by LC (the addition of oxaziridines to the above reactions creates suspensions which can not be monitored by NMR).

Based on this observation it was hypothesized (**Scheme I**) that although *both* enolates are formed at a given temperature (which are in equilibration when hexamethyldisilazine bases are used), it is the faster rate of complexation of the *Z* enolates with the oxaziridines and/or the subsequent faster rate of oxidation of the complexs thus formed in case of *Z* enolates compared to the *E* enolates that determine the final *ee*. Thus, consistent with the observed results[5], the solvent, the base (i. e. the metal ion), the substitution pattern on the oxaziridines (e. g. **3a** vs. **3b**), as well as the substrate influence the *Z/E* ratio, the rates at which they eventually react with oxaziridines, and the resultant *ee*s. This study suggested that a further optimization in *ee*s for **2** may

Scheme I **Mechanism of chiral α-hydroxylation with Oxaziridines:**



be achieved by a change in the substitution pattern on the oxaziridines and/or maintaining the reaction temperature < -78°C (to ensure a more favorable *Z/E* ratio), provided the chemicals do not precipitate out, and an appreciable reaction rate can be maintained under these conditions.

The results obtained under these new conditions for the hydroxylation of **2** are shown in **Table 2.** The lowering of the reaction temperature to -90° did allow for improved *ee*s while maintaining the chemical yields.

Interestingly enough, although a further change in the substitution pattern on oxaziridines lowered the *ees*, it clearly showed that the tetrachloro oxaziridine (**3d**), (formed as a byproduct when the published[12] synthesis of **3b** was used for its preparation) must be completely removed from **3b** for its optimum utilization of **3b**. [13] Since toluene was shown[5] to adversely affect *ees*, the preparation of toluene (often a contaminant in the commercial NaHMDS) free THF solution of NaHMDS also led to a improved, more reproducible *ees* of **2**.

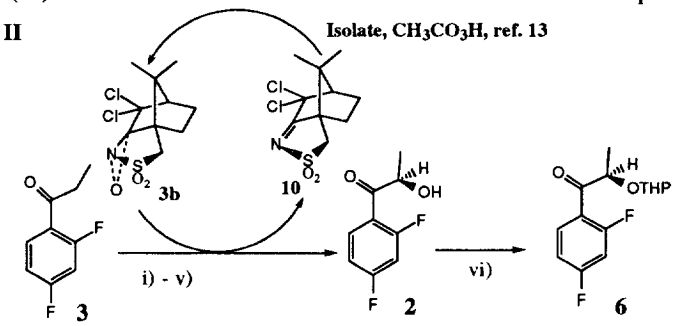
Table 2: Study Towards Improvements in *ees* of **2**:

Oxaziridine	**3a**	**3b**	**3c**[2]	**3d**	**3b**[3]
	A=H, B=H	A=Cl, B=H	A=Br, B=H	A=Cl, B=Cl	A=Cl, B=H
Yield[1]	90%	90%	80%	80%	**93%**
R:S (% *ee*)	85:15 (70)	94:6 (88)	81:19 (62)	33:66 (33)	**96:4 (92)**

Notes: Unless noted otherwise, all reactions were conducted at -90°C to -95°C using the procedure outlined in Scheme II. (1) These are isolated yields. (2) Due to stirring difficulties with this insoluble oxaziridine, this reaction was conducted at -75C to-78°C. (3) Toluene free NaHMDS in THF ($NaNH_2$ + $NH(SiMe_3)_2$, heated in THF to eliminate NH_3) was used.

The above work establishes an efficient synthesis of the key antifungal intermediate **2** with the use of **3b**. However for a multikilo application of this synthesis it was important to recycle the chiral species. This was accomplished by developing a workup procedure for the isolation of **2** that facilitated a recovery of camphorsulfonylimine (**10**) as detailed in the scheme below. [14] An oxidation of **10** with peracetic acid [13] to

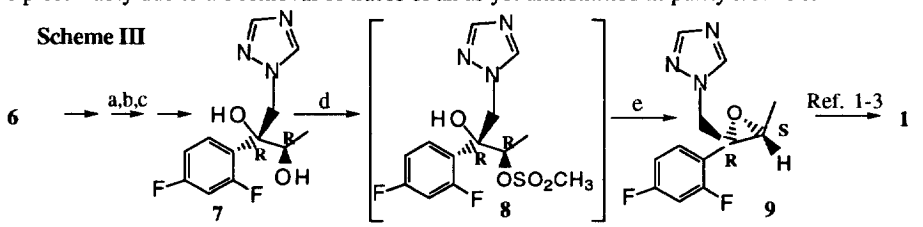
Scheme II



i) N_2/ THF, -90°, 1.2 eq. NaHMDS/THF; ii) 1.2 eq. **3b**; iii) aq. NH_4Cl, warm to r.t.; iv) extract w. EtOAc; v) replace EtOAc w. hexane, cool 0°C, filter to isolate **5** (85-90% recovery); vi) Conc. hexane under vac., add toluene, 4.0 eq. DHP, PPTS, r.t., 3-4hr (90% of **6** from **3**).

the oxaziridine allowed for the reuse of this advanced intermediate. This synthesis has been scaled up in our laboratories to prepare multikilo batches of **2**. In fact, **3b** obtained after three recycles improved *ees* (> 94%) of **2**. This is presumably due to the removal of traces of an as yet unidentified impurity from **3b**.

Scheme III



a) (i) Me_3SOI/DMSO/60% NaH heated to 55°; add **6** in THF; b) DMF/Na -Triazole, 70°C; c) aq. HCl or pTSA/MeOH/H_2O, 60% for three steps (from **6**): d) 0-5°C, iPrOAc, Et_3N, MsCl ; e) iPrOAc, aq. K_2CO_3, r.t., $(Bu)_4NHSO_4$, 90% from **7**.

Finally, moderately stable **2** was trapped as the more stable THP protected intermediate **6** under inert, neutral conditions. Conversion of **2** to the antifungals **1** via the R,S epoxide **9** is described in the **Scheme III**.

Thus an efficient synthesis of the key chiral intermediate **2** in good yield and excellent enantiomeric excess has been achieved. The experimental conditions for this synthesis are reported. This synthesis has been scaled up on multimole scale.

Acknowledgments: We thank Dr. T. M. Chan for performing the low temperature NMR study.

References and Notes

1) (a) For ER-30346 see Toshihiko N.; Katsura, H.; Akihiko T. *Drugs of the Future* **1996**, *21*, 20; (b) For Sch 42427/SM9164 see *Drugs of the Future* **1995**, *20*, 1300.

2) (a) Miyauchi, H.; Kozuki, K.; Tanio, T.; Ohashi, N. *Bioorg. & Med. Chem. Lett.* **1995,** *5*, 1479; (b) Miyauchi, H.; Tanio, T.; Ohashi, N. *Bioorg. & Med. Chem. Lett* **1995,** *5*, 933; (c) Saji, I.; Tamoto, K.; Tanaka,Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. *Bull Chem. Soc. Jpn.* **1994,** *67*, 1427.

3) (a) Gala, D.; DiBenedetto, D. J.; Clark, J. E; Murphy, B. L.; Schumacher, D.; Steinman, M. *Tetrahedron Lett.* **1996**, *37*, 611; (b) Gala, D.; DiBenedetto, D. J. *Tetrahedron Lett.* **1994**, *33*, 8299; (c) Miyauchi, H.; Tanio, T.; Ohashi, N. *Bioorg. & Med. Chem. Lett.* **1995,** *5*, 933; (d) Bennett, F.; Ganguly, A. K.; Girijavallabhan, V. M.; Pinto, P. A. *Synlett* **1995**, 1110.

4) (a) Davis; F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. G. *J. Org. Chem.* **1986**, *51*, 4083; (b) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715.

5) Of the bases evaluated (Na, K, or Li HMDS) Na ion led to the best outcome. NaHMDS was better than NaH, or NaOtBu. Among a variety of solvents evaluated (tBuOMe, Toluene, DME, Ether, THF, diglyme, mixtures there of, with or without trace of DMSO) THF followed by DME were found most suitable.

6) Ketone **4** was synthesized in 85% yield by Friedel-Craft acylation of m-difluorobenzene ($AlCl_3$, 1. 4 eq. propionyl chloride, r.t. to 65°C; product extraction in tBuOMe followed by distillation of **4** at 50°C, 2mm).

7) The *ees* reported in the literature were determined by NMR. The *ees* reported in this article were determined by chiral HPLC (Chiracel OB; 4-7% iPrOH/Hexane, 0.7 to 1.1 ml/min, UV 220nm).

8) For instability of **2** and **5** see: Gala, D.; Puar, M. S.; Kugelman, M.; DiBenedetto, D. J. *J. Pharm. Sci.*,**1992**, *81*, 1199. The higher yields were obtained by maintaining cooler (0-10°C0 temperature, inert atmosphere and neutral pH during the workup and storage of the products as indicated in ref. 3a, and 3b.

9) All oxaziridines used for this research were prepared according to references 4a and 4b.

10) Davis , F. A.; Shepard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am Chem. Soc.* **1990**, *112*, 6679.

11) For this study, commercial solid NaHMDS was dissolved in anhydrous d8-THF which was added to the solution of **4** or **5** in d8-THF at -78°C and analyzed by 400MHz ^1H NMR between -40° to -90°C.

12) In the reported work (ref. 4b), the trichloro byproducts were isolated. In our hand, only the tetrachloro impurity was formed.

13) For a **3b** synthesis free of **3d**, see: Gala, D.; DiBenedetto, D. J.; Mergelsberg, I. *Tetrahedron. Lett.* **1992**, *33*, 161.

14) A recovery of **3a** was also demonstrated using this procedure.

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