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THE SYNTHESIS OF 2,2,4 - TRISUBSTITUTED OXETANES AS NEW AZOLE ANTIFUNGAL AGENTS

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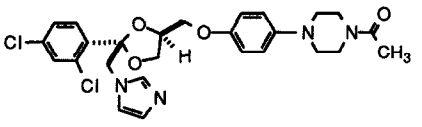
Abstract: Synthesis and biological activities of *cis* - and *trans* - 2,2,4 - trisubstituted oxetanes **4** and **5** are described. The key diol intermediates **9** and **10** exhibited exceptionally good *in vitro* and *in vivo* antifungal activity.

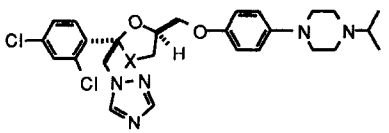
Despite extensive research efforts conducted over the last thirty years to discover novel antifungal agents, the azole class of antifungals has remained a viable structural lead toward the persuit of more efficacious orally active, broad spectrum agents. The azole antifungals are one of the few classes of compounds that clearly targets the cytochrome P - 450 enzyme. The orally active ketoconazole **1** has served as the focal point for extensive structure - antifungal activity relationship studies.[1] Recently, newer agents, *e.g* -- terconazole **2**, have been identified as a result of further structural modification of the azole ring system and the side chain.[2] Terconazole **2**, exhibits a broader spectrum of antifungal activity than ketoconazole **1**.

In general, clinically useful members of this class of azole antifungals contain a ketal ring moiety. Recently, we reported the synthesis of **3** (Sch 38918) wherein the 2,2,5 - trisubstituted tetrahydrofuran ring replaces the ketal functionality in **2**. Sch 38918 was shown to be orally more active than ketoconazole and terconazole.[3,4] This observation prompted us to investigate the synthesis and the antifungal activity of the 2,2,4 - trisubstituted oxetane **4** which may act as substrate analog owing to its structural similarity to **3**, the compound containing the tetrahydrofuran ring. The change in ring size in the nucleoside analogs from furanose to oxetane profoundly effects the specific orientation of the ring substituent. A well-known example is oxetanocin a novel nucleoside which exhibits antiviral, antitumer, and antibacterial activities.[5] Furthermore, we also anticipated that the presence of the rigid oxetane ring in **4** could introduce additional conformational constraints relative to **3**, which might result in the identification of more selective and potent analogs.

We herein report the synthesis and biological properties of the *cis* - and *trans* - 2,2,4 - trisubstituted oxetanes **4** and **5**.



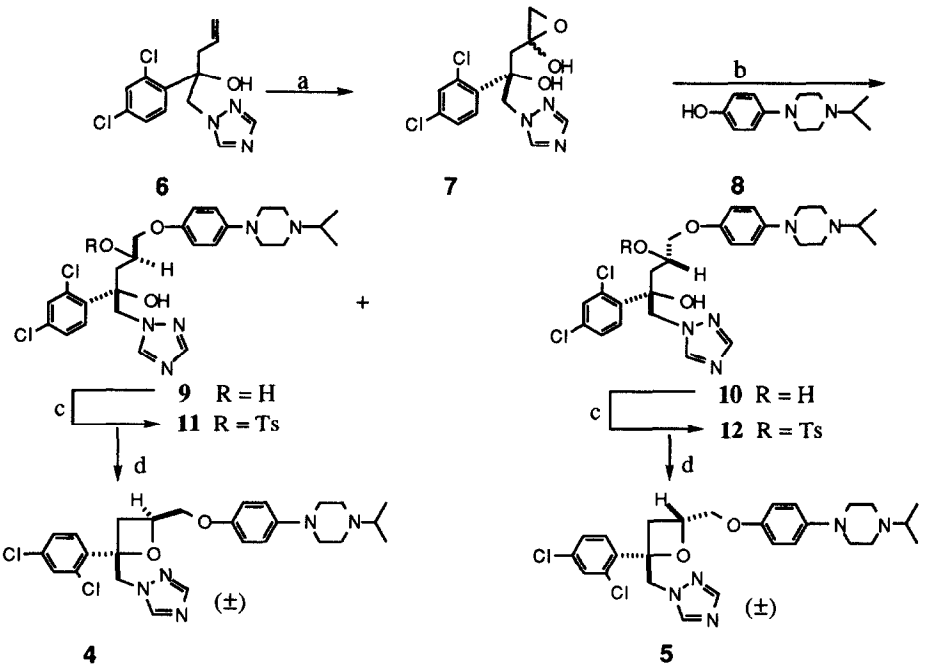
1



2 (X =O)
3 (X = CH_2)

Chemistry

The synthetic route for the preparation of racemic *cis* - **4** and *trans* - **5** oxetanes is described (Scheme 1).[6] The starting material 1-(2',4'-dichlorophenyl)-1-(2-propenyl -(1H-1,2,4- triazol-1-yl)ethanol **6** was prepared in two steps from dichloroacetophenone using the literature procedure.[7,8]



Scheme 1. Synthesis of Compounds 4 and 5

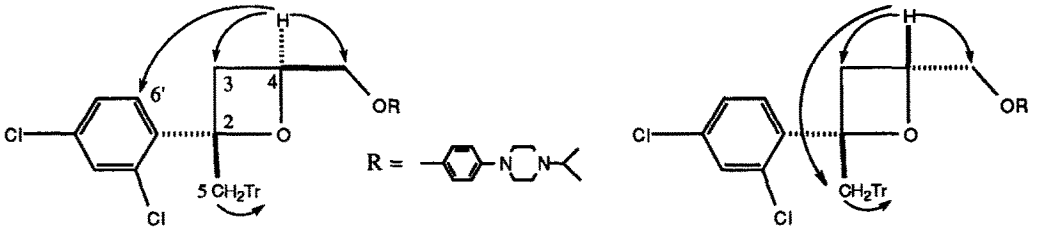
Reagents / Conditions : a) mCPBA, CH_2Cl_2, r.t., 24h; b) NaH, DMSO, 50 °C, 15h; c) TsCl, Pyridine, 0 °C, 15h; d) BuLi, THF, 0°, 15 min, 55 °C, 2h.

Treatment of **6** with m-chloroperoxybenzoic acid in methylene chloride at room temperature gave an inseparable diastereomeric mixture of epoxides **7** in 92% yield. In many cases, these types of 3, 4-epoxy alcohols could be converted to the oxetanes by intramolecular cyclization on treatment with base in 75% aqueous dimethyl sulfoxide.[9] However, using these reaction conditions the epoxy alcohol **7** not only failed to give the oxetane but decomposed. An alternative method for the

synthesis of oxetanes utilizes 1,3-diols as starting materials, and normally requires two steps: (a) conversion of the diol to a monoarenesulfonate; and (b) base -induced ring closure of the monosulfonate by intramolecular nucleophilic displacement.[10] Fortunately, we were able to use this latter approach to synthesize the desired oxetanes. Treatment of the isolated epoxy alcohol **7** with phenoxide anion **8** [11] in DMSO at 50 °C gave a 1 : 1 mixture of diastereomeric diols **9** and **10** (78% yield) which were separated using flash chromatography.[12,13,14] Tosylation of these two diols was accomplished using 1.5 equivalents of p - toluenesulfonyl chloride in pyridine to give the corresponding monosulfonate esters **11** and **12** in 95 and 97% yield respectively.

In the final step each tosylate was cyclized using one equivalent of butyllithium in THF to give the corresponding oxetane **4** and **5** in 80 and 79% yield respectively.[15,16] Cyclization to each oxetane resulted in a reversal of the stereochemistry at C_4 as a result of S_N2 displacement of the tosyl group by the corresponding alkoxide (Scheme 1).

The stereochemical assignment of both oxetanes were confirmed by 1D NOE data. Specifically, the irradiation of methine proton (H_4, δ 4.88) resulted in positive NOE for $H_{6'}$ in the case of *cis* compound **4**, whereas, the irradiation of methine proton (H_4, δ 4.45) gave positive NOE for triazole proton singlet at δ 8.3 for the *trans* compound **5**.



Biological Results

In vitro evaluation : Minimum inhibitory concentrations (MICs) of **3, 4, 5, 9,** and **10** were determined in Sabouraud dextrose broth, pH 5.7, against twelve strains of *Candida*, seven strains of dermatophytes and two strains of *Aspergillus*. Against two strains of *C.parapsilosis* activity was observed with **4, 9,** and **10** with a range of 4-32 mcg/ml and with **3** at 0.125-0.5 mcg/ml. Compound **5** was inactive. Against the other organisms all four compounds were inactive (32- >64 mcg/ml) in this medium, including *C. albicans* C-43 used to infect mice in the *in vivo* study. In Eagles minimal essential medium, pH 7.0, against six strains of *C. albicans* , including *C. albicans* C-43, and one strain of *C. stellatoidea*, compounds **3, 4, 9,** and **10** inhibited the yeast to mycelial transformation at concentrations <0.03 mcg/ml. Compound **5** was only slightly active (16- >64 mcg/ml).

In vivo evaluation : Mice infected intravenously with 1 X 10^6 colony forming units (CFUs) of *C. albicans* C-43 were treated, orally, once a day for four consecutive days. Compounds **3, 9,** and **10** at 50 mg/kg gave 100 percent survival, while untreated controls had only 50 percent survival. Four days post inspection (day five of the experiment) surviving mice were sacrificed and the number of *Candida* in the kidneys were determined. The geometric mean CFUs (log 10) for mice treated with compounds **3, 9,** and **10** were 4.3, 4.2, and 4.4 respectively, compared to 7.7 for the

untreated control group. The compounds were also administered at 10 mg/kg but were inactive (both survival and CFUs were similar to controls). Since only two doses were used a meaningful ED_{50} calculation could not be done. Both *cis* -**4** and *trans* -**5** oxetanes were inactive at these dose level.

Conclusions

This work describes a short and efficient synthesis of a novel class of trisubstituted oxetane azoles. While our objective of replacing the tetrahydrofuran ring system in **3** (Sch 38918) with the oxetane moiety has not been realized, both intermediate diols **9** and **10** exhibited exceptionally good *in vitro* and *in vivo* antifungal activity.

References and Notes:

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6. All new compounds were characterized by high resolution mass spectra and 1H nmr spectra. When necessary 1H-1H decoupling experiments were performed. Elemental analysis were obtained for crystalline compounds only. Selective spectral data is given.
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11. J. Heeres, R. Hendrickx, and J. Van Cutsem, *J. Med. Chem.*, **1983**, 26, 611.
12. The stereochemistry of the diols **9** and **10** described in scheme 1 is relative, and used to illustrate the stereochemistry of the racemic products obtained.
13. **9**: ^{1}H Nmr [$CDCl_3$] δ 1.09 (d, J = 6.5 Hz, 6H), 2.72 (m,1H), 1.73 (dd, J = 1.73, 2.94 Hz, 2H), 2.65 (m, 4H), 3.09 (m, 4H), 3.79 (m, 1H), 3.76 (m, 1H), 4.68 (dd, 1H), 4.78 (dd, 1H), 5.40 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.12 (s, 1H).
14. **10**: ^{1}H Nmr [$CDCl_3$] δ 1.10, (d, J = 6.5 Hz, 6H), 2.73 (m, 1H), 2.42 (dd, J = 14.0 Hz, 8.0 Hz, 1H), 2.50 (dd, J = 14.0, 4.0 Hz, 1H), 2.70 (dd, 4H), 3.10 (dd, 4H), 3.78 (dd, J = 10.0, 4.0 Hz, 1H), 3.84 (dd, J = 10.0, 7.0 Hz, 1H), 4.19 (m, 1H), 4.67 (d, 1H), 5.24 (d, 1H), 5.50 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.0, 2.0 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.00 (s, 1H).
15. **4**: ^{1}H Nmr [$CDCl_3$] δ 1.10 (d, J = 6.5 Hz, 6H), 2.70 (m, 4H), 2.72 (m, 1H), 2.90 (dd, J = 12.0, 8.0 Hz, 1H), 3.10 (dd, J = 12.0, 7.0 Hz, 1H), 3.12 (m, 4H), 3.75 (dd, J = 12.0, 4.0 Hz, 1H), 3.95 (dd, J = 12.0, 3.0 Hz, 1H), 4.60 (d, J = 14.0 Hz, 1H), 4.88 (m, 1H), 5.06 (d, J = 14.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 8.10 (s, 1H).
16. **5**: ^{1}H Nmr [$CDCl_3$] δ 1.10 (d, J = 6.5 Hz, 3H), 2.70 (m, 4H), 2.72 (m, 1H), 2.82 (dd, J = 12.0, 6.0 Hz, 1H), 3.10 (m, 4H), 3.12 (dd, J = 12.0, 8.0 Hz, 1H), 3.43 (dd, J = 11.0, 4.5 Hz, 1H), 3.47 (dd, J = 11.0, 4.0 Hz, 1H), 4.38 (d, J = 15.0 Hz, 1H), 4.45 (m, 1H), 4.90 (d, J = 15.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 8.30 (s, 1H).

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