

Synthesis of the Methanesulfonates of  $\alpha$ -(4-Chlorophenyl)- $\alpha$ -[1-(2-chlorophenyl)ethenyl]-1*H*-1,2,4-triazole-1-ethanol and  $\alpha$ -[1-(2-Chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-1*H*-1,2,4-triazole-1-ethanol, Alpha Styryl Carbinol Antifungal Agents

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The methanesulfonates of  $\alpha$ -(4-chlorophenyl)- $\alpha$ -[1-(2-chlorophenyl)ethenyl]-1*H*-1,2,4-triazole-1-ethanol and  $\alpha$ -[1-(2-chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-1*H*-1,2,4-triazole-1-ethanol (**1a**,**b**) are orally effective  $\alpha$ -styryl carbinol derivatives developed for the treatment and prevention of systemic fungal infections. Practical new processes amenable for the large-scale production of these compounds are described. Of note is the selection of dichlorostyrene as a convenient precursor of the styryl portion, modification of a sensitive Grignard addition into a realistic preparative reaction and the use of 1,2,4-triazole simultaneously as a base transfer agent and nucleophile.

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## Introduction.

The increase in recent years in the numbers of aged, immunocompromised and AIDS patients at risk from opportunistic infections has intensified the search for more efficacious antifungal treatments [1]. This has led to the development of the methanesulfonates of  $\alpha$ -(4-chlorophenyl)- $\alpha$ -[1-(2-chlorophenyl)ethenyl]-1*H*-1,2,4-triazole-1-ethanol (**1a**, DuP P860) and  $\alpha$ -[1-(2-chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-1*H*-1,2,4-triazole-1-ethanol (**1b**, DuP 991) as  $\alpha$ -styrylcarbinols derived from a novel synthetic class of triazole antifungal agents [2]. We describe the development of a viable commercial process to produce these compounds, highlights of which include the selection of dichlorostyrene as a versatile precursor of the styryl portion, the transformation of a difficult Grignard addition into a useful preparative reaction, and the simultaneous use of 1,2,4-triazole as a base transfer agent and nucleophile during the addition of the final ring.

## Results and Discussion.

The preparation of this class of antifungals required the assembly of three non-fused rings. Retrosynthetic analysis (Scheme 1) suggested that the rings could be appended in any order due to the latitude provided by the centrally dis-

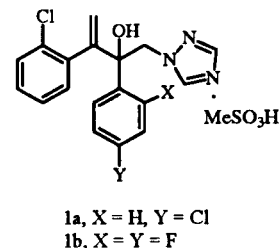
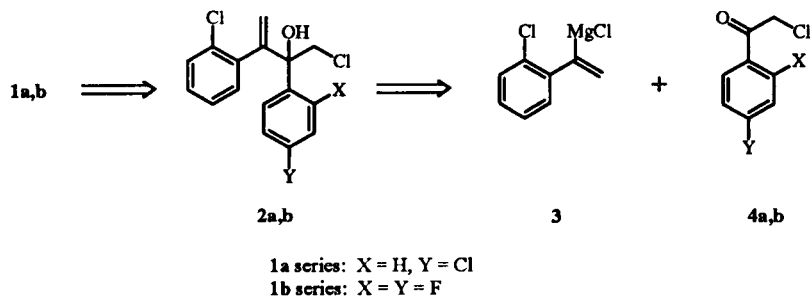


Figure 1

posed tertiary alcohol. As precedent, the rings of the similar  $\beta$ -hydroxyethyl(1,2,4-triazole) antifungals have been connected in various chronologies [3]. However the availability of 2,4'-dichloroacetophenone **4a** directed attention to the condensation of a styryl Grignard agent with **4**, followed by the reaction of the resulting halohydrin **2** (or epoxide **8**) with triazole anion to form the product as the free base [2]. The formation of the methanesulfonate salt would complete the synthesis. This approach was successful for both **1a** and **1b** [4].

Small quantities of **1a** for initial pharmacological screening were first prepared via a seven step synthesis similar to that of the commercial process illustrated in Scheme 2 but employing  $\alpha$ -bromo-*o*-chlorostyrene as the styryl Grignard

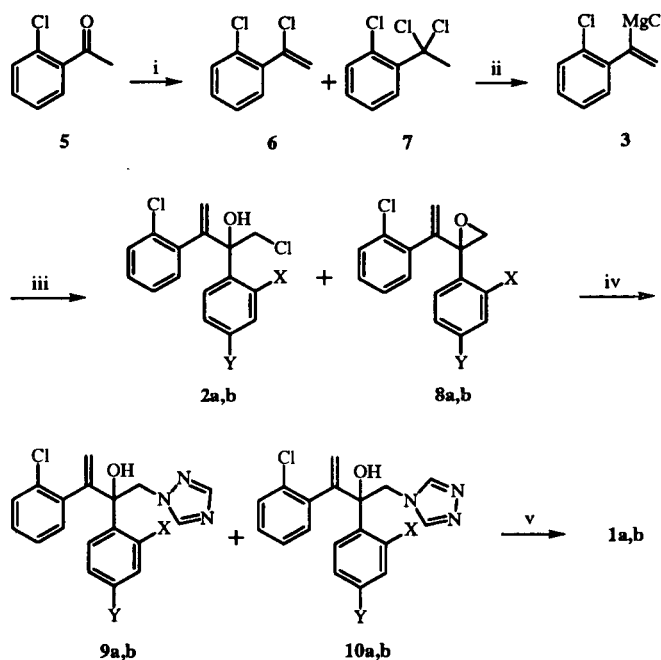
Scheme 1



precursor [2c]. This preparation required the incorporation of several changes when increased in scale. Firstly, dichlorostyrene **6** [5] was more easily prepared and was more robust than bromochlorostyrene. We modified the published preparative conditions of **6** (phosphorus pentachloride, neat) [5b] to include a solvent, heptanes. The product mixture contained variable amounts of the trichloride **7** (4~5 to 1 mole ratio of **6**:**7**). This ratio depended upon the reaction temperature. When the reaction solvent was varied in the hydrocarbon series of pentane to decane, the yield of **6** increased with the boiling point of the refluxing solvent. At first, these observations led us to believe that **7** could dehydrohalogenate to **6** or, less likely, that **6** was in equilibrium with **7** [6]. In the latter case, potentially the higher reaction temperatures could be expelling hydrogen chloride, shifting the equilibrium toward **6**. Several experiments established that neither extending the duration of distillation nor the addition of hydrogen chloride, phosphorus oxychloride, or phosphorus pentachloride affected the ratio of **6**:**7** if the reaction was performed in heptanes. These observations suggest **6** arises not from **7** but rather *via* one or more of the alternative hypothesized mechanisms for the reaction of aromatic ketones with phosphorus pentachloride advanced by Newman [7]. It was possible to dehydrochlorinate the remaining trichloride to **6** by 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile in an overall 50-60% distilled yield. However, this step also produced some of the further dehydrochlorinated product, 2'-chlorophenylacetylene, [8] which tended to quench the initiation of the Grignard reaction in the following step.

Ultimately our pilot plant procedure included heptanes distillation during the addition of **5** while maintaining the volume constant. This removed most of the hydrogen chloride and phosphorus oxychloride by-products, reducing the exothermicity of the subsequent aqueous work-up. The remaining solvent was removed by distillation under nitrogen and **6** was purified by vacuum distillation to yield 70-80% of >90 weight% **6**. Considering its inherently reactive nature, **6** has a good shelf life. A drum of this chemical has survived storage at 4° in the presence of a trace of 4-*t*-butylcatechol for many months.

Scheme 2



(i) PCl<sub>5</sub>, heptanes reflux; (ii) Mg, THF, reflux; (iii) 2,4'-dichloroacetophenone (**1a** route); 2-chloro-2',4'-difluoroacetophenone (**1b** route); THF, 0 °C; (iv) KO<sup>t</sup>Bu, PEG-300, THF, 1,2,4-triazole, 60-70 °C; (v) MeSO<sub>3</sub>H, CH<sub>3</sub>CN, THF, 40 °C.

The conversion of **6** to the organomagnesium reagent **3** was straightforward, but the reaction rapidly overheated upon initiation and was difficult to control until the initial charge of dichloride had reacted. When conducted on a >1 kg scale, this hazard was overcome by the addition of a small amount of **3** which always smoothly initiated the reaction, permitting reduction of the initial charge of dichloride **6**. On a pilot plant scale (up to 30 kg of **6**), this was most easily accomplished by re-using the same vessel *without* cleaning it between reactions.

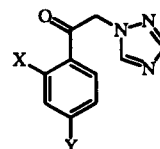
The regioselectivity of organomagnesium formation was not measured but reaction at the aromatic chloride did occur to some extent. The resulting side-product was not

detected at this point but a trace of des-chloro **1a** was eventually detected by hplc in the crude **1a** product mixture. This impurity could arise from the di-metallation of **6** followed by protonation of the aromatic magnesium chloride during the work-up. The organomagnesium content of the the solution was not conveniently measured, but gc was used to ascertain a minimum of **6** at the reaction endpoint. The organomagnesium solution could be stored without decomposition for at least a week under nitrogen at 20-30°.

The successful addition of **3** to the commercially available phenacyl chloride **4a** was difficult since it tended to form the epoxide **8a** if the exotherm was not rigorously controlled. Paralleling the instability of similar epoxides, **8a** was not sufficiently robust to function as an intermediate for our process [9]. This may be due to the activation of the epoxide by both the styryl olefin and the phenyl ring, leading to secondary reactions under the reaction conditions. Success was achieved by the simultaneous addition of the reagents. When tetrahydrofuran streams of **4a** and the Grignard **3** were fed into a small [10], well-stirred reactor that possessed an overflow port leading to a quench vessel, high yields of chlorohydrin **2a** were obtained. This modification produced several benefits: the residence period could be kept short to minimize the spontaneous formation of **8a**; the small volume of the reaction pot allowed efficient cooling of what remained a very exothermic coupling [11]; a constant stoichiometry could be maintained instead of the continuous change in reactant ratio unavoidable in a batch process; and the process was highly amenable to scale-up to commercial quantities. Preparation of large batches (5-6 kg) produced 45-60% yields of **2a** from **6** over two steps, (the ratio of **2a**:**8a** was >10:1.) The yield from dichloroacetophenone was 60-75% [12].

Linkage of 1,2,4-triazole onto **2a** completed the synthesis. The reaction of a mixture of **2a**, potassium *t*-butoxide, 1,2,4-triazole, polyethylene glycol [13], and tetrahydrofuran at 60-70° produced **9a** in 80-90% yield, (40 kg scale). The reaction proceeded by the rapid dehydrochlorination of **2a** to **8a** followed in turn by ring opening by the triazole anion. The presence of 1,2,4-triazole, more acidic than *t*-butyl alcohol, assured the absence of *t*-butoxide after a short mixing time [14]. This is important since the related epoxide **8b** degraded in a 60° tetrahydrofuran solution of potassium *t*-butoxide *without* triazole.

The triazole anion may theoretically open either C-O bond of the epoxide ring or attack in a S<sub>N</sub>2' fashion the epoxide moiety, however the products derived from these alternative openings were not detected. This observation is in line with other 1,2,4-triazole openings of unsymmetrical oxiranes as attack at the less hindered position predominates [9,15]. We did detect the by-product **11a** [9], the result of triazole coupling to **4a**, some of which remained unreacted during the previous step due to alkoxide-induced enolization [16].



11a,b

Alkylation of the triazole was not regioselective, leading to a ~8:1 ratio of **9a**:**10a** [17]. Such isomer mixtures are typical in triazole alkylations [18,19]. In spite of the examination of many combinations of reaction temperature, mole ratios, concentration, and solvent, this ratio resisted improvement.

Isolation of **1a** initially required that most of the polyethylene glycol and *t*-butyl alcohol of the **9a** solution be removed *via* brine washes [20]. Following the dilution of the **9a** solution with acetonitrile or dichloromethane, the addition of two moles of methanesulfonic acid precipitated **1a** in ~80% yield. This material was further purified to bulk drug substance by several recrystallizations from methanolic acetonitrile. Of particular satisfaction was the elimination of the symmetrical isomer by this process as ~80% of **10a** remained behind in solution during the first recrystallization.

In summary, practical, chromatography-free routes to **1a** and **1b** have been developed. Numerous chemical and practical problems were overcome or circumvented, leading to a easily scaled process that produced **1a** in 25-40% overall yield and ≥99.5 weight% purity. Of note was the ability to carry forward intermediate solutions from dichlorostyrene to the final salt forms with minimal isolation and purification of intermediates while still retaining good yields.

## EXPERIMENTAL

The <sup>1</sup>H nmr spectra were determined at 300 MHz, <sup>13</sup>C nmr at 75.4 MHz, and <sup>19</sup>F nmr at 376 MHz, all in dimethyl sulfoxide-*d*<sub>6</sub> unless otherwise specified. Mass spectra (ms) were obtained by ammonia chemical ionization unless otherwise specified. The ir spectra were recorded in a potassium bromide matrix unless otherwise specified. Combustion analyses were performed at Quantitative Technologies Inc., Whitehouse, NJ. Melting points are uncorrected. *R<sub>f</sub>* values indicated refer to thin-layer chromatography on analytical plates coated with a 250 μm layer of silica gel and developed in the solvent indicated. Solvent mixtures are volume/volume mixtures. References to chromatography used 0.040-0.063 mm particle size 230-400 mesh gel. Deactivated silica gel was prepared by absorbing water into Aldrich Chemical grade 62/60-200 mesh silica gel until the weight% = 3.5 to 4.2% water. 2,4'-Dichloroacetophenone and 2-chloro-2',4'-difluoroacetophenone were purchased from Torcan Chemical Co. All solvents except for tetrahydrofuran (anhydrous) were reagent grade and were not further purified. All reactions were carried out under a positive pressure of nitrogen.

1-Chloro-2-(1-chloroethenyl)benzene (**6**).

A slurry of phosphorus pentachloride (94.0 g, 0.45 mole) and heptane (390 ml) were brought to a slow distillation while 2'-chloroacetophenone (53.0 g, 0.34 mole) was added over 2.5 hours (additional heptane was added to maintain a constant pot volume). A total of 150 ml of distillate was collected over this period. The distillation was continued for another 2 hours. The pot was cooled in ice and water (475 ml) was charged over 1.5 hours. The layers were separated and the organic fraction was further washed with water (200 ml). The solution was dried over magnesium sulfate, filtered and concentrated at ambient temperature and ~10 mm Hg. The remaining oil was distilled at 12 mm Hg. Fractions distilling at 90-96° were combined to yield 50.7 g (80%) of colorless oil. Analysis by gc [21] indicated 94 area% purity and <sup>1</sup>H nmr spectroscopy indicated a 6:7 ratio of 19:1; ir (sodium chloride): 1621, 1470, 1430, 1220, 1086, 1043, 896, 816, 759, 733, 651 cm<sup>-1</sup>; ms: (DCI-methane) m/z 173 (M+H); <sup>1</sup>H nmr (deuteriochloroform): 7.45-7.36 (m, 2H), 7.33-7.21 (m, 2H), 5.73 (d, J = 1.5 Hz, 1H), 5.52 (d, J = 1.5 Hz, 1H); <sup>13</sup>C nmr (deuteriochloroform): 137.6, 136.6, 132.4, 130.6, 130.00, 129.95, 126.7, 118.2.

*Anal.* Calcd. for C<sub>8</sub>H<sub>6</sub>Cl<sub>2</sub>: C, 55.53; H, 3.50; Cl, 40.98. Found: C, 55.51; H, 3.53; Cl, 40.84.

4-Chloro-2-(2-chlorophenyl)-3-(4-chlorophenyl)-but-1-en-3-ol (**2a**).

A mixture of **6** (18.7 g, 0.1 mole), magnesium chips (13.1 g, 0.54 mole), and tetrahydrofuran (76 ml) was held at 55-60° until reaction initiation was indicated by a further temperature rise. Additional **6** (56.9 g, 0.3 mole) in tetrahydrofuran (218 ml) was added over 70 minutes so as to maintain the pot at reflux. Reflux was continued for another 3.25 hours and the solution was aged overnight at ambient temperature. The solution of **3** (340 g) was cannulated from unreacted magnesium. Two solutions, one composed of Grignard **3** solution (prepared from **6** (150 g, 0.87 mole) and tetrahydrofuran (total weight = 748 g), and the other composed of **4a** (132 g, 0.70 mole) in tetrahydrofuran (total weight = 744 g), were added both at a rate of 6 g/minute to a 250 ml flask initially containing tetrahydrofuran (72 ml) at 0°. The exit port was so situated as to maintain the 72 ml level in the pot and led to a quench vessel containing water (1041 g), ammonium chloride (107 g, 2.0 moles), and sodium chloride (177 g, 3.0 moles) maintained with stirring at <35°. The pot temperature was maintained at -0° during the addition. Once both solutions had been entirely charged, the reaction pot contents were stirred for another 4 minutes and transferred into the quench vessel. The organic layer was separated and washed with saturated aqueous sodium chloride to produce 1119 g of solution. The hplc analysis [22a] indicated this solution contained 11 weight% **2a** (50% yield from dichloroacetophenone), 0.8% **8a**, 3.0% chlorostyrene, and 0.4% **4a**. An analytical sample of **2a** was prepared by flash chromatography on silica gel with 2.5% ethyl acetate/heptane followed by drying *in vacuo* to white crystals, mp 41-44°; tlc: R<sub>f</sub> (1:9 ethyl acetate:heptane) = 0.41; ir: 3547, 3449 cm<sup>-1</sup>; ms: (CI-ammonia) m/z 344 (M+NH<sub>4</sub>); <sup>1</sup>H nmr (deuteriochloroform): 7.4-7.3 (m, 5H), 7.19 (dt, J = 7.7, 1.8 Hz, 1H), 7.05 (dt, J = 7.7, 1.3 Hz, 1H), 6.66 (dd, J = 7.7, 1.8 Hz, 1H), 5.66 (s, 1H), 4.16 (s, 1H), 4.14 (d, J = 11.4 Hz, 1H), 3.99 (d, J = 11.4 Hz, 1H), 3.13 (s, 1H); <sup>13</sup>C nmr: 148.6, 141.3, 138.3, 132.8, 131.6, 131.0, 129.1, 128.7, 128.5, 127.4, 125.8, 118.2, 77.6, 51.8.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>Cl<sub>3</sub>O: C, 58.66; H, 4.00; Cl, 32.46. Found: C, 58.88; H, 4.03; Cl, 32.63.

1-[1-(2-Chlorophenyl)-ethen-1-yl]-1-(4-chlorophenyl)oxirane (**8a**).

Crude **8a**, obtained by conducting the preparation of **2a** in the usual manner but permitting the temperature to rise to -20°, was purified by gradient flash chromatography on deactivated silica gel using methylene chloride/heptane, (10/90 → 20/80) and dried *in vacuo* to produce waxy white solids; tlc: R<sub>f</sub> (1:1 methylene chloride/heptane) = 0.5; ir (neat): 1493, 1475, 1092, 1052, 1039, 1014, 929, 829, 763, 739, 505 cm<sup>-1</sup>; ms: m/z 308 (M+NH<sub>4</sub>); <sup>1</sup>H nmr (deuteriochloroform): 7.5-7.4 (m, 2H), 7.4-7.3 (m, 1H), 7.3-7.2 (m, 2H), 7.2-7.1 (m, 3H), 5.54 (d, J = 0.9 Hz, 1H), 5.40 (d, J = 0.9 Hz, 1H), 2.97 (q, J = 5.4 Hz, 2H); <sup>13</sup>C nmr: 144.7, 137.0, 136.8, 132.6, 132.1, 130.9, 129.4, 129.3, 129.2, 128.1, 126.8, 120.9, 61.3, 55.1.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>O: C, 66.00; H, 4.15; Cl, 24.35. Found: C, 65.84; H, 4.10; Cl, 24.61.

α-(4-Chlorophenyl)-α-[1-(2-chlorophenyl)ethenyl]-1H-1,2,4-triazole-1-ethanol (**9a**).

Potassium *t*-butoxide (466 g, 4.55 moles) was added in portions to a 15° solution of **2a/8a** (3177 g; 0.94 mole of **2a** and 0.17 mole of **8a**), polyethylene glycol-300 (1785 g, 5.95 moles), 1,2,4-triazole (326 g, 4.72 moles), and tetrahydrofuran (392 g) over 85 minutes at 14-20°. A total of 859 g of solvent was removed by atmospheric distillation over 2.25 hour, tetrahydrofuran (157 g) was charged, and the solution was stirred overnight at 60-70°. The mixture was cooled to 48° and washed sequentially with saturated aqueous sodium chloride (2 x 2.4 l), half-saturated sodium chloride (2 x 2.4 l), and saturated sodium chloride (2.4 l) to produce 1870 g of dark liquid. The hplc analysis [22b] indicated this solution consisted of 18 weight% **9a** (83% yield from **2a**), 2.3% **10a**, and 0.73% **11a**. An analytical sample of **9a** was prepared by recrystallization from 1:7 hexane:methylene chloride, (1 g/6 ml), mp 150-151°; ir: 3423, 1491, 1093, 764, 739, 678 cm<sup>-1</sup>; ms: m/z 360 (M+H); <sup>1</sup>H nmr: 8.33 (s, 1H), 7.80 (s, 1H), 7.37-7.16 (m, 7H), 7.05 (dd, J = 7.1, 2.4 Hz, 1H), 6.11 (s, 1H), 5.75 (s, 1H), 5.10 (s, 1H), 4.87 (d, J = 14.7 Hz, 1H), 4.82 (d, J = 14.3 Hz, 1H); <sup>13</sup>C nmr: 150.1, 148.2, 144.9, 140.5, 138.4, 132.8, 131.7, 131.1, 129.1, 128.8, 128.4, 127.3, 126.0, 118.3, 77.3, 56.5.

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O: C, 60.01; H, 4.20; N, 11.66; Cl, 19.68. Found: C, 59.99; H, 4.24; N, 11.56; Cl, 19.90.

α-(4-Chlorophenyl)-α-[1-(2-chlorophenyl)ethenyl]-1H-1,2,4-triazole-1-ethanol Methansulfonate (**1a**).

The solution of **9a** (1794.4 g, 0.89 mole) prepared in the previous step and acetonitrile (867 g) at 16° was treated with methanesulfonic acid (170.4 g, 1.77 moles) over 1 hour. The resulting slurry was heated to 40° over 25 minutes and cooled overnight. The slurry was cooled further to 11° over 50 minutes, held at this temperature for 3 hours and filtered. The solids were washed several times with acetonitrile (total of 1925 ml) and dried *in vacuo*. Crude **1a** was dissolved into methanol (4.57 l) and clarified by filtration through paper. The filtrate was further diluted with methanol (1025 g) and 2627 g was removed by atmospheric distillation. Distillation was continued while maintaining this solution level with acetonitrile until 3937 ml had been added. The slurry was permitted to cool overnight, further cooled to 12° over 20 minutes, and held at this point for 4 hours. The crystals were filtered, washed with acetonitrile (total of 650 ml), and dried *in vacuo*. The recrystallization was repeated as above using methanol (3737 g) and acetonitrile (3880 ml). The slurry was cooled overnight, further cooled to 5°

over 2 hours and held at 0-5° for 4 hours. The crystals were filtered and washed with acetonitrile (500 ml). The solids were dried *in vacuo* at 70° for 6 days to produce 286.5 g (71% from **9a**) of white crystals, mp 196-203°; ir: 3333 (OH), 3140 (NH<sup>+</sup>), 2975, 1636 (C=C), 1540 and 1490 (aromatic ring), 1433, 1200, 1148, 1136, 1114 (C-O), 1093, 906, 894 (CH<sub>2</sub>=CXY), 845, 768, 758, 739, 663, 637, 550, 537, 523 cm<sup>-1</sup>; <sup>1</sup>H nmr: (400 MHz) 9.06 (s, 1H, CH<sub>2</sub>N=CH), 8.33 (s, 1H, NHCH), 7.34 (m, AA'BB', J = 8.8 Hz, 2H, CH=CHC(Cl)=CHCH), 7.33 (dd, J = 7.8, 1.5 Hz; 1H, C=C(Cl)CH=CH), 7.23 (ddd, J = 7.8, 7.5, 1.8 Hz; 1H, C=C(Cl)CH=CH), 7.28 (m, AA'BB', J = 8.8 Hz, 2H, CHC(Cl)CH), 7.17 (ddd, J = 7.5, 7.5, 1.5 Hz; 1H, C(Cl)=CCH=CH), 7.03 (dd, J = 7.5, 1.8 Hz; 1H, C(Cl)=CCH), 5.76 (s, 1H, C=CHH), 5.12 (s, 1H), 4.96 (s, 2H, NCH<sub>2</sub>), 2.46 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C nmr (100.6 MHz): 147.9 (CH<sub>2</sub>=C), 144.0 (CH<sub>2</sub>N=CH), 146.4 (NNCH), 140.2 (C(OH)C=CH), 138.2 (C(Cl)=CCH), 132.8 (C=C(Cl)), 131.9 (CH=C(Cl)CH), 131.1 (C(Cl)=CCH), 129.2 (C=C(Cl)CH), 128.9 (C(Cl)CH=CHCH), 128.4 (CHCH=C(Cl)CH=CH), 127.4 (CH=C(Cl)CH), 126.0 (C(Cl)=CCH=CH), 118.7 (C=CH<sub>2</sub>), 77.1 (C(OH)), 57.6 (NCH<sub>2</sub>), 39.7 (CH<sub>3</sub>); ms: m/z 360 (M+H); uv (methanol): max 220 nm (ε 18,400).

*Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S: C, 50.01; H, 4.20; N, 9.21; Cl, 15.54; S, 7.03. Found: C, 50.21; H, 4.13; N, 9.27; Cl, 15.27; S, 6.90.

α-(4-Chlorophenyl)-α-[1-(2-chlorophenyl)ethenyl]-4H-1,2,4-triazole-4-ethanol (**10a**).

An impure mixture of the methanesulfonates of crude **9a/10a** (224.0 g) depleted of **1a** by a previous crystallization, was suspended in ethyl acetate (750 ml) and water (700 ml). Concentrated aqueous ammonia (136 ml) was added dropwise and the solution was heated to 45°. The layers were separated and the aqueous layer was extracted with ethyl acetate (250 ml). The combined extracts were evaporated, dissolved into 1:9 methylene chloride/heptanes (500 ml) and filtered through a bed of silica gel (200 g). The bed was eluted with more of the same solvent mixture (250 ml) and the eluate was evaporated to provide white solids (171 g). Part (83.5 g) of this was purified by flash chromatography on silica gel by gradient elution, (methylene chloride/methanol, 100/0 → 90/10). The purest fractions of **10a** (by tlc) were separated and recrystallized from ethyl acetate, (1 g/40 ml); tlc: R<sub>f</sub> (1:9 methanol:methylene chloride) = 0.24. The product was recrystallized again from 1:1 ethyl acetate/heptane, (1 g/60 ml) to yield 4.3 g of fluffy white crystals, mp 198.2-199.4°; ir: 3442, 1538, 1491 cm<sup>-1</sup>; ms: m/z 360 (M+H); <sup>1</sup>H nmr: 8.13 (s, 2H), 7.40-7.14 (m, 7H), 6.89 (dd, J = 7.5, 1.6 Hz, 1H), 6.16 (s, 1H), 5.76 (s, 1H), 5.17 (s, 1H), 4.83 (d, J = 14.3 Hz, 1H), 4.56 (d, J = 14.3 Hz, 1H); <sup>13</sup>C nmr: 148.8, 143.8, 140.3, 138.3, 132.6, 131.8, 131.0, 129.1, 128.8, 128.3, 127.5, 126.0, 118.4, 77.3, 52.4.

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O: C, 60.01; H, 4.20; N, 11.66; Cl, 19.68. Found: C, 60.05; H, 4.25; N, 11.46; Cl, 19.94.

1-(4-Chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (Methanesulfonate of **11a**).

A suspension of sodium bicarbonate (33.30 g, 0.40 mole), 1,2,4-triazole (54.75 g, 0.79 mole), and toluene (850 ml) was brought to reflux and a solution of **4a** (75.00 g, 0.40 mole) in toluene (450 ml) was added over 45 minutes. The mixture was refluxed for another 1.5 hours and was cooled to ambient temperature over 2 hours. The solids were separated and the solution was washed with water (3 x 530 ml), dried over sodium sulfate,

filtered and evaporated. These solids were combined with the insoluble solids from above (27.50 g) and dissolved in methylene chloride (150 ml). Methanesulfonic acid (12.77 g, 0.13 mole) was added over 30 minutes at 15-20°. The slurry was heated to 40° for 30 minutes, cooled to 0° over 2 hours, filtered, and washed with methylene chloride (75 ml). Of the 25.29 g of crude **11a**, 10.36 g was dissolved into methanol (200 ml) at -60°, filtered hot, and reduced by atmospheric distillation to 100 ml. This distillation was continued while the level was maintained with acetonitrile (50 ml). The slurry was cooled to 0° overnight, filtered, and washed with methylene chloride (50 ml). The crystals were dried *in vacuo* to provide 8.30 g (17%) of white needles, mp 198-204.5°; ir: 3454, 1698, 1592, 1227, 1210, 1193, 1094, 1049, 830 cm<sup>-1</sup>; ms: m/z 222 (M+H); <sup>1</sup>H nmr: 8.94 (s, 1H), 8.37 (s, 1H), 8.08 (dt, J = 8.8, 2.4 Hz, 2H), 7.96 (br s, 1H), 7.69 (dt, J = 8.8, 2.4 Hz, 2H), 6.10 (s, 2H), 2.45 (s, 3H); <sup>13</sup>C nmr: 191.0, 147.8, 144.7, 139.4, 132.6, 130.2, 129.2, 56.4, 39.7.

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>4</sub>S: C, 41.58; H, 3.81; N, 13.22; Cl, 11.16; S, 10.09. Found: C, 41.51; H, 3.75; N, 13.18; Cl, 11.35; S, 10.26.

4-Chloro-2-(2-chlorophenyl)-3-(2,4-difluorophenyl)but-1-en-3-ol (**2b**).

Two solutions, one composed of Grignard **3** [prepared from **6** (33 g, 0.19 mole) as described in the preparation of **2a**] in tetrahydrofuran solution (total volume = 230 ml), and the other composed of **4b** (31.1 g, 0.16 mole) in tetrahydrofuran (total volume = 230 ml), were added both at an average rate of 8.5 ml/minute to a 250 ml flask initially containing 50 ml of tetrahydrofuran at 0°. The exit port was so situated as to maintain a 100 ml level in the pot and led to a quench vessel containing water (500 g), ammonium chloride (52.4 g, 1.0 mole), and sodium chloride (104.9 g, 1.8 moles) maintained at <5°. The pot temperature was maintained at <5° during the addition. Addition was continued until both funnels were empty (27 minutes). The pot contents were stirred for another 4 minutes and poured into a second quench vessel containing water (400 g), ammonium chloride (20 g, 0.4 mole) and sodium chloride (40 g, 0.7 mole) at 0°. The solutions were separated, washed with saturated aqueous sodium chloride, dried over sodium sulfate and filtered to produce 332 g of solution. By <sup>1</sup>H nmr spectroscopy, this contained 12 weight% **2b** (69% yield from **6**) and 4 weight% **8b**. An analytical sample of **2b** was prepared by concentration of the above solution to produce 10.43 g which was purified by flash chromatography on silica gel with 3:1 heptane/methylene chloride; tlc: R<sub>f</sub> (2:1 *n*-butyl chloride: heptane) = 0.23. The oily crystalline mass was triturated with hexane (2 x 50 ml) and the remaining crystals were dried *in vacuo* to yield 2.67 g of pale tan crystals, mp 35.0-38.0°; ir (thin film): 3555, 3070, 2976 cm<sup>-1</sup>; ms: (EI) m/z 328 (M<sup>+</sup>); <sup>1</sup>H nmr (400 MHz): 7.55 (ddd, J = 9.0, 9.0, 6.8 Hz, 1H), 7.35 (dd, J = 7.3, 1.5 Hz, 1H), 7.24 (ddd, J = 7.3, 7.3, 1.8 Hz, 1H), 7.19 (ddd, J = 7.3, 7.3, 1.5 Hz, 1H), 7.09 (dd, J = 7.3, 1.8 Hz, 1H), 7.06 (ddd, J = 14.6, 12.1, 3.0 Hz, 1H), 6.99-7.04 (m, 1H), 6.19 (s, 1H), 5.58 (s, 1H), 5.07 (s, 1H), 4.44 (d, J = 11.5 Hz, 1H), 3.97 (dd, J = 11.5, 1.5 Hz, 1H); <sup>13</sup>C nmr: 161.8 (dd, J = 246.4, 12.2 Hz), 158.9 (dd, J = 248.7, 12.2 Hz), 147.4, 137.9, 132.5, 131.6, 131.0 (dd, J = 9.5, 5.7 Hz), 129.0, 128.8, 125.8, 125.2 (dd, J = 12.4, 3.7 Hz), 118.3, 110.6 (dd, J = 20.6, 3.0 Hz), 103.6 (dd, J = 28.2, 25.9 Hz), 76.7 (d, J = 3.8 Hz), 51.1 (d, J = 7.6 Hz); <sup>19</sup>F nmr: -112.3 (m), -107.1 (m).

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>F<sub>2</sub>O: C, 58.38; H, 3.67; Cl, 21.54; F, 11.54. Found: C, 58.09; H, 3.79; Cl, 21.54; F, 11.70.

2-(2-Chlorophenylethene-1-yl)-2-(2,4-difluorophenyl)oxirane (**8b**).

Potassium *t*-butoxide (4.0 g, 35.6 mmol) was added to a solution of **2b** (12 g, 36 mmol) in tetrahydrofuran (100 ml) at 0° over 30 minutes. After 30 minutes, aqueous ammonium chloride (40 ml) was charged and the layers were separated. Most of the organic solvents were removed *in vacuo* and the remainder was diluted with methylene chloride (40 ml). The layers were separated and the aqueous layer re-extracted (40 ml). The organic phase was dried over magnesium sulfate, filtered through a bed of silica gel, and concentrated *in vacuo*. Part of this was purified by flash chromatography on silica gel using heptane/methylene chloride to yield 4.22 g of oily crystals. *tlc*:  $R_f$  (1:2 hexane:*n*-butyl chloride) = 0.28. These were triturated with hexane (2 x 50 ml) and dried *in vacuo* to yield 1.55 g of white crystals. This sample was once more purified by flash chromatography as before for the purposes of the combustion analysis,  $^1\text{H}$  nmr and  $^{13}\text{C}$  nmr spectra, mp 74.5-76.9°; *ir* (carbon tetrachloride) 3096, 3059, 2992  $\text{cm}^{-1}$ ; *ms*: (EI)  $m/z$  292 ( $\text{M}^+$ ),  $^1\text{H}$  nmr (400 MHz): 7.45 (ddd,  $J = 8.5, 8.5, 6.6$  Hz, 1H), 7.41-7.38 (m, 1H), 7.32-7.27 (m, 1H), 7.29-7.24 (m, 1H), 7.23-7.20 (m, 1H), 7.22-7.16 (m, 1H), 7.04 (dddd,  $J = 8.5, 8.5, 2.6, 1.0$  Hz, 1H), 5.43 (dd,  $J = 1.0, 0.7$  Hz, 1H), 5.22 (d,  $J = 1.0$  Hz, 1H), 3.19 (dd,  $J = 5.1, 0.5$  Hz, 1H), 2.97 (d,  $J = 5.1$  Hz, 1H);  $^{13}\text{C}$  nmr: 162.1 (dd,  $J = 247.2, 11.4$  Hz), 160.7 (dd,  $J = 250.2, 12.2$  Hz), 145.1, 136.6, 132.1, 131.3 (dd,  $J = 9.9, 5.3$  Hz), 131.2, 129.4, 129.0, 126.6, 121.5 (dd,  $J = 14.9, 3.4$  Hz), 118.8, 111.2 (dd,  $J = 21.4, 3.8$  Hz), 103.8 (dd,  $J = 25.9, 25.9$  Hz), 57.9, 53.9;  $^{19}\text{F}$  nmr: -110.4 (m), -109.9 (m).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{11}\text{ClF}_2\text{O}$ : C, 65.65; H, 3.79; Cl, 12.11; F, 12.98. Found: C, 65.64; H, 3.88; Cl, 12.14; F, 13.06.

 $\alpha$ -[1-(2-Chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-1*H*-1,2,4-triazole-1-ethanol (**9b**).

Potassium *t*-butoxide (384 g, 3.42 moles) was added in portions to a 7° solution of **2b/8b** (3087 g, 1.15 moles of **2b** and **8b**), polyethylene glycol-300 (2600 g, 8.67 moles), 1,2,4-triazole (270.0 g, 3.91 moles), and tetrahydrofuran (600 g) over 30 minutes at <20°. A total of 1202 g of solvent was distilled, tetrahydrofuran (140 g) was charged, and the solution was refluxed for 65 hours. The mixture was cooled and washed with saturated aqueous sodium chloride (2 x 3 l) to produce 1325.8 g of dark liquid. This solution consisted of 23.3 weight% **9b** (74% yield from **2b**) and 2.6% **10b**. An analytical sample of **9b** was prepared by recrystallization from 1.4:1 ethyl acetate/heptanes, (1 g/5 ml), to produce fluffy, white crystals, mp 129.0-130.9°; *ir*: 3440, 3431  $\text{cm}^{-1}$ ; *ms*: (ESI)  $m/z$  362 ( $\text{M}+\text{H}$ );  $^1\text{H}$  nmr (400 MHz): 8.28 (s, 1H), 7.66 (s, 1H), 7.40-7.35 (m, 1H), 7.30-7.18 (m, 4H), 7.06 (ddd,  $J = 11.6, 9.8, 2.7$  Hz, 1H), 6.84 (dddd,  $J = 9.1, 8.2, 2.7, 0.9$  Hz, 1H), 6.33 (s, 1H), 5.57 (d,  $J = 1.2$  Hz, 1H), 5.14 (s, 1H), 5.06 (d,  $J = 14.1$  Hz, 1H), 4.62 (d,  $J = 14.1$  Hz, 1H);  $^{13}\text{C}$  nmr: 162.0 (dd,  $J = 245.9, 12.2$  Hz), 159.3 (dd,  $J = 248.0, 12.2$  Hz), 150.3, 146.9, 145.0, 138.1, 132.6, 131.8, 130.1 (dd,  $J = 9.9, 5.3$  Hz), 129.3, 129.0, 126.1, 124.6 (dd,  $J = 12.2, 3.4$  Hz), 118.5, 110.5 (dd,  $J = 20.6, 3.0$  Hz), 103.7 (dd,  $J = 28.2, 25.9$  Hz), 75.8 (d,  $J = 3.4$  Hz), 55.1 (d,  $J = 6.5$  Hz);  $^{19}\text{F}$  nmr (282 MHz): -104.8 (m), -112.8 (m).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{ClF}_2\text{N}_3\text{O}$ : C, 59.76; H, 3.90; N, 11.61; Cl, 9.80; F, 10.50. Found: C, 59.63; H, 4.14; N, 11.48; Cl, 9.88; F, 10.54.

 $\alpha$ -[1-(2-Chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-1*H*-1,2,4-triazole-1-ethanol Methanesulfonate (**1b**).

The solution of **9b** (1325 g, 0.85 mole) prepared in the preceding step and methylene chloride (1300 g) at <20° was treated with

methanesulfonic acid (164.0 g, 1.71 moles) over 1 hour. The resulting slurry was stirred for 1 hour, heated to 40° over 85 minutes, and cooled over 2.5 days. The slurry was cooled further to 0° over 2 hours, held at this temperature for 4 hours and filtered. The solids were washed several times with methylene chloride (total of 1255 ml) and dried *in vacuo*. The crude **1b** was dissolved into methanol (6.9 l) and the solution was distilled until 5.0 l had been collected. Distillation was continued while maintaining this level with acetonitrile until 2028 ml had been added. The slurry was cooled overnight and further cooled to 0° over 3.5 hours. The crystals were filtered, washed with methylene chloride (200 ml), and dried *in vacuo*. The recrystallization was repeated twice. The last batch of crystals were dried *in vacuo* at 70° for 3 days to 260.4 g (67%) of white solids, mp 187.3-189.9°; *ir*: 3433, 3423, 1206, 1195  $\text{cm}^{-1}$ ; *ms*: (ESI)  $m/z$  362 ( $\text{M}+\text{H}$ );  $^1\text{H}$  nmr: 9.05 (s, 1H), 8.22 (s, 1H), 7.45-7.37 (m, 1H), 7.34-7.21 (m, 4H), 7.14 (ddd,  $J = 11.8, 9.2, 2.3$  Hz, 1H), 6.89 (dt,  $J = 8.6, 2.6$  Hz, 1H), 5.59 (s, 1H), 5.18 (s, 1H), 5.14 (d of ABq,  $J = 14.1$  Hz, 1H), 4.74 (d of ABq,  $J = 14.1$  Hz, 1H), 2.47 (s, 3H);  $^{13}\text{C}$  nmr: 162.3 (dd,  $J = 247.2, 12.2$  Hz), 159.5 (dd,  $J = 249.5, 13.0$  Hz), 146.5, 146.2, 144.0, 137.9, 132.7, 131.9, 130.2 (dd,  $J = 9.1, 4.9$  Hz), 129.4, 129.2, 126.2, 124.2 (dd,  $J = 12.2, 3.8$  Hz), 119.1, 110.7 (d,  $J = 18.3$  Hz), 103.9 (dd,  $J = 26.7, 26.7$  Hz), 75.4 (d,  $J = 3.8$  Hz), 56.4 (d,  $J = 6.1$  Hz), 39.7;  $^{19}\text{F}$  nmr (282 MHz): d -104.4 (m), -112.2 (m).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{18}\text{ClF}_2\text{N}_3\text{O}_4\text{S}$ : C, 49.84; H, 3.96; N, 9.18; Cl, 7.74; F, 8.30; S, 7.00. Found: C, 50.02; H, 3.97; N, 9.20; Cl, 7.95; F, 8.45; S, 7.05.

 $\alpha$ -[1-(2-Chlorophenyl)ethenyl]- $\alpha$ -(2,4-difluorophenyl)-4*H*-1,2,4-triazole-4-ethanol (**10b**).

The filtrate of several **1b** crystallizations were combined, concentrated *in vacuo* to solids (58.43 g) and dissolved into 1:1 ethyl acetate/water (200 ml). Sufficient concentrated ammonia was charged until the aqueous layer was basic. The layers were separated, the organic layer washed with water (100 ml), and dried over sodium sulfate. The drying agent was removed by filtration through a bed of silica gel and concentrated *in vacuo* to solids (37.6 g). Another 41.1 g was produced in the same manner. These solids were purified by gradient flash chromatography, (1 → 5% methanolic methylene chloride); *tlc*:  $R_f$  (1:7 methanol:methylene chloride) = 0.39. This process was repeated until 12.2 g of solids had been obtained. This was recrystallized from 1:1 ethyl acetate/heptane, (1 g/20 ml), to yield 3.51 g of white crystals, mp 178.3-181.0°; *ir*: 3543, 3140  $\text{cm}^{-1}$ ; *ms*: (ESI)  $m/z$  362 ( $\text{M}+\text{H}$ );  $^1\text{H}$  nmr (400 MHz): 8.12 (s, 2H), 7.41-7.37 (m, 5H), 6.90 (dddd,  $J = 8.8, 8.6, 2.7, 0.9$  Hz, 1H), 6.46 (s, 1H), 5.57 (d,  $J = 1.1$  Hz, 1H), 5.17 (s, 1H), 4.87 (d,  $J = 14.5$  Hz, 1H), 4.40 (d,  $J = 14.5$  Hz, 1H),  $^{13}\text{C}$  nmr: 162.1 (dd,  $J = 247.2, 12.2$  Hz), 158.7 (dd,  $J = 249.5, 12.2$  Hz), 147.0, 143.7 (2C), 138.0, 132.6, 131.6, 130.5 (dd,  $J = 9.9, 5.4$  Hz), 129.3, 129.0, 126.1, 124.4 (dd,  $J = 12.2, 3.7$  Hz), 118.8, 111.0 (dd,  $J = 20.6, 3.0$  Hz), 104.1 (dd,  $J = 27.4, 25.9$  Hz), 76.1 (d,  $J = 4.0$  Hz), 51.0 (d,  $J = 6.3$  Hz);  $^{19}\text{F}$  nmr: -105.3 (m), -112.1 (m).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{ClF}_2\text{N}_3\text{O}$ : C, 59.76; H, 3.90; N, 11.61; Cl, 9.80; F, 10.50. Found: C, 59.72; H, 3.85; N, 11.57; Cl, 9.96; F, 10.64.

1-(2,4-Difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)ethanone (**11b**).

Impure **11b** [26] (3.5 g) was filtered through a bed of silica gel with ethyl acetate. The filtrate was exchanged with hexane until the crystallization appeared complete. This recrystallization was repeated three times to produce 1.80 g of white crystals, mp

113.3-117.3° (lit 105-106°) [9]; ir: 1690, 1613, 1274, 1244, 1148  $\text{cm}^{-1}$ ; ms: (EI)  $m/e$  223 ( $M^+$ );  $^1\text{H}$  nmr (400 MHz): 8.49 (s, 1H), 8.03 (ddd,  $J = 8.6, 8.3, 6.7$  Hz, 1H), 8.01 (s, 1H), 7.51 (ddd,  $J = 11.6, 9.2, 2.5$  Hz, 1H), 7.30 (dddd,  $J = 8.8, 8.3, 2.5, 0.8$  Hz, 1H), 5.81 (d,  $J = 3.0$  Hz, 2H);  $^{13}\text{C}$  nmr (100.5 MHz): 189.4 (d,  $J = 5.3$  Hz), 165.8 (dd,  $J = 256.4, 13.0$  Hz), 162.5 (dd,  $J = 257.9, 13.0$  Hz), 151.4 (s), 145.7 (s), 132.7 (dd,  $J = 11.0, 4.2$  Hz), 119.8 (dd,  $J = 13.7, 3.1$  Hz), 112.8 (dd,  $J = 21.4, 3.8$  Hz), 105.4 (dd,  $J = 26.7, 26.7$  Hz), 57.8 (m);  $^{19}\text{F}$  nmr: -104.2 (m), -101.6 (m).

Anal. Calcd. for  $\text{C}_{10}\text{H}_7\text{F}_2\text{N}_3\text{O}$ : C, 53.82; H, 3.16; N, 18.83; F, 17.02%. Found: C, 54.10; H, 3.26; N, 18.90; F, 17.13.

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- [10] About 5% of the total reactants volume was present in the reaction vessel at any one time.
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- [12] On a kilolab scale (22 l) using a batch process, the yields from **4a** were 40-45%.
- [13] Sozzani and coworkers [23] have demonstrated the value of polyethylene glycols as good solvents for both organic substrates and inorganic salts, in particular potassium salts. Although a wide variety of chemistry is possible in these solvents[24], a literature search indicated the field has been but little exploited. Polyethylene glycol of average molecular weight 300 possessed an attractive combination of solubility, viscosity, toxicity, and cost within our process, and was chosen as the co-solvent.
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