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# HIGHLY STEREOSELECTIVE ACCESS TO NOVEL 2,2,4-TRISUBSTITUTED TETRAHYDROFURANS BY HALOCYCLIZATION: PRACTICAL CHEMOENZYMATIC SYNTHESIS OF SCH 51048, A BROAD-SPECTRUM ORALLY ACTIVE ANTIFUNGAL AGENT

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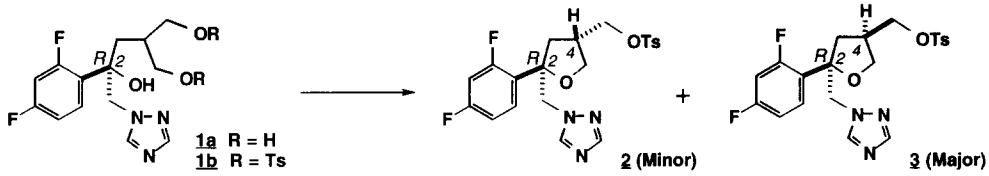
**Abstract:** A convenient synthesis of (-)-(2R)-*cis*-tosylate **2** is reported *via* stereoselective 5-exo iodocyclization of the optically active 2,2-disubstituted olefin **9a**. Enzymatic desymmetrization of the homoallylic diol **4** with Novo SP435 allowed optimal pro-(S) selectivity to provide the desired (-)-(S)-monoacetate **9a**. Under the irreversible reaction conditions, the presence of a bulky aryl substituent on the 2,2-disubstituted olefin seems to determine stereochemical outcome of these halocyclizations.

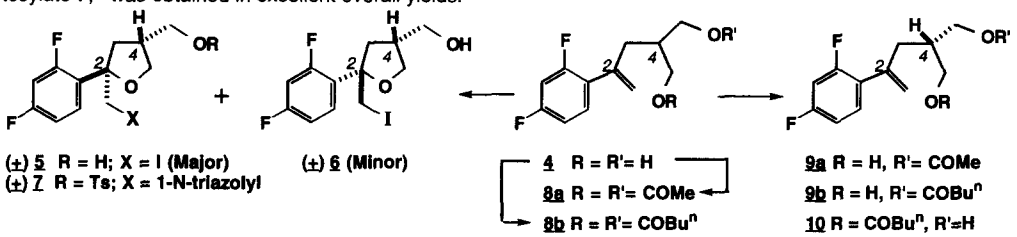
**Sch 51048** is a novel tetrahydrofuran based antifungal agent with improved therapeutic potential over existing drugs against a variety of systemic fungal infections in normal and immunocompromised infection models. Recently we described an enantioselective synthesis of (-)-(2R)-*cis*-tosylate **2**, which acted as a central intermediate towards **Sch 51048** and a variety of highly active analogs.[1, 2] In this earlier route to **2**, we were unable to take advantage of the chirality induced at the benzylic carbon via the Sharpless-Katsuki epoxidation protocol. Thus attempted base-catalysed cyclization of the ditosylate **1b** under a variety of conditions produced a mixture of **2** and the more favored *trans*-stereoisomer **3**. One solution to this problem was offered by the enzymatic desymmetrization of **1a**,[3] but resulted in additional steps to an already protracted sequence.




A conceptually different approach not involving chiral epoxide type intermediates was next considered. Halocyclization provides an effective methodology for construction of substituted tetrahydrofurans.[4] However, except in cases where bulky groups or more than one directing substituents are involved, stereoselectivity in such reactions is often difficult to predict or rationalize. The major success in this context has been in the formation of 2,5-substituted tetrahydrofurans.[5a] We could find no previous example of stereoselective halocyclization of a terminal 2,2-disubstituted olefin such as **4** leading to 2,2,4-trisubstituted tetrahydrofurans. In this instance, it seemed possible that the presence of a bulky 2',4'-difluorophenyl substituent could enforce a directive influence providing, after simple manipulations, the desired 2,2,4-*cis*-tetrahydrofurans such as **2**. We now describe a remarkably efficient enantioselective synthesis of **Sch 51048** *via* a unprecedented 2,4-diastereoselective 5-exo-halocyclization process.

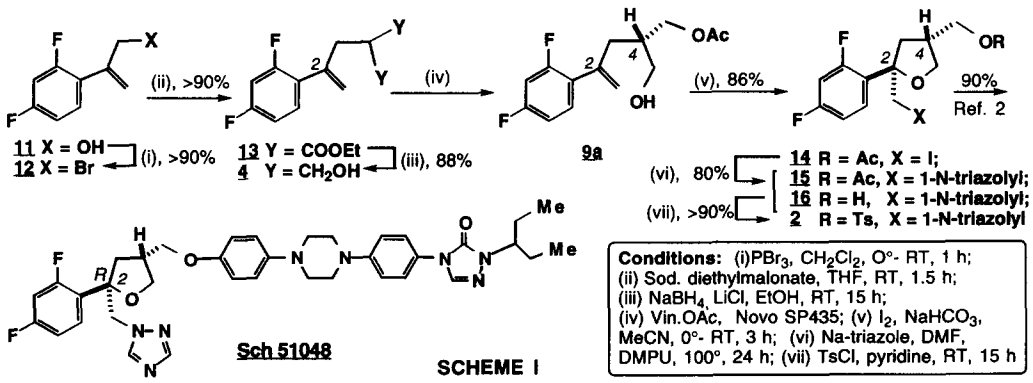
Synthesis of the olefinic homochiral diol **4** was accomplished simply and in high yields from the readily available allyl acohol **11** according to Scheme I. In preliminary experiments, when a solution of **4** in MeCN was treated with $I_2$ (2 equiv.) and $NaHCO_3$ or pyridine (2 equiv.) at room temperature, a mixture of the iodoalcohols (±)-**5** and (±)-**6** was obtained in a 84:16 ratio and in >90% combined yield.[6] This stereoselectivity improved at lower tempertures (0°C to -10°C) to better than 90:10 in favor of the desired diastereoisomer (±)-**5** in which the iodomethyl functionality presented

itself for the direct introduction of the 1-N-triazolyl moiety. Thus, according to steps to be described below, the (±)-*cis*-tosylate **7**,[2] was obtained in excellent overall yields.




From the above successful model experiments, it remained now to devise a convenient synthesis of a suitably desymmetrized diol **4** with desired (4S)-configuration. By the very nature of the highly stereoselective **4** to **5** iodocyclization step, the chirality transfer on the benzylic carbon would follow. The availability of two enzymes (Novo SP 435[7]and Amano CE[8]) with opposite prochiral selectivity allowed three approaches[9] to the preparation of a (4S)-monoester precursor: (i) Novo SP435 catalyzed acylation of diol **4** to give the desired monoester **9a** directly, (ii) Amano CE catalyzed acylation to give the (4R) monoester **10** followed by protection and deacylation, or (iii) Amano CE catalyzed hydrolysis of diester **8b** to give the monoester **9b**.

While all three approaches were explored, we describe here the most direct Novo SP 435 catalyzed acylation strategy. Complete consumption of the diol **4** was imperative to ensure optical integrity of the final product. Of seven solvents examined the best results were obtained in toluene or MeCN at 0°C. The latter was the preferred solvent since the iodocyclization was also carried out in MeCN. The best reaction profiles were obtained using vinyl acetate or butyrate as acylating agents. The enzyme was used at 20:1 (substrate:enzyme) loading, and the catalyst efficiency was demonstrated over 6 cycles without major loss of reactivity.[10] The final conditions for the desymmetrization of **4** to prepare up to 30 kg batches of (-)-(4S)-monoacetate **9a** were: A 20% solution of **4** and two equivalents of vinyl acetate in MeCN at 0°C with 5% enzyme loading was stirred until the enantiometric excess of **9a** was 98 - 99% at which time (4 - 6h) there was <1% diol **4** and ~30% diacetate **8a**.[11,12] Although recoverable **8a** did not interfere with the subsequent iodocyclization, in the present sequence the purified **9a** was utilised. Synthesis of the key (-)-(2R)-*cis*-tosylate **2** was then accomplished as follows. (Scheme I)



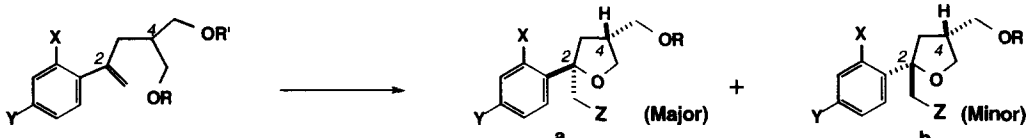

The allyl bromide **12**, available from the corresponding alcohol **11**[2] was treated with the Na-salt of diethyl malonate to provide the diester **13**.[13] Its reduction with $LiBH_4$ generated *in situ* in ethanol afforded **4** which was desymmetrized to the chiral monoacetate **9a** as shown above.[14] Iodocyclization of **9a** ( $I_2$, 2 equiv.; $NaHCO_3$ 2 equiv.;

0°C ) provided the desired iodo acetate **14** and its corresponding diastereoisomer (cf the iodoalcohol **6**) as an inseparable mixture in 90:10 ratio respectively.

Displacement of iodine in a neopentyl-like system in **14** by the highly nucleophilic triazolyl anion posed no problems. A partially hydrolysed mixture of **15** and **16** so obtained was treated with methanolic NaOH to provide **16**[15] and its *trans*-diasteroisomer (<10%) contaminant. Tosylation in neat pyridine finally gave the desired (-)-(2R)-*cis* tosylate **2**, m.p. 96-97°C $[\alpha]_D^{25}$ -39.4° (c = 1.0, $CHCl_3$)[2] readily separable from its *trans*-diastereoisomer by silica gel chromatography in excellent overall yield. Alkylation of sodium or potassium salt of the requisite piperazinyl phenyl side chain with **2** according to previously described conditions [2] completed a very practical synthesis of **Sch 51048**.

We have conducted preliminary experiments to discern origins of the remarkable 2,4-diastereoselectivity observed in the above iodocyclizations. The bromocyclizations were also stereoselective in the same sense (**20a:20b**, 80:20, at 0°C ). Unlike numerous examples of other diastereoselective halocyclizations in which a particular solvent is specifically indicated for optimal results,[16] these cyclizations could be carried out in a variety of solvents such as methylene chloride, diethyl ether, ethyl acetate or tetrahydrofuran with comparable diastereoselectivity.

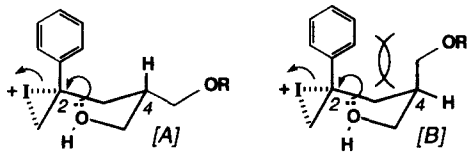
When compared with **4** or **9a** having an *ortho*-fluoro substituent, the absence of *ortho* substituent as in **17** did not affect diastereoselectivity (**21a:21b** 84;16, RT).[17] However in the presence of a bulkier *ortho*-chloro substituent, as in the olefin **18**, retardation in the rate of iodocyclization (~24 h versus 1-2 h with **4** at RT) was observed, accompanied by a relative drop in stereoselectivity (**22a:22b**, 78:22). These reactions were all carried out under non-equilibrating conditions in the presence of a weak base ( $NaHCO_3$ or pyridine). When the benzyl ether **19** was iodocyclized under the equilibrating conditions according to Rychnovsky and Bartlett,[5a] the **23a:23b** ratio also dropped to 70:30. [5b]



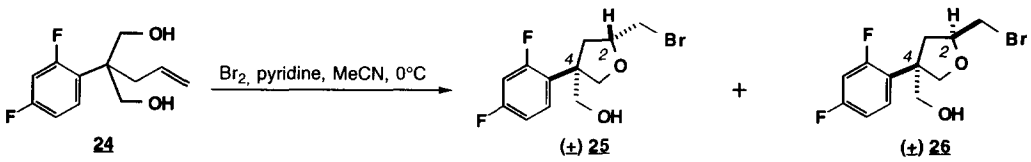

**4** : R = R'= H, X = Y = F
**17**: R = R'= H, X = H, Y = F
**18**: R = R'= H, X = Y = Cl
**19**: R = Ac, R'= Bn, X = Y = F

**20** a,b: R = H, X = Y = F, Z = Br
**21** a,b: R = H, X = H, Y = F, Z = I
**22** a,b: R = H, X = Y = Cl, Z = I
**23** a,b: R = Ac, X = Y = F, Z = I

The above results appear to support the importance of a 2-aryl substituent on the olefinic end as being responsible for the observed 2,4-diastereoselectivity. Considering a chairlike transition state first proposed by Harding and Burks for the amidomercuration of olefinic amides,[18] equatorial disposition of the 4-hydroxymethyl substituent as depicted in *[A]* may account for the major **5** type products. A minor pathway such as *[B]* will have unfavorable steric repulsion between the 2-aryl and the axially disposed 4-hydroxymethyl substituents.




Iodocyclizations of optically active 2,3-disubstituted olefins have been reported to favor *trans* orientation of the resulting 2,4-disubstituted tetrahydrofurans.[16a] In the present halocyclizations of 2,2-disubstituted olefins, influence of the bulky aryl group is evident in the formation of 2,2,4-trisubstituted tetrahydrofurans having exocyclic iodine-bearing carbon in a *cis* relationship to a hydroxy or acetoxymethyl substituent. Where this factor is missing, for example in the 5-*exo* bromocyclization of the terminal olefin **24**, a 50:50 mixture of 2,4,4-trisubstituted tetrahydrofurans **25** and **26** was obtained.




In conclusion we have demonstrated a simple and highly stereoselective synthesis of (-)-(2R)-*cis*-tosylate **2** *via* iodoetherfication of optically active diol monoacetate **9a**. This key intermediate was utilized in a practical enantioselective synthesis of **Sch 51048**, a subject for possible clinical evaluation.[1] The above 2,4-diastereoselective halocyclizations provide versatile intermediates for a variety of selective transformations. These studies as well as further examples of electrophilic cyclizations of such 2,2-disubstituted homoallylic olefins will be reported shortly.

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**References and Notes:**

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5. (a) S. D. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 3963; (b) We have not studied these cyclizations with other bulky ethers. In any event we speculate that the significant steric effect of the aryl substituent on the 2,2-disubstituted olefin may not allow complete reversal of stereoselectivity; such olefins also have the potential to provide additional stablization of benzylic cation species. It would be interesting to study these cyclizations with bulky alkyl substituted olefins.
6. All new compounds were characterised by $^{1}H$, $^{13}C$, NMR and high resolution mass spectra. When necessary diff NOE, COSY and NOESY spectra were obtained. **5:6** ratio of the reaction mixture was determined by comparing the areas under proton H4 and the aromatic positions (δ 6.85, 2H). Proton H4 is shifted downfield in **6** (δ 2.77) as compared to **5** (δ 2.56). In addition resonances at δ 4.23dd or 3.98dd assigned to $CH_2O$ moiety in **6** could also be utilized with excellent reproducibility and applied to all such cases. $^{13}C$ NMR shifts correlated just as well. Elemental analysis were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selected spectral data are given here.
7. From a screen of 169 available hydrolases, only 6 displayed desirable reactivity and selectivity under acylating conditions, and only Novo SP 435 (Novozyme 435 from Novo Nordisk) showed enhanced pro-(S) selectivity under the conditions of the screen; Novo SP 435 is a lipase whose gene coding has been transferred from a selected strain of *Candida antarctica* to a host organism, *Aspergillus oryzae* . The enzyme produced by the host organism is immobilized on a macroporous acrylic resin.
8. Amano lipase CE (Amano Intern. Enzyme Co.) is prepared by the fermentation of a selected strain of *Humicola lanuginosa.*
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10. Isopropenyl acetate and trifluoroethyl acetate were much slower under comparable acylation conditions.; with extended reaction time (e.g., overnight) the substrate : enzyme ratio could be brought down to as low as 100 : 1.
11. Enantiomeric excess (ee) was determined by HPLC using a Chiralpak AS column (0.46x25 cm; Chiral Technologies Inc.). Conditions: 5% EtOH/Hexane, 1.0 mL/min, RT, 233 nm.
12. A solution of **4** (5.01 g, 21.95 mmol), and Novo SP435 (0.26 g) in tank car MeCN (25 mL) was cooled in an ice bath and vinylOAc (4.0 mL, 43.4 mmol) added. The course of the reaction was followed by HPLC and stopped after 6 h. The enzyme was removed by filtration and washed with EtOAc (30 mL), and the combined filtrate evaporated at 30°C. The residue was purified by column chromatography to yield (-)-(4S)-monoOAc **9a** (4.23 g, 71.3%),(ee = 98.2%); $[\alpha]_D^{25}$ = -13.9° (c=1.68, EtOH)); $^{1}H$ NMR [$CDCl_3$] δ 1.81 (m 1H), ~1.9 (bs 1H), 2.06 (s, 3H), 2.54 (m, 2H), 3.53 (m, 2H), 4.12 (m, 2H), 5.22 (s, 1H), 5.28 (s, 1H), 6.77-6.88 (m, 2H), 7.20-7.28 (m, 1H).
13. **13:** $^{1}H$ NMR [$CDCl_3$] δ 1.21 (t, J = 7.2 Hz, 6H), 3.04 (d, J = 9.0 Hz, 2H), 3.36 (t, J = 9.0 Hz, 1H), 4.13 (q, J = 7.1 Hz, 4H), 5.16 (s, 1H), 5.28 (s, 1H), 6.73-6.87 (m, 2H), 7.13-7.21 (m, 1H).
14. **4:** $^{1}H$ NMR [$CDCl_3$] δ 1.67-1.79 (m,1H), 2.07 (bs, $D_2O$ exchangeable, 2H), 2.47 (d, J = 6.0 Hz, 2H), 3.62 (dd, J = 6.0, 10.7 Hz, 2H), 3.76 (dd, J = 3.8, 10.7 Hz, 2H), 5.19 (s, 1H), 5.25 (s, 1H), 6.74-6.86 (m, 2H), 7.16-7.26 (m, 1H).
15. **16:** $^{1}H$ NMR [$CDCl_3$] δ 2.04 (m, 1H), 2.26 (bs, $D_2O$ exchangeable, 1H), 2.41 (m, 2H), 3.43 (m, 2H), 3.73 (dd, J = 6.6, 8.8 Hz, 1H), 4.04 (dd, J = 6.6, 8.0 Hz, 1H), 4.57 (q, J = 14.4 Hz), 2H), 6.75-6.90 (m, 2H), 7.27-7.41 (m, 1H), 7.82 (s, 1H), 8.17 (s, 1H).
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17. Synthesis of these olefins was carried out in the same manner as **4** and will be described elsewhere.
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