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Synthesis and antimycotic properties of hydroxy sulfides derived from *exo*- and *endo*-4-phenyl-3,5,8-trioxabicyclo[5.1.0]octanes

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Both *exo*- and *endo*-isomers of 4-phenyl-3,5,8-trioxabicyclo[5.1.0]octane were reacted with thiophenol to afford individual diastereomers of hydroxy sulfides which were further processed in search for new antimycotic substances.

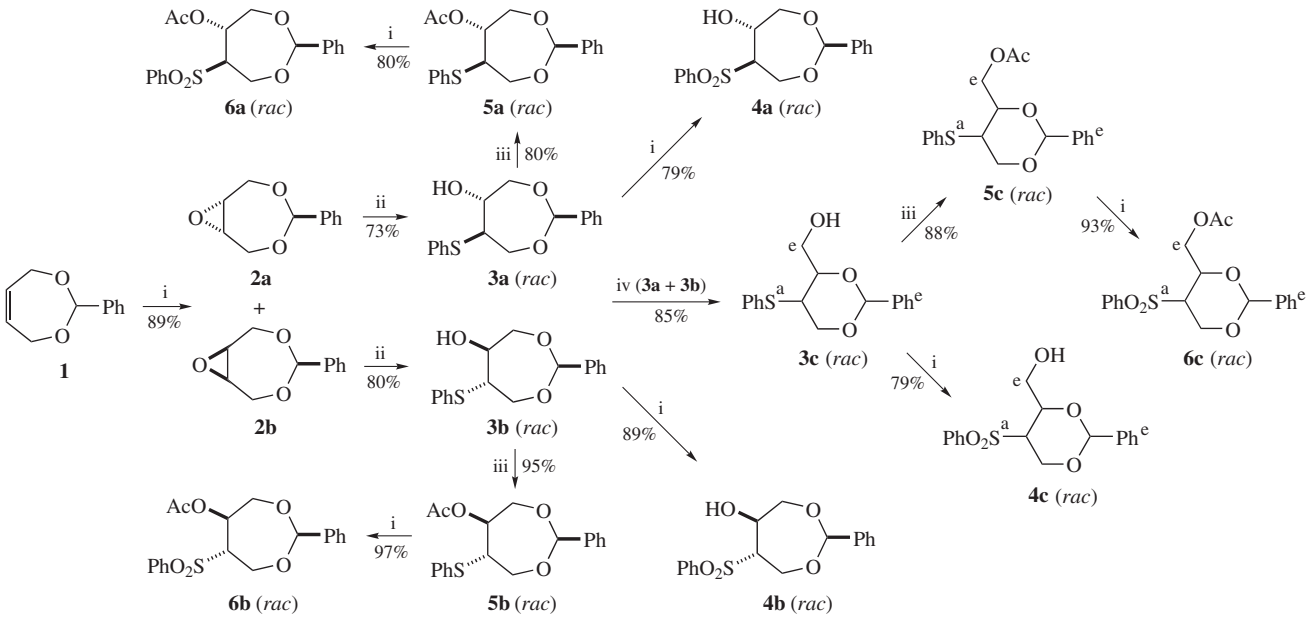
β-Hydroxy sulfides are used in the synthesis of allylic alcohols,[1] cyclic sulfides,[2] thioketones,[3] natural compounds and compounds with biological activity.[4,5] β-Hydroxy sulfones can be transformed into lactones,[6] 2,5-disubstituted tetrahydrofurans[7] and vinylsulfones.[8] Moreover, compounds containing phenylsulfonyl fragment are widely used in fine organic synthesis.[9]

In the continuation of our research,[10] we report herein the results on thiolysis of *exo*- and *endo*-isomers of 4-phenyl-3,5,8-trioxabicyclo[5.1.0]octane with thiophenols, leading to 1,3-dioxepane β-hydroxy sulfides as a result of oxirane ring opening. Isomerization of such hydroxy sulfides in the presence of *p*-toluenesulfonic acid was also studied (Scheme 1).†

Starting 2-phenyl-1,3-dioxacyclohept-5-ene **1** was obtained by acetalization of benzaldehyde with *cis*-but-2-ene-1,4-diol as described.[11] Epoxidation of compound **1** with oxone gave the corresponding epoxides **2a** and **2b**.[12] According to ^{1}H NMR data the ratio of these epoxy acetals is 2:1 in favour of the *endo*-isomer **2b**. Products **2a** and **2b** were separated by column chromatography on silica gel. Their neat reactions with thiophenol in the presence of K_2CO_3 afford β-hydroxy sulfides **3a** and **3b**, respectively, each of them being racemic individual diastereomer. The retention of the 7-membered dioxepane cycle was confirmed by 2D ^{1}H-^{1}H COSY NMR spectroscopy.

Hydroxy acetals **3a** and **3b** on keeping in chloroform in the presence of *p*-toluenesulfonic acid, completely isomerise to the 6-membered acetal **3c** as a result of intramolecular transacetalization. Structure of acetal **3c** was determined by means of 1D and 2D NMR spectroscopy, mass spectrometry and X-ray single crystal diffraction of its derivative **5c** (Figure 1).‡ To extend diversity of new compounds, the corresponding acetates **5a–c** and sulfones **4a–c**, **6a–c** were prepared.

The 1,3-dioxepanes herein obtained demonstrate antimycotic properties. To adequately study the influence of their structure on the biological activity, we tried to separate these racemic



Scheme 1 *Reagents and conditions*: i, Oxone, acetone, $NaHCO_3$, H_2O; ii, PhSH, K_2CO_3, heat; iii, Ac_2O, DMAP, Et_3N, CH_2Cl_2; iv, TsOH, $CHCl_3$.

† For syntheses and characteristics of compounds **2–6**, see Online Supplementary Materials.

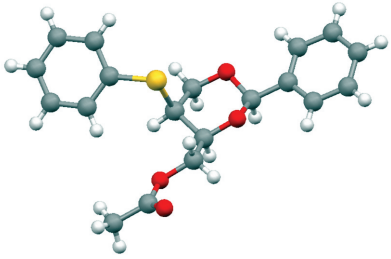
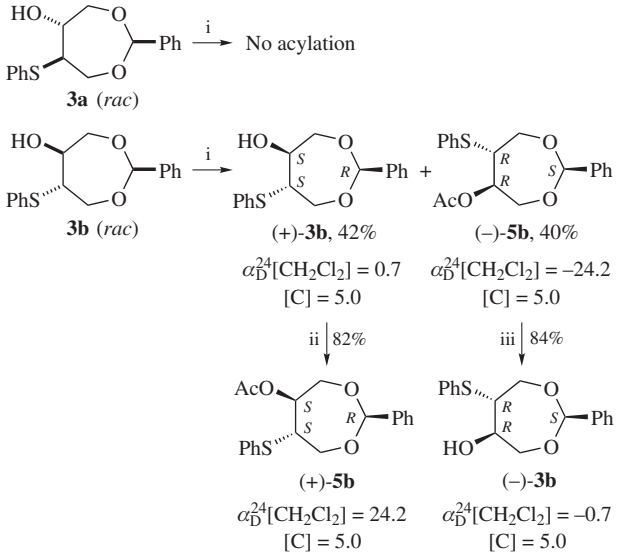


Figure 1 Crystal structure of compound **5c**.

compounds into enantiomers by lipase PS-catalyzed acylation with vinyl acetate as the source of acetyl moiety (Scheme 2).†

Interestingly, under the same acylation conditions diastereomeric alcohols **3a** and **3b** differed in their behaviour. Alcohol **3b** was separated into enantiomers by two-stage synthesis (Scheme 2), whereas its isomer **3a** did not undergo enzymatic acylation. The moduli of rotation angles of the obtained enantiomeric alcohols **3b** and particularly their acetates **5b** (see Scheme 2) were identical what allowed judging of high enantioselectivity of this enzymatic separation. Unfortunalely, the attempted use of chiral shift-reagent to directly determine their *er* values was unsuccessful. The configuration of chiral carbon atom at the hydroxy group was ascribed on the basis of the literature data,[13] since it is known that in the presence of lipase PS only alcohols, having the hydroxy group at the chiral carbon atom with *R*-configuration, are prone to acylation. Hence, under conditions of *trans*-opening of epoxy cycle by thiophenol the configurations of chiral carbon atoms in enantiomers obtained correspond to those presented in Scheme 2.

We have theoretically evaluated biological activity of the compounds synthesized by means of PASS Program.[14–16] According to the data obtained, compounds **3a–c** most likely have high



Scheme 2 *Reagents and conditions*: i, lipase PS, vinyl acetate, THF, 40 °C, ~90 days stirring; ii, Ac_2O, DMAP, Et_3N, CH_2Cl_2; iii, K_2CO_3, MeOH, room temperature.

‡ *Crystal data for* **5c**: colourless crystal, $C_{19}H_{20}O_4S$ (M = 344.42) monoclinic, space group *C*2/*c*, at 298(2) K: a = 30.710(4), b = 5.1147(6) and c = 22.411(3) Å, β = 93.819(1)°, V = 3512.3(8) Å^3, Z = 8, d_{calc} = 1.303 g cm^{-3}, μ = 0.203 mm^{-1}, R_{int} = 0.039, θ_{max} = 27.0°, Bruker Smart Apex II CCD diffractometer, 17922 reflections collected, 2585 observed reflections with $I > 2\sigma(I)$, final R = 0.0593, wR_2 = 0.1372, 3814 independent reflections with $F^2 \geq 2\sigma(I)$, S = 1.04.

CCDC 863301 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.

Table 1 Minimal inhibiting concentrations (MIC/mg cm^{-3}) of synthesized hydroxysulfides **3a–c**.

Compound	*Candida albicans* (clinical strain)	*Aspergillus fumigatus* (typical strain)	*Epidermophyton floccosum* (clinical strain)
3a (*rac*)	~40	~40	~40
3b (*rac*)	~10	~10	~10
3c (*rac*)	>80	>80	~80
(+)-**3b**	~5	~5	~5
(–)-**3b**	~10	~10	~10
Fluconazole	<0.5	<0.5	~0.6

antifungal activity. This type of activity of these substances, both racemic and optically pure ones, have been investigated with the use of clinical and typical strains of some fungi (Table 1).§

Table 1 demonstrates that the antimycotic activity of compound **3c** is significantly lower compared to that of racemic isomers **3a** and **3b**. Meanwhile, the MICs of stereoisomers **3a** and **3b** also significantly differ. So, dioxepane **3b** with *cis*-position of hydroxy and phenyl groups in the cycle has four times higher activity than its stereoisomer **3a** with the same substituents in *trans*-position. The dextrorotatory enantiomer, whose MIC is 5 mg cm^{-3} was found to be more active as compared to levorotary enantiomer with MIC of 10 mg cm^{-3} for all fungi investigated.

In conclusion, we have shown that compounds obtained may be considered as prospective ones concerning their antifungal activity: seven-membered isomers are more active than six-membered ones, the activity of *cis*-isomer of dioxepane series is significantly higher than that of *trans*-isomer, and the dextrorotatory enantiomer is more active as compared with levorotatory one.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.05.003.

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§ For determination of the fungal activity, see Online Supplementary Materials.