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ORIGINAL PAPER

Rac-(2R*,3R*)-*S*-Ethyl-4-Chloro-3-Hydroxy-2-Phenylbuthanethioate and Rac-(2R*,3R*)-*S*-Ethyl-2-Phenyl-3-(tosyloxy)buthanethioate: Dichotomy of the Stereoselectivity of the Mukaiyama Reaction

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Abstract The title compounds, rac-(2R*,3R*)-*S*-ethyl-4-chloro-3-hydroxy-2-phenylbuthanethioate (**I**) and rac-(2R*,3R*)-*S*-ethyl-2-phenyl-3-(tosyloxy)buthanethioate (**III**), are both composed of a *S*-ethyl 2-phenylbutanethioate moiety but have different geometries. Compound **I** is substituted in the 3 and 4 positions by a hydroxyl group and a chlorine atom, respectively. In compound **III** the hydroxyl group in the 3 position of rac-(2R*,3R*)-*S*-ethyl-3-hydroxy-2-phenylbuthanethioate (**II**), has been tosylated in order to obtain suitable crystals for X-ray analysis. In compound **I** the phenyl substituent and the hydroxyl group have a *syn* arrangement, whereas in the tosylate derivative of **II**, i.e., compound **III**, they have an *anti* arrangement. In the crystal structure of **I** centrosymmetric hydrogen bonded dimers are formed via O–H···O hydrogen bonds, involving the hydroxyl group and the carbonyl O-atom. In the crystal structure of **III** symmetry related molecules are connect via a weak C–H···O intermolecular interaction, involving a tosylate O-atom and a phenyl H-atom, so forming zigzag chains propagating in the c direction. The compounds were prepared by the Mukaiyama crossed aldol reaction between the silyl enol ether of *S*-ethyl 2-phenylethanethioate and simple aldehydes, like 2-chloroacetaldehyde (for **I**) and acetaldehyde (for **II**). The *syn/anti* stereo descriptors clearly indicate that the stereoselectivity of the Mukaiyama aldol reaction has switched from a *syn* selective process for the reaction using 2-chloroacetaldehyde to an *anti* selective process for the reaction with acetaldehyde. In both compounds the relative stereochemistry at the newly created chiral centers, positions 2 and 3, is R/R.

Keywords Mukaiyama aldol reaction · Stereoselectivity · X-ray analysis · Hydrogen bonding

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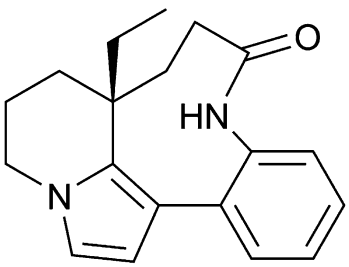
Introduction

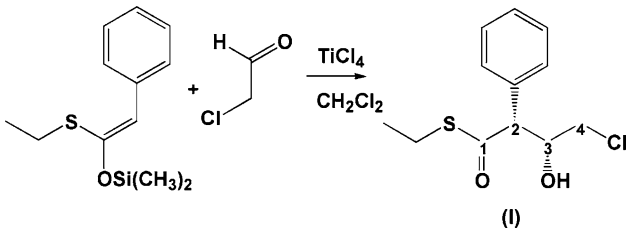
The number of pyrrole containing natural products has steadily increased in recent years, certainly due to the application of more sophisticated isolation procedures [1].

(−)-Rhazinilam, a natural product whose unusual structure was determined in the early 1970s [2], showed interesting cytotoxic and pharmaceutical properties due to its interference with the tubulin–microtubule equilibrium [3, 4].

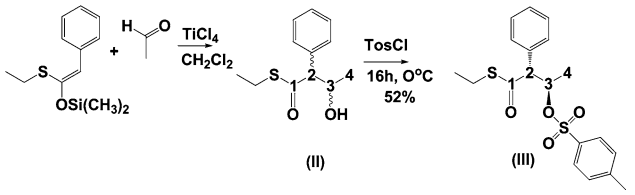


(-)-Rhazinilam

The crystal structure of (−)-Rhazinilam and of a *t*-butoxycarbonyl derivative, have been reported recently [5]. We have been exploring the scope and applicability of a pyrrole synthesis based on the two step sequence



Scheme 1 Synthesis of Rac-(2R*,3R*)-*S*-ethyl-4-chloro-3-hydroxy-2-phenylbuthanethioate (**I**)



Scheme 2 Synthesis of *S*-Ethyl 3-hydroxy-2-phenylbutanethioate (**II**) and Rac-(2R*, 3R*)-*S*-ethyl-2-phenyl-3-(tosyloxy)buthanethioate (**III**)

Mukaiyama cross-aldol reaction [6], followed by the Staudinger reaction [7, 8]. To assemble the key elements, we have studied the Mukaiyama crossed aldol reaction between the silyl enol ether of *S*-ethyl 2-phenylethanethioate and simple aldehydes, like 2-chloroacetaldehyde (Scheme 1) and acetaldehyde (Scheme 2). This modified version allowed us to obtain the condensation products needed for our planed Rhazinilam synthesis in reasonably good yields, whereas the use of the silyl enol ether of 2-phenylacetaldehyde has only lead to the formation of polymers [9].

Experimental

Synthesis

Rac-(2R*,3R*)-*S*-ethyl-4-chloro-3-hydroxy-2-phenylbuthanethioate (**I**) was prepared (Scheme 1) by dissolving chloroacetaldehyde (306 mg, 3.9 mmol) in dry CH_2Cl_2 (20 mL). $TiCl_4$ (2.6 mL, 23.4 mmol), freshly distilled over polyvinylpyridine, was added at −78 °C under Argon. 1-Ethylsulfanyl-2-phenyl-vinyloxy)trimethylsilane (0.983 g, 3.9 mmol) dissolved in CH_2Cl_2 (6 mL) was added drop-wise to the reaction mixture. The solution became dark orange. After 1 h at −78 °C under stirring, sat. $NaHCO_3$ (50 mL) was added to the cold solution. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were collected together and washed three times with water and brine, then dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product obtained was purified by flash chromatography (AcOEt/Hexane 1:3) (Yield 51%). Crystals of **I**, suitable for X-ray analysis, were obtained from ether/hexane (v:v = 1:1).

S-Ethyl 3-hydroxy-2-phenylbutanethioate (**II**) was prepared in the same manner as compound **I** (Scheme 2). Rac-(2R*,3R*)-*S*-ethyl-2-phenyl-3-(tosyloxy)buthanethioate (**III**) was prepared by tosylation of compound **II**: *p*-TosCl (680 mg, 3.57 mmol) dissolved in pyridine (5 mL), and compound **II** (391 mg, 1.74 mmol) were added to the reaction vessel at 0 °C, and stirred for 16 h. 10 mL of water were added to the reaction mixture and the aqueous phase was extracted three times with CH_2Cl_2. The organic phases were combined and washed twice with 1 M HCl, then with a saturated $NaHCO_3$ solution, and then dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product was purified by flash chromatography (AcOEt/Hexane 1:3) (Yield 52%). Crystals of compound **III**, suitable for X-ray analysis, were obtained from ether/hexane (v:v = 1:1).

Crystal Structures Determinations

Intensity data for compound **I** were collected at r.t. on a Stoe AED2 4-circle diffractometer [10], using CuKα graphite monochromated radiation ($\lambda = 1.54186$ Å) with $2\theta/\omega$ scans in the 2θ range 5–120°. The intensity data for compound **III** were collected at 153 K on a Stoe Image Plate Diffraction System [11] using MoKα graphite monochromated radiation. Image plate distance 70 mm, ϕ oscillation scans 0–200°, step $\Delta\phi = 1.5°$, 2θ range 3.27–52.1°, $d_{max} - d_{min} = 12.45$–0.81 Å. The structures were solved by direct methods using the program SHELXS-97 [12]. The refinement and all further calculations were carried out using SHELXL-97 [12]. The non-H atoms were refined anisotropically using weighted full-matrix least-squares on F^2, and a weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = [(F_o^2 + 2F_c^2)/3]$. All hydrogen atoms could be located in difference Fourier maps. The hydroxyl H-atom in **I** was freely refined, while in both **I** and **III** the C-bound H-atoms were included in calculated positions and treated as riding atoms. Further crystallographic data and refinement details are given in Table 1, and the structures are illustrated in Figs. 1–4 [13].

Results and Discussion

The crystal structures of the title condensation products, rac-(2R*,3R*)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbuthanethioate (**I**), and rac-(2R*,3R*)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate (**III**) [compound **II** in its derivatized crystalline form] were carried out in order to ascertain the relative configuration of the two newly created chiral centers at positions 2 and 3. The product of the reaction described in Scheme 1, using 6 equivalents of $TiCl_4$, lead

Table 1 Crystallographic data and refinement details for compounds **I** and **III**

Compound	**I**	**III**
Empirical formula	$C_{12}H_{15}ClO_2S$	$C_{19}H_{22}O_4S_2$
Formula weight	258.75	378.49
Crystal habit, colour	Rod, colorless	Plate, colorless
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a (Å)	11.2422(19)	5.7792(5)
b (Å)	5.4674(11)	20.0506(14)
c (Å)	20.685(4)	17.0331(16)
α (°)	90	90
β (°)	97.236(14)	98.151(11)
γ (°)	90	90
Volume (Å^3)	1,261.3(4)	1,953.8(3)
Z	4	4
Density (calc. g cm^{-3})	1.363	1.287
Temperature (K)	293(2)	153(2)
Radiation type/λ (Å)	Cu Kα/1.54186	Mo Kα/0.71073
Absorption coeff. (mm^{-1})	4.093	0.292
F(000)	544	800
Crystal size (mm)	0.53 × 0.46 × 0.19	0.40 × 0.40 × 0.20
Reflections measured	3,624	16,245
Independent reflections	1,833	3,546
R_{int}	0.048	0.0587
Observed reflns. [$I > 2\sigma(I)$]	1,719	2,461
Number of parameters	151	229
Goodness-of-fit on F^2	1.065	0.907
a, b For weighting scheme	0.0463, 0.591	0.0556, 0.0
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0405$, $wR_2 = 0.1052$	$R_1 = 0.0346$, $wR_2 = 0.0814$
R indices [all data]	$R_1 = 0.0422$, $wR_2 = 0.1065$	$R_1 = 0.0553$, $wR_2 = 0.0873$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.182, −0.265	0.307, −0.375
CCDC deposition no.	723826	723827

to the formation of compound **I** with a yield of 51%. Compound **II** was obtained (Scheme 2) in a higher yield, 70%, also using 6 equivalents of $TiCl_4$. In order to obtain crystals suitable for X-ray analysis compound **II** was tosylated to give compound **III** (Scheme 2).

A search of the Cambridge Structural Database [14], last update November 2008, revealed no entries for the moiety 3-hydroxy-2-phenylbutanethioate. The molecular structure of compound **I** is illustrated in Fig. 1. The bond lengths and angles are in normal ranges [14, 15]. The phenyl ring and the hydroxyl group are directed to the opposite side of the molecule with respect to the chlorine atom and the methyl group of the buthanethioate moiety.

The phenyl substituent at position 2 (C2) and the hydroxyl group at position 3 (C3) have a *syn* arrangement. The mean plane of the thioate moiety (S1/C1/O2/C2) is inclined to the phenyl ring (C5–C10) by 72.89(11)°, while

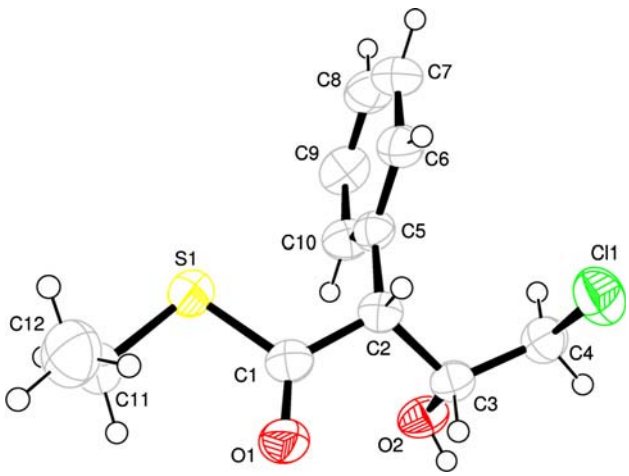


Fig. 1 Molecular structure of compound **I**, showing the atom labelling scheme and the displacement *ellipsoids* drawn at the 50% probability level

Table 2 Hydrogen bonding parameters (D–H···A; Å,°) and Intermolecular interactions (D–H···A; Å,°) for compounds **I** and **III**, and Intra- and intermolecular C–H···π (X–H···Cg; Å,°) interactions for compound **III**

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
I				
O2–H2O···O1^{i}	0.77 (3)	2.06 (3)	2.832 (3)	175 (3)
C2–H2···O2^{ii}	0.98	2.59	3.39 (3)	139
III				
C8–H8···O4^{iii}	0.95	2.44	3.180(3)	135
X–H···Cg	*X–H*	*H···Cg*	*C···Cg*	*X–H···Cg*
C12–H12A···*Cg*1	0.98	2.96	3.902(3)	161
C11–H11B···*Cg*2^{iv}	0.99	2.84	3.613(3)	135

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $x, y-1, z$; (iii) $x-1/2, -y+3/2, z+1/2$; (iv) $2-x, 2-y, 1-z$

Centroids $Cg1$ = (C13–C18); $Cg2$ = (C5–C10)

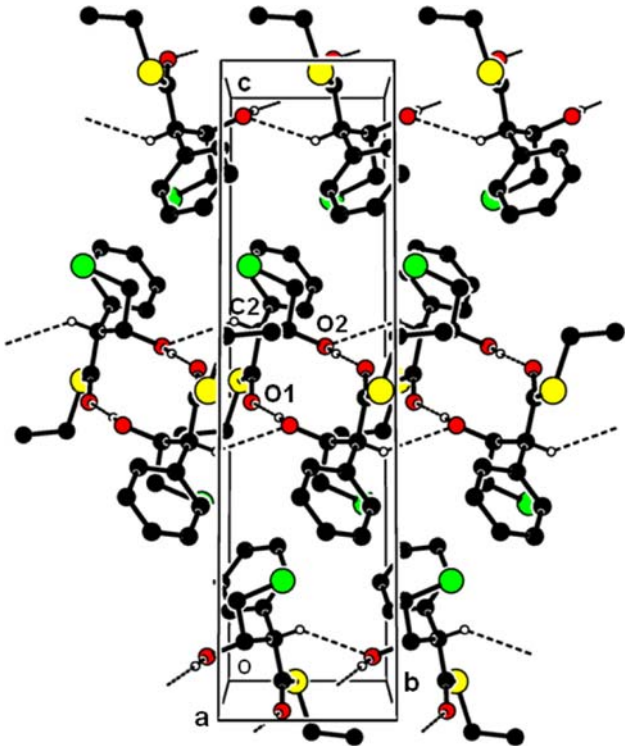


Fig. 2 A view along the *a* axis of the crystal packing of compound **I**, showing strong O2–H20···O1^{i} hydrogen bonds and weak C2–H2···O2^{ii} intermolecular interactions as *dashed lines* forming a ribbon-like structure along the (011) plane of the unit cell (see Table 2 for details; H-atoms not involved in hydrogen bonding have been omitted for clarity)

torsion angles O1–C1–C2–C5 and C5–C2–C3–O2 are 162.2(2) and −67.5(2)°, respectively.

In the crystal structure of **I**, centrosymmetric hydrogen bonded dimers are formed via O2–H2O···O1^{i} hydrogen bonds involving the hydroxyl group (O2) and the thioate O-atom (O1) (Table 2; Fig. 2). These dimmers are further linked by weak C2–H2···O2^{ii} intermolecular interactions involving the H-atom at position 2 (H2) and the hydroxyl O-atom (O2). This gives rise to the formation of a ribbon-like structure along the (011) plane of the unit cell.

The molecular structure of compound **III** is illustrated in Fig. 3. Again the bond lengths and angles are in normal ranges [14, 15]. Here the phenyl substituent at position 2 (C2) and the tosylated hydroxyl group at position 3 (C3) have an *anti* arrangement. The conformation of the molecule is similar to that in compound **I** with the mean plane of the thioate moiety (S1/C1/O2/C2) being inclined to the phenyl ring (C5–C10) by 68.00(9)°. However, torsion angles O1–C1–C2–C5 and C5–C2–C3–O2 are now 80.8(2) and 177.94(13)°, respectively, compared to 162.2(2) and −67.5(2)°, respectively, in compound **I**.

In the crystal structure of **III**, symmetry related molecules are connect by weak C8–H8···O4 intermolecular interactions to form zigzag chains propagating in the c direction (Table 2; Fig. 4). There are also weak intramolecular (C12–H12A···Cg1) and intermolecular (C11–H11···Cg2^{ii}) C–H···π interactions present in the crystal

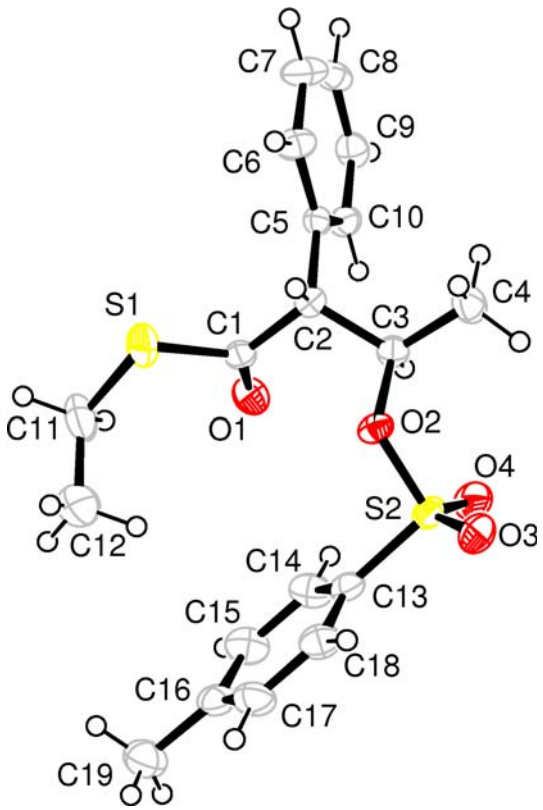


Fig. 3 Molecular structure of compound **III**, showing the atom labeling scheme and the displacement *ellipsoids* drawn at the 50% probability level

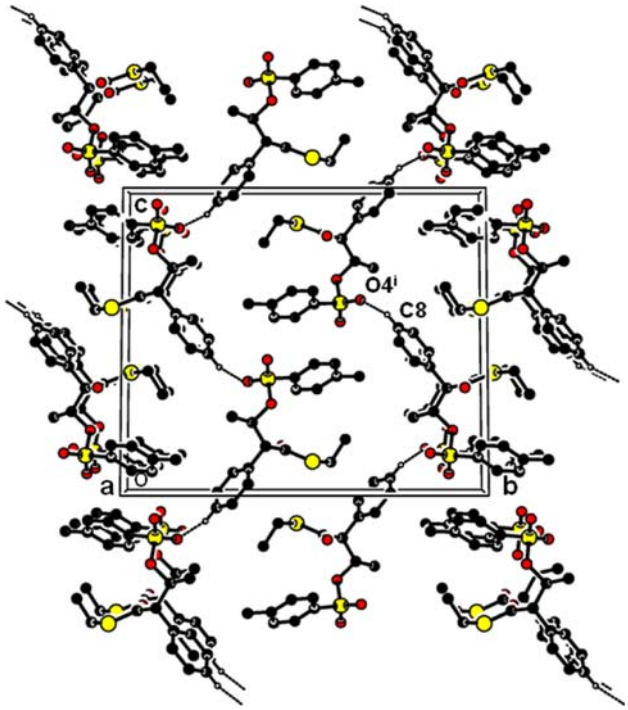


Fig. 4 A view along the *a* axis of the crystal packing of compound **III**, showing weak C8–H8···O4^{i} intermolecular interactions as *dashed lines* (see Table 2 for details; H-atoms not involved in hydrogen bonding have been omitted for clarity)

structure of **III** [where Cg1 = centroid of ring (C13–C18) and Cg2 = centroid of ring (C5–C10), see Table 2].

Conclusions

The *syn/anti* stereo descriptors clearly indicate that the stereoselectivity of the Mukaiyama aldol reaction has switched from a *syn*-selective process for the reaction using the larger substituted aldehyde, 2-chloroacetaldehyde, to an *anti*-selective process for the reaction with the smaller unsubstituted aldehyde, acetaldehyde. In both compounds the relative stereochemistry at the newly created chiral centers (C2 and C3) is R/R. This dichotomy is compatible with the predictions based on the Cornforth transition state model [16, 17] and the polar Felkin–Anh model [18], as has been discussed recently in the literature.

Supplementary Material

Crystallographic data (excluding structure factors) for the structures **I** and **III** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 723826 (**I**) and CCDC 723827 (**III**). Copies of the data can be obtained free of charge on application to CCDS, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccds.cam.ac.uk].

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References

1. Gossauer A (2003) Progress in the chemistry of organic natural products, 1st edn. Springer, Vienna, Austria
2. De Silva KT, Ratcliffe AH, Smith GF, Smith GN (1972) Tetrahedron Letters 913
3. David B, Sevenet T, Morgat M, Guenard G, Moisand A, Tollon Y, Thoison O, Wright M (1994) Cell Motil. Cytoskeleton 28:317
4. Thoison O, Guenard D, Sevenet T, Kan-Fan C, Quirion JC, Husson HP, Deverre JR, Chan KC, Potier P (1987) C R Acad Sci Ser II 304(4):157
5. Décor A, Monse B, Martin MT, Chiaroni A, Thoret S, Guenard D, Gueritte F, Baudoin O (2006) Bioorg Med Chem 14:2314
6. Mukaiyama T, Banno K, Narasaka K (1974) J Am Chem Soc 96:7503
7. Staudinger H, Meyer J (1919) Helv Chim Acta 2:635
8. Vallat O (2004) Ph.D. Thesis. Universitè de Neuchâtel, Switzerland
9. Vallat O, Buciumas AM, Neels A, Stoeckli-Evans H, Neier R (2009) (in preparation)
10. Stoe & Cie (1997) STADI4 & XRED Software. Stoe & Cie GmbH, Darmstadt, Germany
11. Stoe & Cie (2000) IPDS-I Bedienungshandbuch. Stoe & Cie GmbH, Darmstadt, Germany
12. Sheldrick GM (2008) Acta Cryst A64:112
13. Spek AL (2009) Acta Cryst D65:148
14. Allen FH (2002) Acta Cryst B58:380
15. Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R (1987) J Chem Soc Perkin Trans 2:S1
16. Evans DA, Siska SJ, Cee VJ (2003) Angew Chem Int Ed 42:1761
17. Marco JA, Carda M, Diaz-Oltra S, Murga J, Falomir E, Roeper H (2003) J Org Chem 68:8577
18. Evans DA, Cee VJ, Siska SJ (2006) J Am Chem Soc 128:9433