

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

Oliver Vallat · Ana-Maria Buciumas ·
Reinhard Neier · Helen Stoeckli-Evans

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Abstract The title compounds, rac-(2R*,3R*)-S-ethyl-4-chloro-3-hydroxy-2-phenylbutanethioate (**I**) and rac-(2R*,3R*)-S-ethyl-2-phenyl-3-(tosyloxy)butanethioate (**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-phenylbutanethioate (**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

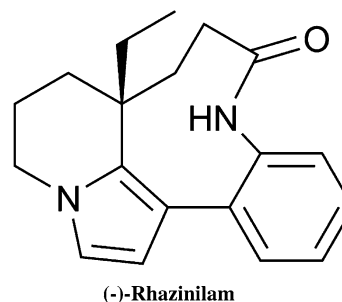
aldol reaction has switched from a *syn* selective process for the reaction using 2-chloroacetaldehyde to an *anti* selective process for the reaction with acetaldehyde. In both compounds the relative stereochemistry at the newly created chiral centers, positions 2 and 3, is R/R.

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

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].

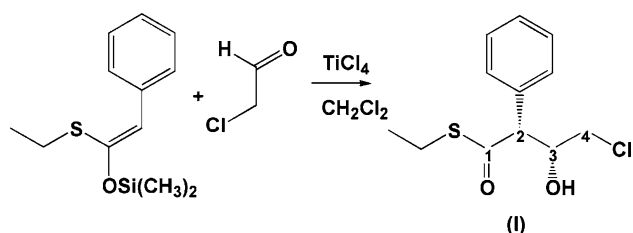


The crystal structure of (–)-Rhazinilam and of a *t*-butoxycarbonyl derivative, have been reported recently [5]. We have been exploring the scope and applicability of a pyrrole synthesis based on the two step sequence

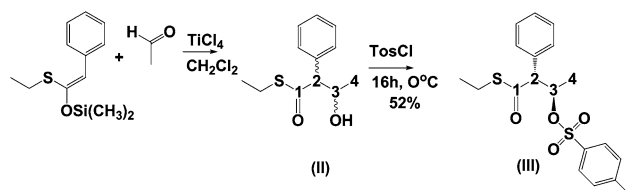
O. Vallat · A.-M. Buciumas · R. Neier
Institute of Chemistry, University of Neuchâtel,
rue Emile-Argand 11, 2009 Neuchâtel, Switzerland

R. Neier
e-mail: reinhard.neier@unine.ch

H. Stoeckli-Evans (✉)
Institute of Physics, University of Neuchâtel,
rue Emile-Argand 11, 2009 Neuchâtel, Switzerland
e-mail: Helen.stoeckli-evans@unine.ch



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



Scheme 2 Synthesis of *S*-Ethyl 3-hydroxy-2-phenylbutanethioate (**II**) and *Rac*-(2*R**, 3*R**)-*S*-ethyl-2-phenyl-3-(tosyloxy)butanethioate (**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 planned 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-(2*R**,3*R**)-*S*-ethyl-4-chloro-3-hydroxy-2-phenylbutanethioate (**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*-(2*R**,3*R**)-*S*-ethyl-2-phenyl-3-(tosyloxy)butanethioate (**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 $\text{CuK}\alpha$ graphite monochromated radiation ($\lambda = 1.54186 \text{ \AA}$) with $2\theta/\omega$ scans in the 2θ range $5\text{--}120^\circ$. The intensity data for compound **III** were collected at 153 K on a Stoe Image Plate Diffraction System [11] using $\text{MoK}\alpha$ graphite monochromated radiation. Image plate distance 70 mm, ϕ oscillation scans $0\text{--}200^\circ$, step $\Delta\phi = 1.5^\circ$, 2θ range $3.27\text{--}52.1^\circ$, $d_{\text{max}} - d_{\text{min}} = 12.45\text{--}0.81 \text{ \AA}$. 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*-(2*R**,3*R**)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbutanethioate (**I**), and *rac*-(2*R**,3*R**)-*S*-ethyl 2-phenyl-3-(tosyloxy)butanethioate (**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 ₂ S | C ₁₉ H ₂₂ O ₄ S ₂ |
| Formula weight | 258.75 | 378.49 |
| Crystal habit, colour | Rod, colorless | Plate, colorless |
| Crystal system | Monoclinic | Monoclinic |
| Space group | <i>P</i> 2 ₁ / <i>c</i> | <i>P</i> 2 ₁ / <i>n</i> |
| <i>a</i> (Å) | 11.2422(19) | 5.7792(5) |
| <i>b</i> (Å) | 5.4674(11) | 20.0506(14) |
| <i>c</i> (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) |
| <i>Z</i> | 4 | 4 |
| Density (calc. g cm ⁻³) | 1.363 | 1.287 |
| Temperature (K) | 293(2) | 153(2) |
| Radiation type/ λ (Å) | Cu K α /1.54186 | Mo K α /0.71073 |
| Absorption coeff. (mm ⁻¹) | 4.093 | 0.292 |
| <i>F</i> (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 |
| <i>R</i> _{int} | 0.048 | 0.0587 |
| Observed reflns. [<i>I</i> > 2 σ (<i>I</i>)] | 1,719 | 2,461 |
| Number of parameters | 151 | 229 |
| Goodness-of-fit on <i>F</i> ² | 1.065 | 0.907 |
| <i>a</i> , <i>b</i> For weighting scheme | 0.0463, 0.591 | 0.0556, 0.0 |
| Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)] | <i>R</i> ₁ = 0.0405, <i>wR</i> ₂ = 0.1052 | <i>R</i> ₁ = 0.0346, <i>wR</i> ₂ = 0.0814 |
| <i>R</i> indices [all data] | <i>R</i> ₁ = 0.0422, <i>wR</i> ₂ = 0.1065 | <i>R</i> ₁ = 0.0553, <i>wR</i> 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 TiCl₄. 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 butanethioate 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

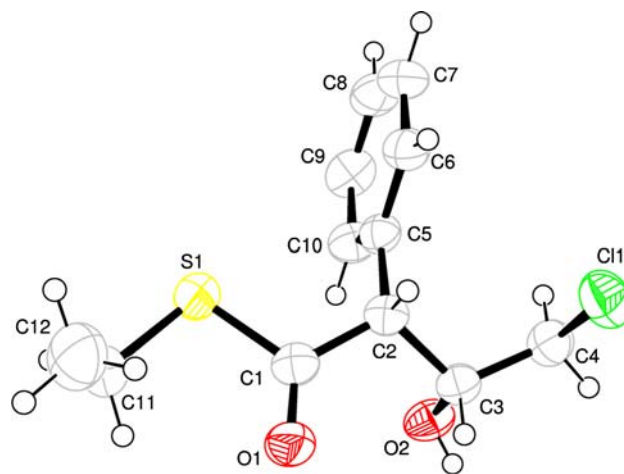
**Fig. 1** Molecular structure of compound **I**, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level

Table 2 Hydrogen bonding parameters ($D-H\cdots A$; Å, °) and intermolecular interactions ($D-H\cdots A$; Å, °) for compounds **I** and **III**, and Intra- and intermolecular $C-H\cdots\pi$ ($X-H\cdots Cg$; Å, °) interactions for compound **III**

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|---------------------------|----------|--------------|--------------|----------------|
| I | | | | |
| $O2-H2O\cdots O1^i$ | 0.77 (3) | 2.06 (3) | 2.832 (3) | 175 (3) |
| $C2-H2\cdots O2^{ii}$ | 0.98 | 2.59 | 3.39 (3) | 139 |
| III | | | | |
| $C8-H8\cdots O4^{iii}$ | 0.95 | 2.44 | 3.180(3) | 135 |
| $X-H\cdots Cg$ | $X-H$ | $H\cdots Cg$ | $C\cdots Cg$ | $X-H\cdots Cg$ |
| $C12-H12A\cdots Cg1$ | 0.98 | 2.96 | 3.902(3) | 161 |
| $C11-H11B\cdots Cg2^{iv}$ | 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 $Cg1 = (C13-C18)$; $Cg2 = (C5-C10)$

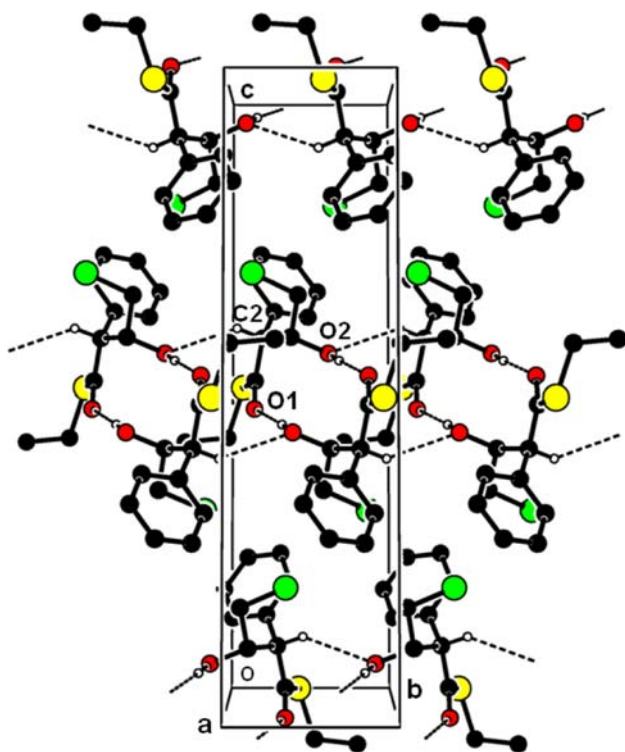


Fig. 2 A view along the a axis of the crystal packing of compound **I**, showing strong $O2-H2O\cdots O1^i$ hydrogen bonds and weak $C2-H2\cdots O2^{ii}$ intermolecular interactions as dashed lines forming a ribbon-like structure along the (011) plane of the unit cell (see Table 2 for details; H-atoms not involved in hydrogen bonding have been omitted for clarity)

torsion angles $O1-C1-C2-C5$ and $C5-C2-C3-O2$ are $162.2(2)^\circ$ and $-67.5(2)^\circ$, respectively.

In the crystal structure of **I**, centrosymmetric hydrogen bonded dimers are formed via $O2-H2O\cdots O1^i$ hydrogen

bonds involving the hydroxyl group (O2) and the thioate O-atom (O1) (Table 2; Fig. 2). These dimers are further linked by weak $C2-H2\cdots O2^{ii}$ 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 $68.00(9)^\circ$. However, torsion angles $O1-C1-C2-C5$ and $C5-C2-C3-O2$ are now $80.8(2)^\circ$ and $177.94(13)^\circ$, respectively, compared to $162.2(2)^\circ$ and $-67.5(2)^\circ$, respectively, in compound **I**.

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

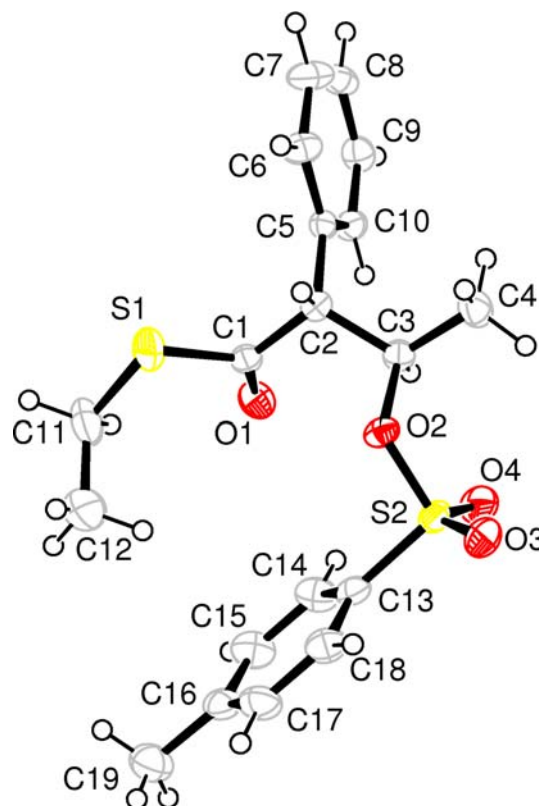


Fig. 3 Molecular structure of compound **III**, showing the atom labeling scheme and the displacement ellipsoids drawn at the 50% probability level

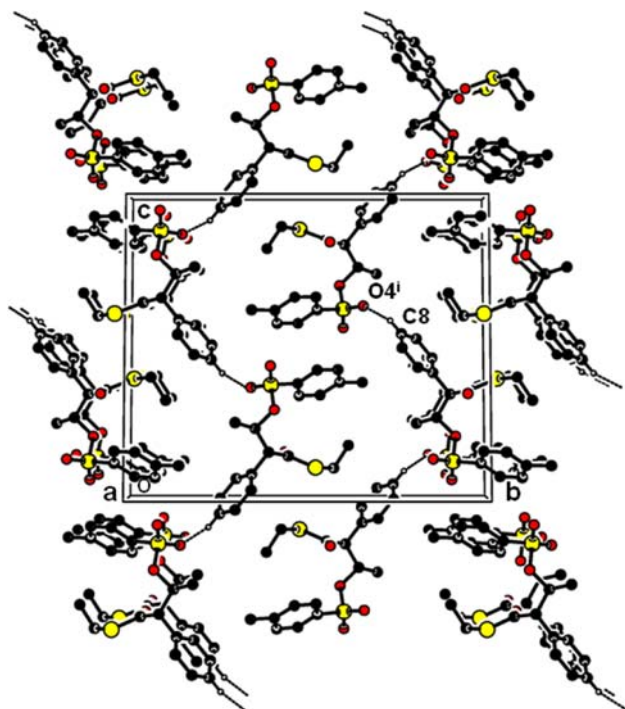


Fig. 4 A view along the *a* axis of the crystal packing of compound **III**, showing weak C8–H8...O4ⁱ intermolecular interactions as *dashed lines* (see Table 2 for details; H-atoms not involved in hydrogen bonding have been omitted for clarity)

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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