Article

Stereoselective Solvolysis in the Synthesis of Dorzolamide Intermediates

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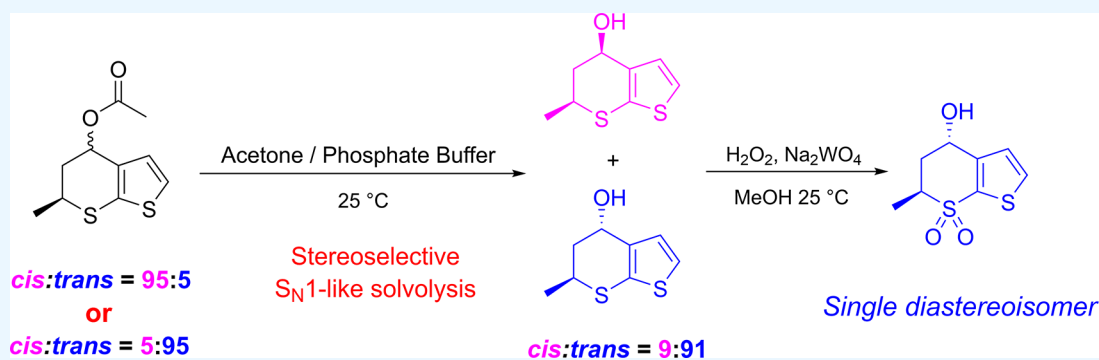
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ABSTRACT: The key intermediate in the synthesis of dorzolamide, (4S,6S)-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-ol-7,7-dioxide, can be obtained in the diastereoisomerically pure form in two straightforward steps starting from diastereoisomeric mixtures of cis/trans-(6S)-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-yl acetate, regardless of their ratio. The reaction of crucial importance in this scheme is a remarkably stereoselective solvolysis of the acetate ester in an acetone/phosphate buffer mixture as the solvent system. Investigation of this so far unrecognized stereoselective reaction reveals that it proceeds via an S_N1-like pathway as indicated by the correlation of the solvolysis rate constants with the Y_{OTs} values of different solvent mixtures and by trapping of the reaction intermediate with sodium azide. The structure of (4S,6S)-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-ol-7,7-dioxide was confirmed by single-crystal X-ray analysis.

INTRODUCTION

Dorzolamide, (4S,6S)-2-(aminosulfonyl)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-7,7-dioxide (**1**) (Scheme 1), is an inhibitor of carbonic anhydrase (CA), which displays activity in the low-nanomolar range, especially against human CA isoenzyme II.[1,2] Aqueous solutions of its hydrochloride salt are used topically as ophthalmic drops (Trusopt), often in association with the β blocker timolol,[3] for the reduction of elevated intraocular pressure (IOP) in glaucoma patients.[4] Dorzolamide was also proved to act as an inhibitor of bacterial carbonic anhydrases such as those derived from *Helicobacter pylori*[5] and *Mycobacterium tuberculosis*.[6] More recently, dorzolamide was reported as an inhibitor of oseltamivir-resistant H1N1 influenza viruses with the H275Y mutation at the neuraminidase gene.[7] These findings suggest the possibility of repositioning this already approved drug as an antibacterial or antiviral, with significant reduction of the cost and time associated with the introduction of new drugs into clinical use.[8−10] In this context, it is worth mentioning that the inhibition of bacterial CA is emerging as an approach to target potentially drug-resistant microorganisms[11] or alternative to antibiotics.[12−15] Besides the activity of

dorzolamide itself, the functionalization of its molecular framework is presently pursued as a strategy to achieve new chemical entities with increased activity for IOP management. Indeed, in seeking improved IOP-reducing agents, dorzolamide was used as a scaffold for decoration with nitric-oxide-releasing moieties, providing compounds with promising activity in an *in vivo* IOP-lowering model.[16]

The synthesis of dorzolamide was first achieved in Merck's laboratories in 1989.[17−19] Afterward, some attention was paid to increasing the overall yield of **1** by improving the preparation of the key intermediate *trans*-**2** or its precursor *trans*-**3** (Scheme 1).
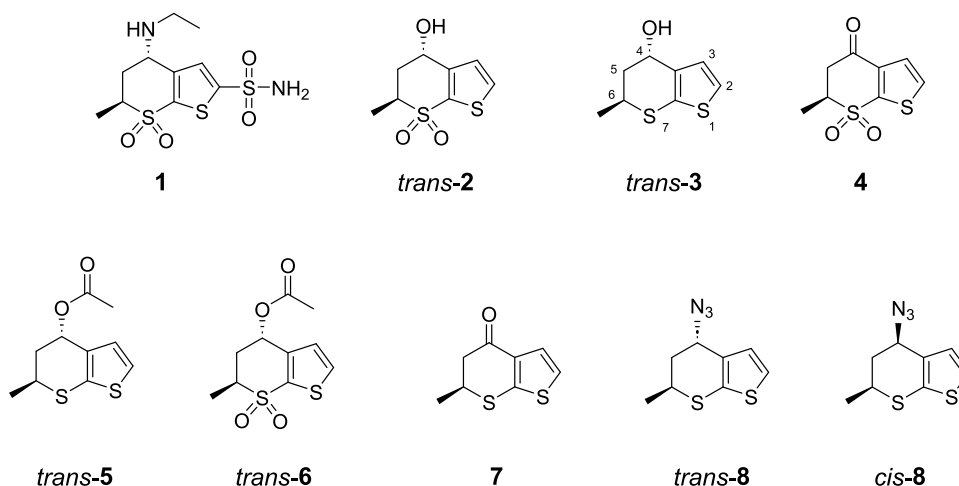
These efforts were led by the observation that achieving diastereoisomerically enriched mixtures of *trans*-**2** is pivotal for the efficacy of the subsequent Ritter reaction required in the

Scheme 1. Molecular Structures of Dorzolamide 1 and Its Synthetic Intermediates[a]

[a]Numbering scheme of the 5,6-dihydro-4H-thieno[2,3-b]thiopyran moiety is displayed on *trans*-3.

synthetic route to **1**, as outlined by Blacklock and Sohar.[20] Among the strategies deployed to this end, the bioreduction of the 4-ketosulfone **4** promoted by *Neurospora crassa* whole cells[21−23] or *Pichia halophila*[21,22] (Zeneca) allowed the preparation of *trans*-**2** with a selectivity of 95% and conversions of 100%. In addition, the kinetic resolution of *rac-cis*-**3** and *rac-trans*-**3** by acylation and epimerization were described, in a detailed study, using lipase in organic solvents.[24]

As a part of our studies aimed to develop a new synthetic approach to **1**, we took into consideration the kinetic resolution of diastereoisomeric mixtures of esters **5** or **6** by exploiting *Candida antarctica* lipase B (CALB) in hydrolytic reactions. However, these attempts were unsuccessful as a parallel, uncatalyzed reaction led to diastereoisomeric mixtures of alcohols **3** largely unbalanced toward the desired *trans*-isomer with a *cis/trans* ratio of up to 7:93. Control experiments confirmed that the enzymatic reaction was essentially abrogated under these conditions. We found that this remarkably stereoselective process is entirely consistent with an S_N1-like solvolytic reaction of **5**, and we report here some mechanistic observations on this, so far unrecognized, stereoselective process. Moreover, we propose the oxidation of **3** (*cis/trans* 9:91) to the corresponding sulfone *trans*-**2** that can be obtained diastereomerically pure by crystallization.

■ **RESULTS AND DISCUSSION**

To study the experimental conditions for the kinetic resolution of **5** via hydrolysis with the enzyme CALB (Table 1), we prepared a *cis/trans* diastereoisomeric mixture of **5** with a ratio close to 50:50. To this end, alcohol **3** was obtained in 98% yield by the reduction of the corresponding 4-ketosulfide **7** with LiAlH₄ in toluene.[20] The reaction yields a diastereoisomeric mixture of **3** with a *cis/trans* ratio of 95:5, in agreement with literature reports. Afterward, the *cis/trans*-**3** ratio was changed to 52:48 by a controlled acid-catalyzed epimerization according to the procedure reported by Blacklock.[20]

The ester **5** (*cis/trans* = 52:48) was obtained by the acylation of **3** (*cis/trans* = 52:48) with acetic anhydride in the presence of excess DMAP. Preliminary kinetic resolutions of the ester **5** (*cis/trans* 52:48) at 0.1 mmol concentration were run at 25 °C using 250 U of CALB supported on an acrylic resin suspended in 5 mL of phosphate buffer (PB; 0.1 M, pH

**Table 1. Experiments for the Screening**[a] **of Solvent Systems for the Solvolysis of 5**
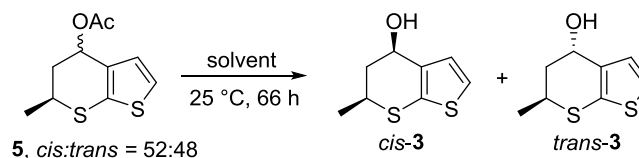
5, *cis:trans* = 52:48

no.	solvent system	conv., %[b]	dr cis/trans-3[b]	dr cis/trans-5[b]
1	acetone/water 80:20	6	12:88	54:46
2	acetone/water 50:50	27	14:86	56:44
3	acetone/PB (0.1 M) 50:50	68	10:90	53:47
4	acetone/PB (0.3 M) 50:50	61	9:91	54:46
5	TFE/water 40:60	100	24:76	0
6	TFE/PB (0.1 M) 40:60	100	6:94	0
7	TFE/PB (0.1 M) 40:60[c]	99	5:95	N.D.[d]
8	TFE/PB (0.3 M) 40:60	100	6:94	0
9	NaNO₃ (aq., 0.1 M)[e]	100	25:75	0
10	Na₂SO₄ (aq., 0.1 M)[e]	100	27:73	0
11	water[d]	100	30:70	0
12	PB (0.01 M)[d]	81	20:80	56:44
13	PB (0.1 M)[d]	81	7:93	60:40
14	PB (0.1 M)[c,d]	37	8:92	56:44
15	PB (0.3 M)[d]	100	6:94	0
16	acetic acid	2	N.D.	16:84
17	HFIP/H₂O 90:10	N.D.	degradation	degradation

[a]Reaction conditions: 5 mg of **5** (*cis/trans* = 52:48); 1.1 mL of the solvent system; 25 °C. [b]Determined by integration of the appropriate ¹H NMR signals as reported in the Supporting Information. [c]Experiment run at 10 °C. [d]N.D. = not determined. [e]Reaction mixture is heterogeneous.

7.4). The reaction was monitored with time by ¹H NMR (see details in the Supporting Information), observing the complete conversion of the starting material to the alcohols that were obtained with a *cis/trans* ratio of up to 7:93, which remained constant throughout the reaction. This result is not compatible with either ester hydrolysis or the known enzymatic activity of CALB because it necessarily requires the loss of stereochemical integrity at carbon 4. In order to assess whether the uncatalyzed formation of alcohols accompanied the enzymatic reaction or was the only active process in the solution, the ester
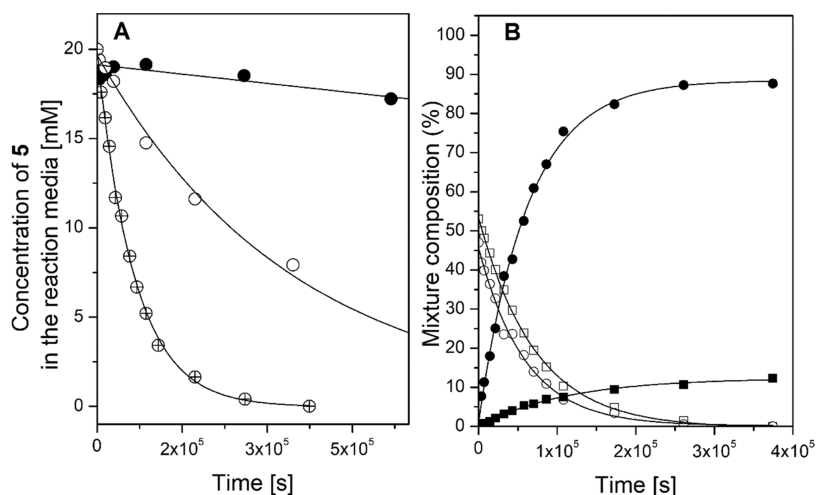
Figure 1. (A) Comparison of the conversion of isomeric mixture **5** in different solvent systems; the conversion is expressed as the residual concentration of **5** determined at a given time; legend: solid circles: acetone/water 80:20; open circles: acetone/water 50:50; crossed circles: acetone/water 45:55. (B) Typical reaction kinetic profile for the solvolysis of **5** in acetone/water 45:55; legend: open squares: *cis*-**5**; open circles: *trans*-**5**; solid squares: *cis*-**3**; solid circles: *trans*-**3**.

5 was suspended in PB (0.1 M, pH 7.4) at 25 °C in the absence of the enzyme. Under these conditions, alcohol **3** was obtained with the same diastereoisomeric ratio observed in the attempts of kinetic resolution, confirming that the enzymatic reaction was essentially inoperative. Furthermore, in control experiments, we established that the alcohols **3** are stereochemically stable in PB (0.1 M, pH 7.4) at 25 °C (see Figure S1), a further indication that the reaction occurred on esters **5**. Based on this experimental evidence, we put forth the hypothesis that this reaction could proceed through a solvolytic pathway with S_N1 characteristics.

This assumption seemed reasonable because the structure of the reagent allows the formation of a secondary carbenium ion stabilized by conjugation with the thiophene ring and by the sulfur atom in position 7 through the thiophene ring. Control experiments performed on sulfone esters **6** (*cis/trans* = 50:50), which are incapable of such a stabilization, either because of the less electron-rich thiophene moiety or because of the oxidized sulfur atom at position 7, did not yield solvolysis products after the reaction at 25 °C (Figure S2). Accordingly, to validate this working hypothesis and to preliminarily analyze the effect of the solvent on the conversion and diastereoisomeric ratio of the products, we performed a small-scale screening of reaction conditions by using different solvent systems including solutions of electrolytes (Table 1). In this screening, the reactions were performed at 25 °C and arbitrarily stopped after 66 h. After solvent removal and work-up, the composition of the crude materials was assessed by ¹H NMR. The conversion of the reagents was determined from the integral ratio of the signals at 6.02 ppm pertaining to 4-H of **5** and at 4.89 ppm pertaining to 4-H of **3**. The diastereoisomeric ratio of **5** was determined as the ratio between the integrals of the signals at 6.88 and 7.02 ppm pertaining to 2-H of *cis*-**5** and 3-H of *trans*-**5**, respectively. The diastereoisomeric ratio of isomers **3** was determined from the integrals of the signal at 7.10 ppm pertaining to 3-H of *cis*-**3** and by the integration of the signals between 7.08 and 7.04 ppm due to protons 3-H of *trans*-**3** and 2-H of *cis*-**3**.[25] In all of the cases, a significant amount of *trans*-**3** in excess to the amount of *trans*-**5** originally present in the reaction mixture could be observed. Moreover, an increase in the polarity of the

medium leads to higher conversions over 66 h (Table 1, entries 1, 2, and 5). In addition, under the conditions explored, increased conversion to *trans*-**3** was obtained by using either PB (pH 7.4) as a cosolvent (entries 3–4 and 6, 7, 8) or as the sole solvent (entries 12–15); however, in the latter case, the reaction system was heterogeneous. The effect of phosphate concentration was briefly explored by running the reactions in 0.01 and 0.1 M PB (pH 7.4) (entries 12–14), and a monotonic increase in the *trans*-selectivity with respect to water was observed (entry 11); further increasing the PB concentration to 0.3 M (entry 15) had no effects. Other electrolyte solutions devoid of buffer properties such as 0.1 M NaNO₃ or 0.1 M Na₂SO₄ (entries 9, 10) were ineffective in increasing the selectivity toward the *trans* isomer, producing **3** with the same diastereoisomeric composition observed in water (entry 11). Upon acetolysis of **5** with a *cis/trans* ratio of 52:48 (entry 16), the diastereoisomeric composition of the recovered ester changed to *cis/trans* = 16:84, further confirming the solvolytic nature of the process under analysis.[26] Higher proportions of *trans*-**3** were obtained by using a 40:60 solvent mixture of 2,2,2-trifluoromethylethanol (TFE):0.1 M PB at either 25 or 10 °C; in both conditions, the product was obtained with an identical diastereoisomeric composition: *cis/trans* ratios = 6:94 (entry 6) and 5:95 (entry 7), respectively. The limited effect of the temperature on the selectivity was also observed for the reactions carried out in 0.1 M PB at 25 or 10 °C (entries 13 and 14, respectively). Attempts to explore other fluorinated alcohols such as hexafluoro-2-propanol (HFIP) led to extensive degradation of the reagents (entry 17).[27]

To derive a quantitative insight into the mechanism of the reaction, the solvolysis of esters **5** was performed in a series of binary solvent mixtures of different ionizing power, defined according to the Y_{OTs} scale.[28,29] The reactions were run at 30 °C, and the kinetic profiles were obtained by ¹H NMR analysis by sampling at selected reaction times. The conversions of **5** to the corresponding alcohols become faster in solvent systems with a higher ionizing power. Figure 1A shows the overall conversion of the isomeric mixtures of esters **5** for some selected acetone:water mixtures, while a typical reaction kinetic profile is displayed in Figure 1B. The formations of *cis*-**5** and

Table 2. Observed First-Order Rate Constants for the Solvolysis of Esters 5 in the Different Solvent Systems Explored[a]

solvent system[b]	Y_{OTs}[c]	$10^6 k_C$, s^{-1}	log k_C[d]	$10^6 k_T$, s^{-1}	log k_T[d]	dr cis/trans-3[e]
acetone/H$_2$O 80:20	−0.94	0.2 ± 0.5	−6.70 ± 2.50	0.2 ± 0.3	−6.70 ± 1.50	13:87[f]
acetone/H$_2$O 50:50	1.26	2.9 ± 0.2	−5.54 ± 0.07	3.0 ± 0.1	−5.52 ± 0.03	13:87
acetone/H$_2$O 45:55	1.56[g]	13.9 ± 0.2	−4.86 ± 0.01	18.0 ± 0.7	−4.74 ± 0.04	12:88
acetone/H$_2$O 60:40	0.66	2.04 ± 0.1	−5.69 ± 0.05	1.75 ± 0.1	−5.76 ± 0.06	13:87
ethanol/H$_2$O 80:20	0.00	1.3 ± 0.1	−5.89 ± 0.08	0.57 ± 0.06	−6.24 ± 0.11	10:90[h]
ethanol/H$_2$O 67:33	0.57[g]	4.4 ± 0.3	−5.36 ± 0.07	2.76 ± 0.08	−5.56 ± 0.03	8:92
TFE/H$_2$O 60:40	2.02[g]	123 ± 7	−3.91 ± 0.06	246 ± 8	−3.61 ± 0.03	23:77
TFE/H$_2$O 40:60	2.14[g]	144 ± 6	−3.81 ± 0.04	221 ± 30	−3.66 ± 0.14	20:80

[a]k_C is referred to as cis-5; k_T is referred to trans-5. [b]Solvent composition: refer to v/v percentage before mixing. [c]From ref 5. [d]Errors are calculated by the uncertainty propagation method. [e]At complete conversion, unless otherwise stated. [f]At 80% conversion. [g]Extrapolated from data in ref 23. [h]At 70% conversion.
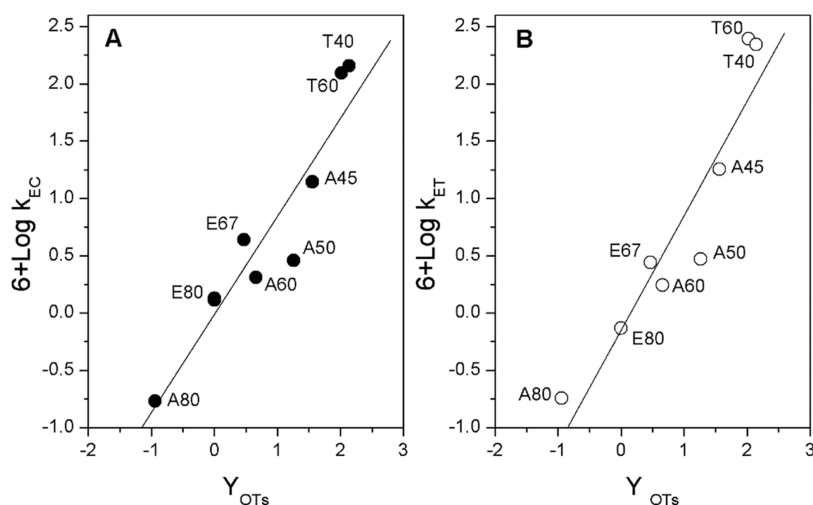

Figure 2. (A) Log k_C as a function of Y_{OTs} values of the solvent systems employed. Abbreviations: A, acetone; E, ethanol; T, 2,2,2-trifluoroethanol; the regression line has R^2 = 0.86. (B) Log k_T as a function of Y_{OTs} values of the solvent systems employed; the regression line has R^2 = 0.89. Abbreviations of the solvent systems as in (A).

trans-5 are clearly first-order processes; the observed first-order rate constants for the solvolysis of cis-5 (k_C) and trans-5 (k_T) were calculated by the nonlinear fitting of the experimental data and are reported in Table 2.

Despite some scattering, not infrequent in these types of analyses, the logarithms of k_C and k_T yield acceptable linear correlations with the Y_{OTs} pertinent to the solvent mixtures used (Figure 2). The slopes of the fitting curves are 0.9 ± 0.1 for cis-5 and 1.0 ± 0.1 for trans-5, in line with an S$_N$1 reaction.

If the hypothesis of an S$_N$1-like solvolysis holds true, the final composition of the products should not depend on the composition of the starting material; indeed, when the solvolysis experiments were performed on a mixture of ester 5 with a cis/trans ratio of 95:5,[30] the composition of the alcohol 3 obtained was the same as that observed when starting from 5 with a cis/trans ratio equal to 52:48. The intervention of a cationic intermediate was also confirmed by running the solvolysis of 5 in the presence of 50 molar equiv of sodium azide in acetone/water (45:55) (Table 3).

As in the preceding cases, the reaction kinetics was monitored by ^{1}H NMR analysis of aliquots of the reaction mixture withdrawn at selected reaction times; a typical kinetic profile is reported in Figure 3A. Under the reaction conditions employed, we observed the almost exclusive formation of azides 8, while only traces of alcohol 3 were detected.

A comparison of the ^{1}H NMR spectra of mixtures of 3, 5, and azides 8 is reported in Figure S3. Azides 8 were obtained

Table 3. First-Order Rate Constants for the Consumption of Esters 5 in the Presence and Absence of 50 Equiv of NaN$_3$ in Acetone/Water (45:55)[a]

5, cis:trans =52:48   cis-8   trans-8

NaN$_3$ (equiv)	$10^6 k_C$, s^{-1}	$10^6 k_T$, s^{-1}	dr cis/trans-8[b]
0	12.7 ± 0.6	16.3 ± 0.8	N/A
0	13.9 ± 0.2	18.0 ± 0.7	N/A
50	13.9 ± 0.4	19.5 ± 0.3	36:64
50	13.7 ± 1.8	19.8 ± 1.5	36:64

[a]k_C refers to cis-5; k_T refers to trans-5. [b]Determined by ^{1}H NMR.

with a cis/trans ratio of 36:64, closer to the original diastereoisomeric ratio of the reactants and to the cis/trans ratio of products 3 observed for the solvolyses in the absence of azides. The chemical nature and the stereochemistry of the azides were confirmed by mass spectrometry and NOE experiments (see Supporting Information page S15 and Figures S3 and S40).

In solvolysis experiments performed in the presence of NaN$_3$, the first-order rate constants (average of the two last entries in Table 3) for the consumption of cis-5 and trans-5 were (13.8 ± 0.1) × 10^{-6} and (19.7 ± 0.2) × 10^{-6} s^{-1},
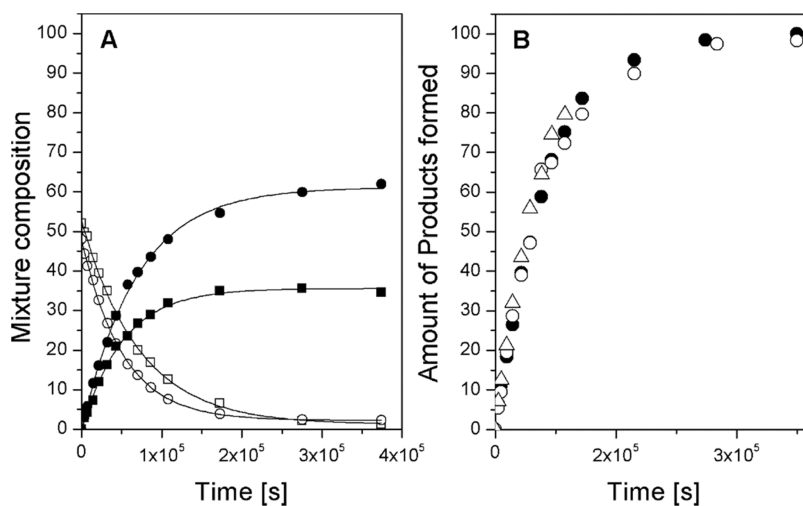
Figure 3. (A) Typical reaction kinetic profile for the solvolysis of **5** in acetone/H$_2$O (45:55) in the presence of 50 equiv of NaN$_3$. Legend: open squares, *cis*-**5**; open circles, *trans*-**5**; solid squares, *cis*-**8**; solid circles, *trans*-**8**. (B) Formation of products **3** and **8** in the reactions run in acetone/H$_2$O (45:55) in the absence and presence of NaN$_3$, respectively. Legend: solid circles, sum of *cis* and *trans*-**3** for the solvolysis run in the absence of NaN$_3$; open circles and open triangles: sum of the products *cis*-**8** and *trans*-**8** obtained in the presence of 50 equiv of NaN$_3$ in the first run and second run, respectively.

Scheme 2. Proposed Mechanism for the Solvolysis of Diastereoisomeric Mixtures of Esters 5[a]
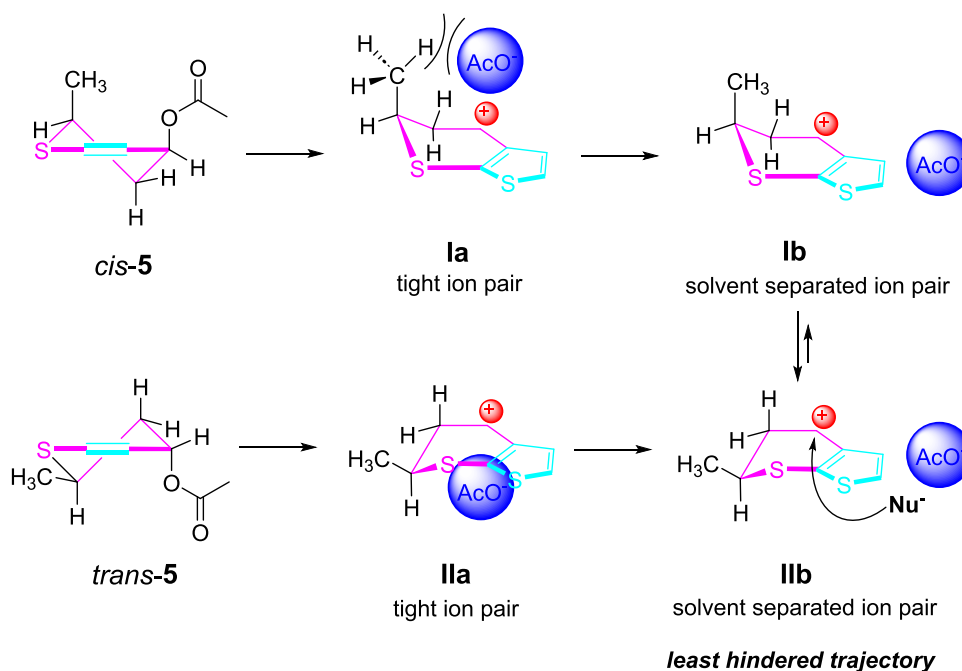
[a]The thiophene ring has been omitted for clarity in the side view structures of *cis*-**5** and *trans*-**5**.

respectively. These values are in keeping with the rate constants observed in the same solvent system but in the absence of added azide anions (Table 3). The overall rate of formation of the azides **8** was the same as that observed for the overall formation of alcohols **3** in the same solvent system without the addition of NaN$_3$ (Figure 3B). This confirms that the azide anion does not participate in the rate-determining step of the reaction, but rather, it likely traps the cationic species formed from the starting material. Changing the solvent system to acetone:PB (45:55) had no influence on the diastereoisomeric composition of azide **8** (Figure S4). Hence, in this case, PB did not shift the formation of the products toward the *trans* isomer of the azide **8** at variance with that

observed in the solvolysis experiments. All of these data may be accounted for by an S$_N$1 mechanism in which the first ionization products are in equilibrium with each other, as summarized in Scheme 2. Ionization, with the initial formation of two diastereoisomeric ion pairs **Ia** and **IIa**,[31] is likely to occur on the half chair conformations of *cis*-**5** and *trans*-**5** with the leaving group in the pseudo-axial position because, only in this case, a favorable overlap between the developing, vacant, p orbital, and the π system of the thiophene ring is possible.[32,33]

Equilibration of the two diastereoisomeric ion pairs via migration of the leaving group from one face of the carbenium ion to another is unlikely. Indeed, this is a relatively slow process compared to the dissociation of the ion pair, as
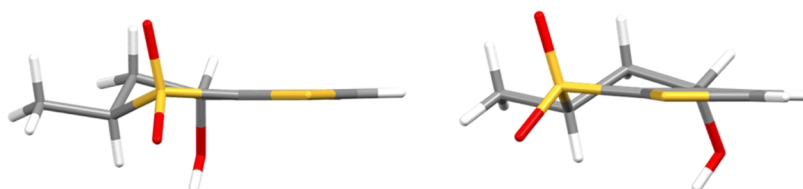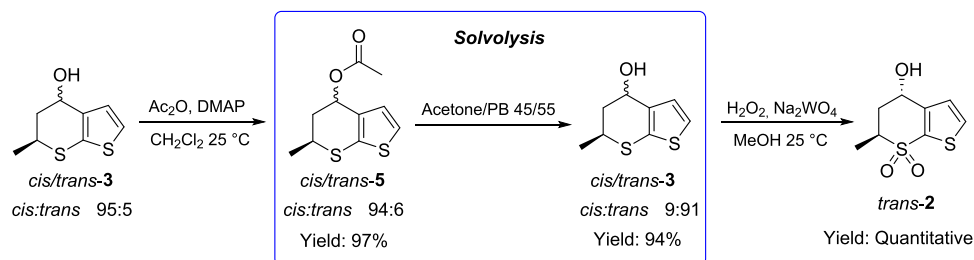
Scheme 3. Implementation of the Solvolysis of 5 in the Synthesis of *Trans*-2

Figure 4. Stick representations of the structures of the two independent molecules of *trans*-**2** from crystallographic data.

reported by Mayr for the solvolysis of 1,3-diarylallyl 4-nitrobenzoates,[34] and repeatedly shown to be undetectable in the S$_N$1 solvolysis reactions of 5-methyl-2-cyclohexenyl acid phthalates,[35] 4-nitrobenzoates,[36,37] and chlorides[38] studied by Goering. It is worth emphasizing here that the substrates studied by Goering are structurally similar to esters **5**. In addition, migration of the leaving group from one face of the carbenium ion to the other could have led to the geometric isomerization of *cis*-**5** to *trans*-**5** and vice versa, a process that we did not observe. Hence, most likely, each of the initial products of heterolysis evolves toward the reasonably free carbenium ion **Ib** or **IIb**. These carbenium ions are conformers that can easily interconvert into one another by the flipping of the 6-C from one face of the plane to another. It is reasonable that an incoming nucleophile acting on **Ib** or **IIb** would form, preferentially, a pseudo-axial bond, as suggested by Goering, and this will give the products the same stereochemistry as the starting materials.[33] However, the attack of nucleophiles on the *re* face of **Ib** (upper panel in Scheme 2) will be hindered by the presence of the methyl group at 6-C, while an attack on the *si* face (lower panel in Scheme 2) will not form a pseudo-axial bond; both of these pathways are unfavorable. In contrast, an attack on the *si* face of **IIb** is the least hindered approach of the nucleophile and produces a pseudo-axial bond, resulting in the preferential formation of *trans* products, as observed experimentally. When water is used as a nucleophile, the reaction proceeds with high selectivity; instead, in the case of the azide ion, which reacts with the cationic species with a rate constant close to the diffusion limit,[39] a lower selectivity is obtained. This is in line with an equilibration of the intermediates **Ib** and **IIb**, which remains likely unattained in the case of the azide nucleophile.

The role of phosphate buffer in this reaction is probably to trap the equivalence of acid formed upon solvolysis, as can be inferred from an inspection of the data in Table 1. Indeed, in the absence of phosphate buffer, the diastereoisomeric compositions of the alcohols **3** obtained upon solvolysis in the various solvent mixtures are very similar, and, on average, the *cis/trans* ratio is 22:78 (entries 1, 2, 5, 9, 10, and 11 in Table 1). This value is very close to the equilibrium *cis/trans* ratio of 24:76 obtained in the acid-catalyzed epimerization of *cis/trans*-**3** by Blacklock and Sohar.[20] In the reactions where

acid is not formed, such as in the formation of the azides **8**, the presence of PB does not produce any increase in the *cis/trans* ratio, vide supra.

To assess the viability of this stereoselective process in the synthesis of *trans*-**2** (Scheme 3), the reaction was performed on 0.50 g of **5** using acetone/PB (45:55) as the solvent system at a 20 mM concentration of **5**; the alcohol **3** (*cis/trans* 9:91) was obtained in 93% isolated yield.

Oxidation of **3** in the presence of hydrogen peroxide and Na$_2$WO$_4$·2H$_2$O in methanol afforded hydroxysulfone **2** (*cis/trans* 9:91) quantitatively. Slow crystallization by vapor diffusion of *n*-hexane into an ethyl acetate solution of the crude *trans*-**2** afforded the spectroscopically pure compound in 89% yield over these last two steps based on the amount of *trans*-**2** present in the starting material before crystallization. This represents a significant improvement over the procedure developed by Blacklock and Sohar,[20] in which **3** could be obtained with a *cis/trans* ratio of 24:76 and, upon oxidation, afforded **2** with the same *cis/trans* ratio. In addition, the reactions of Scheme 2 are straightforward and much simpler with respect to the bioreduction of ketone **4** by *N. crassa* whole cells.[21] Most notably, the concentration of **4** described in the Zeneca process (30 mM)[21] is similar to that employed in the solvolytic process described here, which also has the benefit of having a lower impact from the point of view of waste management.

The structure of *trans*-**2** was confirmed by single-crystal X-ray analysis. Indeed, the crystals of *trans*-**2** (see the Supporting Information for further details) were of suitable quality for structure determination. *Trans*-**2** crystallizes in the orthorhombic form in the chiral space group *P*2$_1$2$_1$2$_1$ with cell parameters *a* = 7.8834(2) Å, *b* = 9.2510(3) Å, *c* = 26.4745(9) Å, and volume = 1930 Å^3. The asymmetric unit consists of two independent molecules (Figures 4 and S5). After gently grinding the bulk material, the X-ray powder diffraction data of *trans*-**2** (Figure S6) were collected and compared to the expected pattern calculated for *trans*-**2**, on the basis of single-crystal data (Figure S6). The structures of the two molecules of *trans*-**2** displayed in Figure 4 enable one to appreciate the planarity of 4-C and 7-S, substituents of the thiophene ring, with the 5-membered ring plane.

CONCLUSIONS

Given the continuing interest in dorzolamide as a therapeutic agent itself or as a scaffold for the development of new chemical entities targeting carbonic anhydrase, either human or bacterial, improved synthetic routes to this species are highly desirable.[40] In this paper, we described the preparation of diastereoisomerically pure (4S,6S)-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-ol-7,7-dioxide, *trans*-2, a key intermediate in the synthesis of dorzolamide, by a straightforward and cost-effective route exploiting previously unrecognized and remarkably stereoselective solvolysis of esters 5 to *trans*-3. By this reaction, *trans*-3 was obtained with a diastereomeric ratio of 91:9 starting from 5, regardless of the diasteroisomeric ratio of the reagent. It was successfully demonstrated that the reaction proceeds via an S_N1-like mechanism through a detailed kinetic analysis and trapping of the cationic intermediate by the very efficient nucleophilic azide anion. Oxidation of diastereoisomerically enriched *trans*-3 affords *trans*-2, which, upon crystallization, is obtained in the diastereoisomerically pure form in 87% yield starting from diastereoisomeric mixtures of 3 largely unbalanced toward the *cis* isomer. The yield and stereoselectivity allowed by the process described are comparable, if not superior, to some of the methods previously described for the synthesis of dorzolamide.

MATERIALS AND METHODS

All commercially available reagents and solvents were purchased from Aldrich and Fluka and used as received, with the exception of enantiomerically pure ketosulfone 4 and ketosulfide 7 provided by ZaCh system S.p.A.; anhydrous solvents were obtained by distilling commercial solvents over sodium-benzophenone ketyl under an argon atmosphere. The chlorinated solvents (CH_2Cl_2, $CHCl_3$, and $CDCl_3$) were treated with K_2CO_3 for at least 24 h before use. Purifications by flash column chromatography were performed using Merck silica gel 60 (230 ÷ 400 mesh). TLC analyses were performed on Merck TLC silica gel 60 F254 plates. ^{1}H NMR, ^{13}C NMR, H−H COSY, and HSQC spectra were recorded in $CDCl_3$ at 298 K on a Varian 500 MHz spectrometer (operating at 500 MHz for proton and at 125 MHz for carbon), ^{1}H NMR spectra are referenced to signals of the residual nondeuterated solvent. Coupling constants are reported in Hz, and the multiplicity is described as follows: s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), m (multiplet), and br (broad signal). The melting points were determined by using a Buchi SMP-20 apparatus. Electrospray ionization (ESI) mass analyses were performed on a Perkin Elmer APII at 5600 eV by Dr. Fabio Hollan of the Department of Chemical and Pharmaceutical Sciences of the University of Trieste.

Detailed synthetic methods and characterization data are provided in the Supporting Information.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03959.

> Preparation procedures of compounds 2−6 and characterization data, kinetic analyses, and solid-state characterization of *trans*-2; NMR spectra (PDF)
>
> *trans*-2 data (CIF)

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Notes

The authors declare no competing financial interest.

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