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Catalytic thiolysis of chemoenzymatically derived vinylepoxides. Efficient synthesis of homochiral phenylthioconduritol F

Ana Bellomo and David Gonzalez*

Departamento de Química Orgánica, Facultad de Química, Universidad de la República, C.C. 1157, Montevideo, Uruguay

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Abstract—The chemoenzymatic synthesis of enantiomerically pure phenylthioconduritol F obtained in 44% overall yield is described. The key step of the synthesis is the Yb(III) thiolysis of a vinyl epoxide, which was studied in depth. The methodology is amenable to scale up and expandable to the preparation of other thiocyclitols.

1. Introduction

β-Hydroxysulfides are important compounds in organic synthesis.[1,2] They can be found as subunits in many biologically active natural and synthetic products,[3] and are of interest in the synthesis of leukotrienes and thiosugars.[4,5]

A direct route for the preparation of β-hydroxysulfides is the ring opening of epoxides by sulfur-containing nucleophiles.[4,6,7] As special types of heterocycles, epoxides are susceptible to reaction with a number of nucleophiles (amines, alcohols, thiols, cyanides, etc.) leading to a wide range of functionalized intermediates.[8–11] It is well documented that the nucleophilic ring opening of the oxirane ring with thiophenol can be promoted by Brønsted acids, Lewis acids, metal salts,[12–15] alumina,[16,8] and under solvent-free conditions.[17] However, despite the rich literature on the chemistry of epoxide ring opening, there are only a few reports concerning the nucleophilic ring opening of vinyloxiranes with sulfur reagents.[18,19]

In connection with our ongoing effort on the preparation of chiral building blocks of chemoenzymatic origin,[20,21] we herein report a practical route to homochiral phenylthioconduritol derivatives. We have optimized the conditions regarding catalysts, reaction temperature, and solvent, and applied them to the synthesis of the previously unreported thiocyclitol **8**.

2. Results and discussion

Phenylthioconduritol F **8** was prepared from bromobenzene as depicted in Scheme 1. The key intermediate in this sequence is the known epoxide **3**[22] available in two steps from the homochiral metabolite **1** biosynthesized by whole-cell fermentation of bromobenzene with *Pseudomonas putida* F39/D.[23] *cis*-Dienediol **1** was protected as its corresponding acetonide **2** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid. Oxidation of the more reactive double bond at 0 °C with *m*-chloroperbenzoic acid, rendered exclusively the α-oxirane as previously described.[22,24–26]

With the α-epoxide in hand, we subjected it to several acid catalyzed ring-opening conditions with thiophenol to improve the yield of the desired hydroxysulfide (Scheme 1).

In order to optimize the reaction yield and stereoselectivity of the ring-opening process, we performed the reaction under a variety of conditions regarding the nature of the acid, the reaction temperature, and the solvent used. $Yb(OTf)_3$ and $CeCl_3$ were chosen as representative Lewis acids and *p*-toluenesulfonic acid (*p*-TsOH) as a typical Brønsted catalyst. The reactions were carried out from below room temperature, up to 60 °C over periods ranging from 20 min to several days. We analyzed the nature and yield of the products and determined the best reaction conditions.

Table 1 shows some of our initial observations. In the absence of a catalyst, the reaction does not proceed

* Corresponding author. Tel.: +598 29247881; fax: +598 29241906; e-mail: davidg@fq.edu.uy

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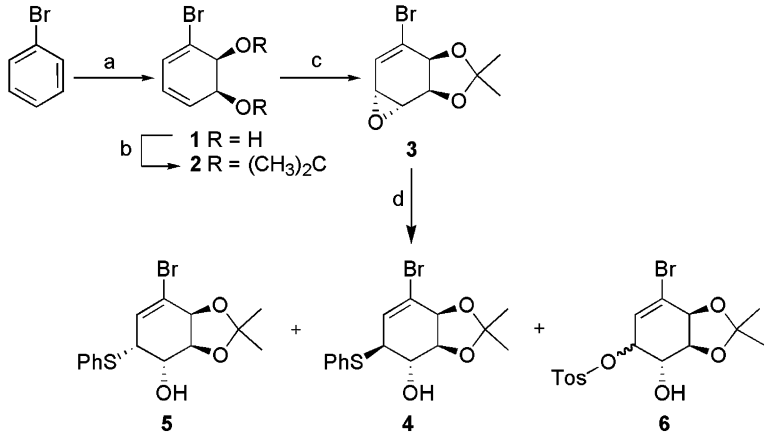


Scheme 1. Synthesis and thiolysis of vinyl epoxide **3**. Reagents and conditions: (a) toluene dioxygenase expressed in *P. putida* F39/D, 3 g/L; (b) 2,2-dimethoxypropane, *p*-TsOH, acetone, rt, 30 min, 98%; (c) *m*-chloroperbenzoic acid, CH_2Cl_2, rt, overnight, 85%; (d) see Tables 1 and 2.

practically at or below room temperature (entries 1–4). Even after 14 days most of the starting material remained in the solution with only a maximum of 30% combined yield of sulfides **4** and **5** was obtained. If the uncatalyzed reaction was carried out at 60 °C, the starting material disappeared rapidly. Nevertheless, stereoselectivity was totally lost and the isolated yield of sulfides did not improve (entry 4).

We initially tested the ability of *p*-TsOH, a common and economical Brønsted acid, and it showed a significant catalytic effect. Complete consumption of the starting material was observed in 1 h, but the yield of the desired sulfides was prohibitively low (entry 5). Interestingly, an epimeric mixture of tosylates **6** was formed in a significant, 15% isolated, yield. Consequently, we decided to use Lewis acids as ring-opening promoters. Although the use of cerium chloride as a catalyst in various organic transformations is well documented,[27] when applied to this system, 90% of the starting material was recovered unchanged (entry 6). Thus, we decided to use it in combination with potassium iodide as a cocatalyst to reinforce the activity of $CeCl_3$.[28] Although the reaction was complete in only 20 min at room temperature, it rendered the desired product in only 10% isolated yield, with very low stereoselectivity (entries 6 and 7). Our best results were obtained using $Yb(OTf)_3$ (entry 11). The epimeric sulfides were obtained in 89% combined yield and in a good (7.5:1) *antilsyn* ratio.

We studied the effect of the reaction temperature in this system and found that it had a large influence on the reactivity and selectivity of the reaction (Table 1, entries 8–11). When the reaction of **3** with thiophenol was carried out at room temperature, it went to completion in an hour and hydroxysulfide **4** was afforded in 78% yield. However, the same reaction run at −5, 0, and 4 °C produced only small amounts of the desired product. The good catalytic effect of the Yb(III) triflate in the present thiolysis can be attributed to the strong oxophilicity of the lanthanide(III) in this compound, which allows the metal to tightly coordinate to the oxirane oxygen, favoring the nucleophilic ring-opening process.

Once the nature of the catalyst was defined, we attempted to uncover the best reaction solvent and to minimize the amount of catalyst used in the reaction. We concluded that the use of less than 30% molar of the catalyst slowed down the reaction rate, as well as reducing the obtained yield as described in Table 2 (entries 1–5). The solvent effect is not remarkable but, as expected, the use of an oxygenated solvent is detrimental to the reaction results (entry 5–7).

Literature precedent,[29] as well as our previous experience in the regiospecific opening of vinyl epoxides of type **3**, indicated that the regiochemistry is controlled by stereoelectronic effects, through a 1,2-addition process (S_N2 process) to give the *anti*-1,2-adducts, as

Table 1. Thiolysis of epoxide **3** under various catalytic conditions[a]

Entry	Catalyst[b]	Reaction time	*T* (°C)	*antilsyn* (**4**/**5**) ratio	Isolated yield (%)
1	No catalyst	8 h	0	1.0	Traces
2	No catalyst	48 h	rt	1.0	Traces
3	No catalyst	2 weeks	rt	1.2	30
4	No catalyst	1 h	60	1.1	30
5	*p*-TsOH	1 h	rt	1.0	15
6	$CeCl_3{\cdot}7H_2O$	8 h	rt		Traces
7	$CeCl_3{\cdot}7H_2O$/KI	20 min	rt	1.7	10
8	$Yb(OTf)_3$	3 weeks	−5	7.0	Traces
9	$Yb(OTf)_3$	8 h	0	7.0	Traces
10	$Yb(OTf)_3$	24 h	4	7.5	30
11	$Yb(OTf)_3$	1 h	rt	7.5	89

[a] All reactions were carried out in toluene as solvent.
[b] 30% mol unless otherwise stated.

Table 2. Effect of the amount of catalyst and nature of the solvent in the reaction result[a]

Entry	Catalyst (mol %)	Solvent	Reaction time (h)	*anti*/*syn* (**4**/**5**) ratio	Isolated yield (%)
1	5	Toluene	48		Traces
2	10	Toluene	24		Traces
3	15	Toluene	24	7.0:1	50
4	20	Toluene	24	7.5:1	50
5	30	Toluene	1	7.5:1	89
6	30	CH_2Cl_2	2	7.0:1	80
7	30	THF	8	5.0:1	50

[a] All reactions were carried out at rt.

we observed experimentally. In the conditions used, the *syn*-hydroxysulfide was always formed in addition to the expected *anti*-isomer, resulting from the trans-diaxial attack of the nucleophile.[30,31] The formation of **5**, under Lewis acid catalysis could be rationalized considering that the catalyst is able to polarize the oxirane C–O bond until its complete rupture determining the generation of a stable allylic carbocation species. The formation of the *syn*-adduct was minimized when the acidic catalyst present in the reaction medium was $Yb(OTf)_3$ (Table 1).

In order to convert sulfide **4** into a deoxyconduritol analogue, it was subjected to reductive dehalogenation conditions affording **7**, which was treated with a cation-exchange resin in order to remove the acetonide group. Subsequent resin filtration, concentration, and purification by flash chromatography rendered optically active (+)-**8** as a white solid in 44% overall yield from metabolite **1** (Schemes 1 and 2).

The structures of all new compounds were unequivocally established by ^1H NMR and ^{13}C NMR spectroscopy, and fully characterized. In the cases of compounds **4** and **5** NOE experiments were performed in order to assign the correct stereochemistry.

3. Conclusion

In conclusion, an effective chemoenzymatic route to enantiomerically pure phenylthioconduritol F has been developed using only a sub-stoichiometric amount of $Yb(OTf)_3$ to catalyze the thiolysis of vinylepoxide **3**. The strategy is of wide scope and can be expanded to the preparation of other thioconduritol analogues. The use of compound **7** as a building block in the synthesis of cyclitol conjugates with sugars and terpenes, as well as the inhibition properties of **8** toward glycosidases are the focus of our current research.

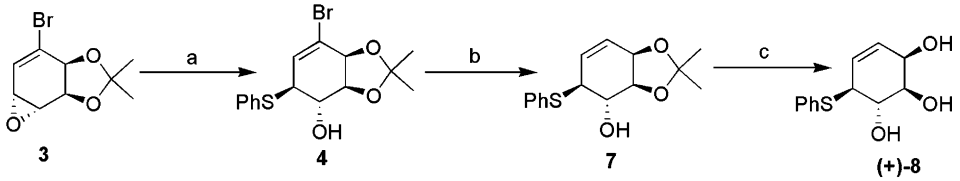
4. Experimental

4.1. General method

All non-hydrolytic reactions were carried out under a nitrogen atmosphere with standard techniques for the exclusion of moisture. All solvents were purified and dried prior to use. The commercially available reagents were purchased from Aldrich and used without further purification. Melting points were determined on a Leitz Microscope Heating Stage, Model 350 apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker Avance DPX-400 instrument with chloroform-D as a solvent. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured using a Zuzi 412 automatic polarimeter with a 7 mL cell (concentration *c* given as g/100 mL). Infrared spectra were recorded in KBr and measured in cm^{-1}, using a Matheson Excalibur spectrometer. Low-resolution mass spectra were recorded on a Shimadzu GS-MS QP 1100 EX instrument using the electron impact mode. High-resolution mass spectra were recorded in a Q-TOF mass spectrometer (Micromass, Manchester, UK). Elemental analyses were performed in a Fisons EA 1108 CHNS-O analyzer. Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or anisaldehyde–H_2SO_4–AcOH as detecting agent. Flash column chromatography was performed in silica gel (Kieselgel 60, EM Reagents, 230–400 mesh).

4.2. General procedure for the thiolysis of epoxide 3

A solution of vinyl epoxide **3** (119.5 mg, 0.48 mmol) in anhydrous toluene (3.0 mL) was treated with PhSH (0.1 mL, 0.97 mmol) and $Yb(OTf)_3$ (0.14 mmol, 30 mol %). The reaction mixture was stirred for 1 h at room temperature until consumption of the starting material monitored by TLC. The mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, and



Scheme 2. Optimized route for the preparation of phenylthioconduritol F. Reagents and conditions: (a) PhSH, $Yb(OTf)_3$, toluene, rt, 1 h, 78%; (b) Bu_3SnH, AIBN, THF, reflux, 4 h, 75%; (c) Dowex 50-H^+, MeOH–H_2O, rt, 1 h, 90%.

aq NaCl. The organic layer was dried over anhyd $MgSO_4$ and removed under reduced pressure to afford a crude oily product consisting of a mixture of phenylthioderivatives **4** and **5**, which was purified by flash column chromatography (80:20 hexane/ethyl acetate) furnishing pure **4** (137.7 mg, 78% yield) and **5** (18.8 mg, 11% yield).

4.3. (1*S*,2*R*,3*S*,6*S*)-6-(Phenylthio)-2,3-isopropylidendioxy-4-bromocyclohexene-1-ol 4

Colorless oil; $[\alpha]_D^{20} = +73.6$ (*c* 3.2, $CHCl_3$); IR (neat) 3500–3400 b, 1219.2, 1074.5, 868.1, 748.5, 692.5; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.43 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.80 (br s, 1H, OH), 3.56 (d, 1H, *J* 8.4 Hz, H-6), 3.66 (t, 1H, *J* 8.4 Hz, *J* 8.4 Hz, H-1), 4.21 (t, 1H, J_{21} 8.1 Hz, *J* 6.1 Hz, H-2), 4.66 (d, 1H, *J* 6.2 Hz, H-3), 6.30 (d, 1H, *J* 2.4 Hz, H-5), 7.35 (m, 3H, Ph), 7.49 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.3, 28.6, 52.2, 71.2, 77.7, 78.9, 111.1, 119.6, 128.7 (di), 129.7 (di), 132.6, 133.5 (di); EIMS (relative intensity): 218 ($M^+-Br-C_3H_6O$, 44), 110 (PhS, 100), 77 (Ph, 14), 65 (70); Anal. Found C, 50.68; H, 4.88; $C_{15}H_{17}BrO_3S$ requires C, 50.43; H, 4.80.

4.4. (1*S*,2*R*,3*S*,6*R*)-6-(Phenylthio)-2,3-isopropylidendioxy-4-bromocyclohexene-1-ol 5

White solid; mp: 118–120 °C; $[\alpha]_D^{20} = -103.3$ (*c* 0.7, $CHCl_3$); IR (neat) 3500–3400 b, 1221.1, 1076.4, 870.0, 750.4, 692.5; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.41 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 4.03 (m, 1H, H-6), 4.12 (t, 1H, *J* 5.4 Hz, *J* 9.5 Hz, H-1), 4.39 (t, 1H, *J* 11.1 Hz, *J* 5.6 Hz, H-2), 4.58 (d, 1H, *J* 5.5 Hz, H-3), 6.16 (d, 1H, *J* 3.5 Hz, H-5), 7.36 (m, 3H, Ph), 7.51 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.5, 28.1, 51.4, 68.0, 76.5 (di), 110.5, 123.9, 128.7, 128.9, 129.1, 129.4, 129.8, 132.6, 133.3; EIMS (relative intensity): 218 ($M^+-Br-C_3H_6O$, 44), 110 (PhS, 100), 77 (Ph, 20), 65 (75); Anal. Found C, 50.97; H, 5.03; $C_{15}H_{17}BrO_3S$ requires C, 50.43; H, 4.80.

4.5. (1*S*,2*R*,3*R*,6*S*)-6-(Phenylthio)-2,3-isopropylidendioxy-cyclohex-4-ene-1-ol 7

Tri-*n*-butyltin hydride (148.4 mg, 0.51 mmol) was added to a mixture of azoisobutyronitrile (19.4 mg, 0.17 mmol) and compound **4** (120.5 mg, 0.34 mmol) in dry tetrahydrofuran (15 mL). The reaction mixture was refluxed for 4 h. Concentration at reduced pressure and purification of the oily residue by flash chromatography (70:30 hexane/ethyl acetate) furnished the pure product **7** as a colorless oil (70.9 mg, 75%). $[\alpha]_D^{24} = +43.4$ (*c* 0.90, CH_2Cl_2); IR (neat) 3500–3400 b, 1217.2, 1062.9, 900.9, 746.5, 692.5; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.90 (br s, 1H, OH), 3.56 (d, 2H, J_{23} 3.2 Hz, H-2 and H-3), 4.14 (m, 1H, H-1), 4.60 (m, 1H, H-6), 5.88 (dd, 1H, *J* 9.7 Hz, *J* 3.6 Hz, H-5), 5.98 (d, 1H, *J* 9.9 Hz, H-4), 7.30 (m, 3H, Ph), 7.49 (d, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.5, 28.6, 51.1, 72.1, 72.6, 78.9, 110.5, 124.9, 128.3, 129.5 (di), 130.0, 132.9, 133.1, 133.4; EIMS (relative intensity): 278 (M^+, 30), 110 (PhS, 100), 83 (91), 77 (Ph, 19), 65 (75), 59 (61), 55 (76); HRMS: calcd for $C_{15}H_{18}O_3S$ (M^++Na^+): 301.0863; found: 301.0744. Δm (%): 0.004.

4.6. (1*S*,2*R*,3*R*,6*S*)-6-(Phenylthio)-cyclohex-4-ene-1,2,3-triol 8

A mixture of compound **7** (60.4 mg, 0.22 mmol), Dowex-50 (H^+ form) resin (650 mg) and MeOH–H_2O (3.0–0.1 mL) was stirred at room temperature for 1 h. After completion of the reaction, the resin was filtered off and the solvent was removed under reduced pressure. Purification by flash chromatography (20:80 hexane/ethyl acetate) rendered optically active (+)-**8** as a white solid (47.2 mg, 90%). Mp: 108–111 °C; $[\alpha]_D^{22} = +127.2$ (*c* 0.64, MeOH); IR (neat) 3476–3279 b, 1124.6, 1066.8, 877.7, 738.8, 688.7; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.44 (br s, 3H, OH), 3.58 (d, 1H, *J* 8.6 Hz, H-6), 3.68 (m, 1H, H-2), 3.79 (t, 1H, *J* 9.4 Hz, *J* 9.2 Hz, H-1), 4.28 (br d, 1H, *J* 4.3 Hz, H-3), 5.87 (m, 1H, *J* 11.9 Hz, *J* 7.8 Hz, H-5), 5.92 (d, 1H, *J* 11.7 Hz, H-4), 7.32–7.35 (m, 3H, Ph), 7.51 (d, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 53.0, 66.4, 70.4, 73.4, 127.3, 128.4 (di), 129.5 (di), 132.5, 132.9, 133.6; EIMS (relative intensity): 238 (M^+, 16), 110 (PhS, 100), 77 (Ph, 11), 65 (46), 55 (40); Anal. Found C, 60.43; H, 5.81; $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92.

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