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Seven-Membered Cyclic Sulfite Eudesmane Derivatives: Partial Synthesis, Structural Determination, and Enzymatic Resolution

Andrés García-Granados, Andrés Parra,* Francisco Rivas, and Alejandro J. Segovia

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, E-18071 Granada, Spain

aparra@ugr.es

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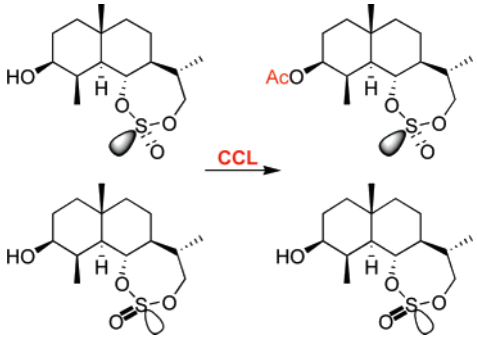

Two chromatographically inseparable, diastereomeric eudesmane cyclic sulfites have been semisynthesized from α-santonin. This diastereomeric mixture was resolved by enzymatic acetylation with CCL. Each cyclic sulfite derivative was individually characterized on the basis of its spectroscopic and crystallographic properties.

Sesquiterpenoid lactones with a eudesmane skeleton are found in several plant species. The most abundant of them, α-santonin, has often been used as a starting material to synthesize diverse naturally occurring terpenoid compounds.[1,2]

Cyclic sulfites are well-known compounds and have often been the object of investigation as a result of not only a theoretical interest in their chemical reactivity and structural features but also their potential practical applications. Apart from this, cyclic sulfites express pesticidal[3] and antibiotic[4] activities and have been used as endocrine[5] agents. Moreover, cyclic sulfites are recognized as being activated diols that can be oxidized to cyclic sulfates and, as a consequence of their possible regioselective ring opening,[6] employed for a variety of nucleophilic displacement reactions. This type of compound has been used to obtain episulfides, olefins, thio sugars,[7] and bicyclonucleoside analogues.[8] The regioselectivity of their nucleophilic ring-opening reactions has been studied both theoretically and experimentally.[9]

The synthetic importance of employing isolated enzymes or microorganisms in organic chemistry lies in the regio- and stereoslective performance of either technique. Of all known enzymes, lipases have attracted the most scientific interest. In addition to their natural function of hydrolyzing carboxylic ester bonds, lipases can catalyze various reactions such esterification, transesterification, and aminolysis in organic solvents. Consequently, lipases are currently studied because of their potential industrial applications in the detergent, food, and flavor industry; biocatalytic resolution of racemates; making of fine chemicals and agrochemicals; use as biosensors; bioremediation; and cosmetics and perfumery.[10] In the synthesis of enantiomerically pure organic compounds, lipases have been widely used in three main types of reactions. These are kinetic resolutions of racemates, enantioselective group differentiations of *meso* compounds, and enantiotopic group differentiation of prochiral substrates.[11] Lipase-catalyzed reactions are highly enantioselective and versatile methods that have allowed the resolution of racemic alcohols, acids, esters, or amines.[12] Thus, lipases have been used to resolve chiral diols via their cyclic sulfite derivatives.[13] Also, a cyclohexanone monooxygenase (CHMO) has been utilized to resolve cyclic sulfites by the enantioselective oxidation to cyclic sulfates.[14] Several studies into six-membered cyclic sulfite eudesmane diastereomers have recently been undertaken.[15] These compounds have been used as substrates in several biotransformation processes with the fungus *Rhizopus nigricans*. The sulfur configuration of these cyclic sulfites was assigned by means of experimental and theoretical NMR

* To whom correspondence should be addressed. Tel: +34-958-240480. Fax: +34-958-248437.

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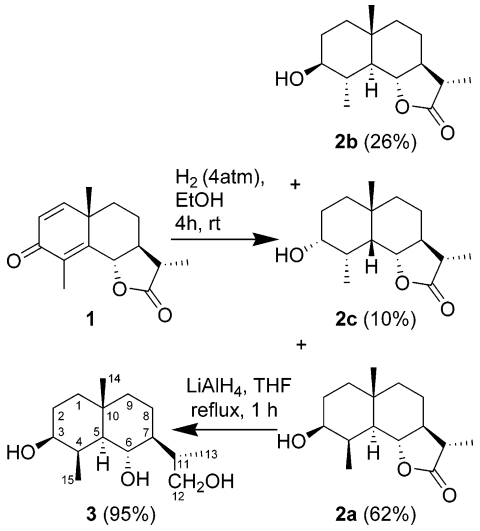
SCHEME 1. Semisynthesis of Triol 3 from α-Santonin



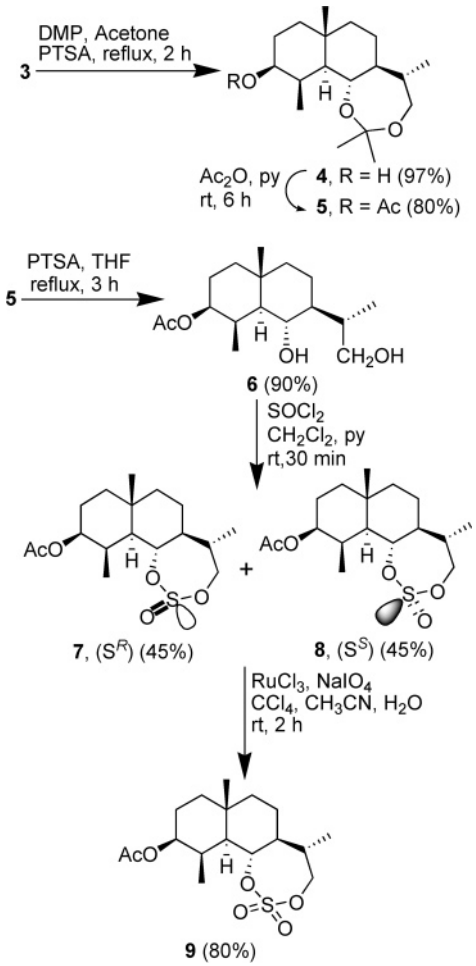
chemical shifts or by X-ray data. The semisynthesis and structural determination of five-membered cyclic sulfite oleanene derivatives have also been undertaken.[16]

We report here on the semisynthesis of two new seven-membered eudesman-6,12-diyl-*S*-cyclic sulfite diastereomers obtained from α-santonin. The absolute configurations of the sulfur atom and the conformational arrangement of these molecules were confirmed by X-ray crystallography. We also checked some acetylation or deacetylation processes with several immobilized lipases with both cyclic sulfites. This allowed the resolution of both diastereomers by means of *Candida cylindracea* lipase (CCL), due to the complete selective acetylation at C-3 of the *S*-cyclic sulfite.

Catalytic hydrogenation of α-santonin (**1**) gave a mixture of hexahydro derivatives **2a** (62%), **2b** (26%), and **2c** (10%) (Scheme 1). The main product of this hydrogenation (**2a**) was isolated by selective acetylation with *Candida antarctica* lipase (CAL) and then treated with $LiAlH_4$, yielding triol **3** (Scheme 1).[2] To protect the hydroxyl group at C-3, compound **3** was first treated with 2,2-dimethoxypropane (DMP) in acetone to give the acetonide derivative (**4**) between the hydroxyl groups at C-6 and C-12 (Scheme 2). Acetonide **4** was then acetylated at C-3, and this acetyl derivative (**5**) was treated with PTSA to deprotect these hydroxyl groups, opening the acetonide ring and affording compound **6**. The reaction of **6** with thionyl chloride in pyridine for 30 min at room temperature yielded a diastereomeric pair of cyclic sulfites (**7** and **8**, both at 45%) between these hydroxyl groups (Scheme 2). The relative ratio of compounds **7** and **8** from this mixture was established by an analysis of their ^1H and ^{13}C NMR spectra, which revealed that they were present in approximately the same quantity. These compounds showed different spectral and physical properties but an identical molecular formula ($C_{17}H_{28}O_5S$) and could not be distinguished by thin-layer chromatography or isolated by flash column chromatography. Oxidation of this mixture of **7** and **8** with $RuCl_3/NaIO_4$ in $CCl_4/CH_3CN/H_2O$ at room temperature for 2 h (Scheme 2) afforded the single cyclic sulfate derivative **9**.

Several assays were made to isolate and identify compounds **7** and **8**. First this mixture was treated with KOH/MeOH for

SCHEME 2. Partial Synthesis of Cyclic Sulfites 7 and 8 and Cyclic Sulfate 9



7.5 h, affording a mixture of 3-deacetylated derivatives (**10** and **11**, both at 35%) together with **6** (20%) and triol **3** (5%) (Scheme 3). In the light of the fact that this new mixture of deacetylated cyclic sulfites (**10** and **11**) was also chromatographically inseparable and furthermore that the sulfite ring was partially affected, we tested the deacetylation reaction by enzymatic methods using nine lipases. Only the lipases that produced deacetylated compounds are included in Table 1, but none of these produced any high yield via a selective reaction.

The third assay to resolve cyclic sulfites **7** and **8** started from the mixture of the 3-deacetylated derivatives **10** and **11** and was carried out by enzymatic acetylation. The same nine lipases were tested. Vinyl acetate (VA) was employed as solvent and acetylating agent, and the enzyme/substrate ratio was fixed at 6:1. In this case there were two lipases that selectively acetylated one of the cyclic sulfites from the mixture at a satisfactory yield (Scheme 3 and Table 2). Thus, treatment of the mixture of **10** and **11** with CCL for 5 h produced the complete acetylation of compound **11** to give the 3-acetyl derivative **8**, which was then isolated chromatographically. In this way the cyclic sulfites **7** and **8** and their corresponding 3-deacetylated derivatives **10** and **11** could be isolated and identified by their physical, spectroscopic, and crystallographic properties.

The main differences between the ^1H NMR spectra of **7** and **8** were the chemical shifts of the signals of H-6β (δ 4.88 for **7**, δ 4.08 for **8**) and 2H-12 (δ 3.80 and 3.86 for **7**, δ 3.59 and 4.73 for **8**). Similar differences were observed between the ^1H

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SCHEME 3. Enzymatic Resolution of Cyclic Sulfites 10 and 11

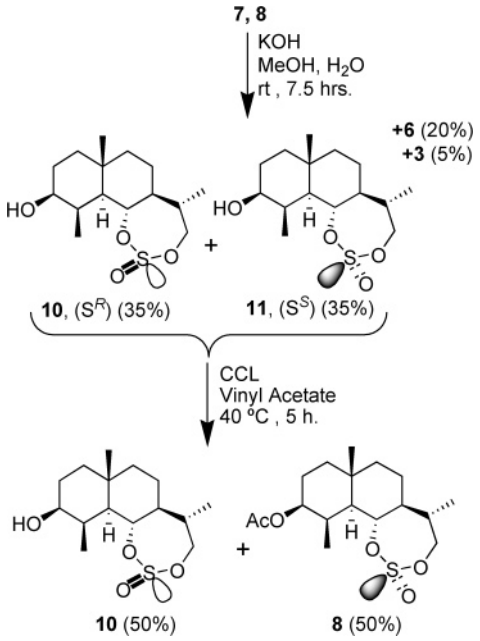

TABLE 1. Enzymatic Deacylations of Mixture of 7 and 8

		% deacylation[a]			
lipase	time (days)	**7**	**8**	**10**	**11**
CAL	8	40	40	10	10
CCL	8	40	45	10	5
MML	8	40	45	10	5
CRL	12	45	35	5	15
PFL	12	20	15	30	35

[a] Determined by ^{1}H and ^{13}C NMR.

TABLE 2. Enzymatic Acylations of Mixture of 10 and 11

		% acylation[a]		
lipase	time (h)	**8**	**10**	**11**
CCL	5	50	50	0
CRL	48	20	50	30

[a] Determined by ^{1}H and ^{13}C NMR.

NMR spectra of **10** and **11**. Moreover, the ^{13}C NMR spectra of both pair of compounds differed fundamentally in the chemical shifts of C-12 (δ 69.2 for **7** and **10**, δ 65.5 for **8** and **11**).

Because the *trans*-decalin skeleton of eudesmane compounds is highly rigid, only the seven-membered sulfite ring could adopt different conformations. Nevertheless, the X-ray crystallographic data of **7** and **8** (Figures 1 and 2) showed that both compounds presented an almost "twisted-boat" conformation for this ring.

We determined the sulfur configuration in each diastereomer (**7** and **8**) and therefore in their corresponding deacetylated derivatives (**10** and **11**) by their experimental ^{1}H and ^{13}C NMR and X-ray data.

The ^{1}H NMR data of **7** revealed that the signal of H-6β was deshielded (δ 4.88), which can be put down to an almost 1,3-diaxial interaction between this hydrogen atom and the S → O bond (Figure 1) at the β-face (*R* sulfur atom configuration), whereas the signals of 2H-12 were lesser affected (δ 3.80 and 3.86) due to the greater distance between these hydrogen atoms and the S → O bond. This arrangement of the S → O bond was

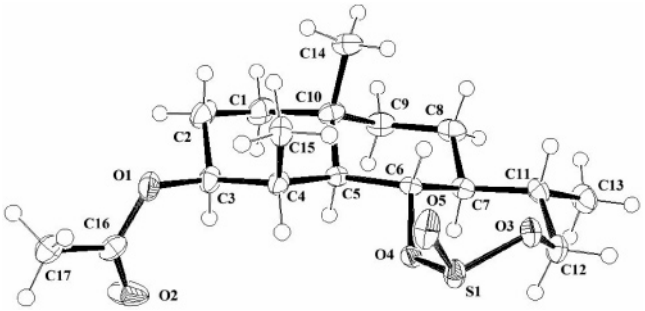

FIGURE 1. ORTEP drawing of **7**.

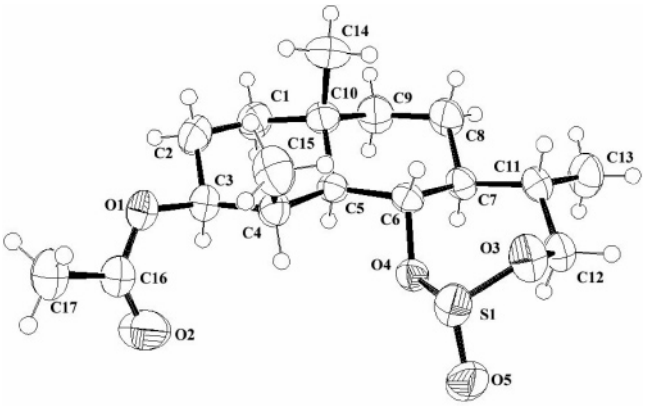

FIGURE 2. ORTEP drawing of **8**.

confirmed by the deshielded ^{13}C NMR chemical shift of C-12 (δ 69.2) caused by a γ-*anti* effect between this carbon atom and the S → O bond. The ^{1}H and ^{13}C NMR data were similar for the deacetylated derivative **10**.

The ^{1}H NMR data of **8** indicated that the S → O bond was situated at the α-face of the molecule (*S* sulfur atom configuration) (Figure 2) and spatially close to a proton at C-12 (δ 4.73). This was confirmed the ^{13}C NMR chemical shift of C-12 (δ 65.5) caused by a γ-*gauche* arrangement between this carbon atom and the S → O bond.

In conclusion, we have resolved a mixture of diastereomeric eudesmane cyclic sulfites by enzymatic acetylation with CCL and determined the configurational and conformational arrangement of these cyclic sulfite derivatives by their spectroscopic and crystallographic properties.

Experimental Section

Formation of Cyclic Sulfites 7 and 8. To a solution of **6** (295 mg, 0.99 mmol) in 5 mL of CH_2Cl_2 and 5 mL of pyridine was added 0.3 mL of tionyl chloride at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2, washed with HCl, and neutralized with $NaHCO_3$. The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The mixture of sulfites was purified by column chromatography yielding 314 mg (0.91 mmol, 92%) of a mixture of **7** and **8** in a 1:1 rate.

Data for 7: white solid; mp = 83 °C; $[\alpha]^{25}_D = -170$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, δ) 4.88 (1H, dd, $J_1 = 9.1$ Hz, $J_2 = 11.1$ Hz), 4.75 (1H, ddd, $J_1 = J_2 = 4.8$ Hz, $J_3 = 12.2$ Hz), 3.86 (1H, dd, $J_1 = 10.4$ Hz, $J_2 = 12.4$ Hz), 3.80 (1H, dd, $J_1 = 3.7$ Hz, $J_2 = 12.4$ Hz), 2.41 (1H, m), 2.02 (3H, s), 0.96 (3H, d, $J = 7.4$ Hz), 0.93 (3H, s), 0.90 (3H, d, $J = 6.9$ Hz); ^{13}C RMN ($CDCl_3$, 300 MHz, δ) 170.6 (s), 76.1 (d), 73.4 (d), 69.2 (t), 50.0

(d), 48.9 (d), 42.9 (t), 40.6 (d), 39.8 (t), 34.9 (s), 30.6 (d), 26.1 (t), 22.5 (t), 21.4 (q), 20.7 (q), 15.6 (q), 8.3 (q); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}) 2935, 1732, 1460, 1386, 1246, 1211, 989; HRMS calcd for $C_{17}H_{28}O_5SNa$ 367.1555, found 367.1553.

Data for 8: white solid; mp = 145 °C; $[\alpha]^{25}_D = -73$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, δ) 4.76 (1H, ddd, $J_1 = J_2 =$ 5.1 Hz, $J_3 = 11.0$ Hz), 4.73 (1H, dd, $J_1 = 11.7$ Hz, $J_2 = 12.1$ Hz), 4.08 (1H, dd, $J_1 = 9.5$ Hz, $J_2 = 11.2$ Hz), 3.59 (1H, dd, $J_1 = 3.4$ Hz, $J_2 = 12.1$ Hz), 2.56 (1H, m), 2.03 (3H, s), 0.92 (3H, d, $J =$ 6.6 Hz), 0.91 (3H, s), 0.88 (3H, d, $J = 7.4$ Hz); ^{13}C RMN ($CDCl_3$, 300 MHz, δ) 170.3 (s), 75.7 (d), 73.4 (d), 65.5 (t), 50.3 (d), 49.5 (d), 42.4 (t), 38.6 (d), 39.5 (t), 34.5 (s), 30.4 (d), 26.3 (t), 22.4 (t), 21.4 (q), 20.5 (q), 15.2 (q), 8.7 (q); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}) 2923, 1734, 1459, 1368, 1246, 1208, 966; HRMS calcd for $C_{17}H_{28}O_5SNa$ 367.1555, found 367.1560.

Enzymatic Acetylation of Compounds 10 and 11 with CCL. CCL (100 mg) was added to a solution of compounds **10** and **11** (20 mg) in vinyl acetate (2 mL). The suspension was shaken on an orbital shaker (180 rpm) at 40 °C for 5 h. The reaction was finished by filtration of the enzyme, and the products were isolated by flash chromatography. Compound **8** (10 mg, 50%) was formed, and compound **10** (10 mg, 50%) was recovered unaltered.

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Supporting Information Available: Experimental procedures and spectral and crystallographic data in CIF format for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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