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Serendipitous synthesis of 3-hydroxy tetrahydrofurans from tin catalyzed sulfonylation of acyclic 1,2,4-triols

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ABSTRACT

The reaction of *syn*-1,2,4-triols under sulfonylation conditions catalyzed by Bu_2SnO (5 mol %) results in cyclization and the formation of 3-hydroxy tetrahydrofurans (56–85%) while the *anti*-1,2,4-triols react to give C1-*O*-sulfonyl derivatives in good yields (66–83%) and the cyclization product in poor yield (5–12%). A mechanism that justifies these observations is proposed to occur via the tosylation of the primary hydroxyl followed by an intramolecular tin acetal rearrangement to a 1,3-stannylene which then undergoes a 5-*exo*-*tet*-cyclization. The difference in rates of cyclization reactivity is due to the energetically more stable tin acetals of *syn*-1,3-diols compared to those of *anti*-1,3-diols.

As part of an ongoing investigation on the characterization of the unsaponifiable fraction of avocado oil, we are interested in the methods of analysis and isolation of some polyhydroxylated compounds (acetogenins) that constitute 5–40% of the oil, depending on the maturity of the fruit.[1–7] These compounds have a common structural motif, where one terminus is highly oxygenated either as a 1,2,4-triol or a 4-oxo-1,2-diol, which may have mono acetyl protection at the C1 or C2-hydroxyl group (Fig. 1).

We hypothesized that the tin-catalyzed regioselective sulfonylation of diols could be useful in a discriminatory derivatization of the 1,2,4-triol and 1,2-diol compounds within the complex matrix of avocado oil.[8–11] A test of the Martinelli protocol on model 1,2-diol substrates showed that the reaction was complete within 3.5 h, but in our hands we found it necessary to heat the reaction to a gentle reflux in dichloromethane instead of carrying out the reaction at room temperature where it was sluggish.[10] Additionally, we found it expedient to increase the catalytic tin oxide load from 2 to 5 mol %. The avocado 1,2,4-triols **11a** and **12a**, and the other triol analogues, were prepared from commercially available (*S*)-malic acid according to the method reported by Sato and co-workers as shown in Scheme 1. [†12]

The diastereomeric products of the Grignard reactions (**9a–c** and **10a–c**) were easily separated by column chromatography, while the 2,4-diol relative stereochemistry of the triols **11a–c** and **12a–c** was confirmed by acetal protection as the 2,4-dioxolanes as described by Rychnovsky.[13,14]

When the triols **11a** and **12a** were subjected to the sulfonylation conditions for the C1-*O*-tosylation, the results were quite unexpected (Scheme 2).[‡] While the *anti*-1,2,4-triol (**12a**) was efficiently converted to the C1-*O*-sulfonyl derivative **14a** (75%), a minor impurity **14b** was also formed in the reaction (12%); this compound

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† Physical data for avocado triols **11a** (mp 66–67 °C; Lit mp 66.5–67 °C) and **12a** (mp 82–83 °C; Lit mp 82-82.5 °C).

‡ *General method of sulfonylation:* Into a 50 mL two-neck round-bottom flask equipped with a condenser was added compound **11a** (0.05 g, 0.175 mmol), *p*-TsCl (0.04 g, 0.192 mmol), Bu_2SnO (2 mg, 0.0087 mmol) and Et_3N (0.05 mL, 0.192 mmol) and the mixture heated at reflux in CH_2Cl_2 (2 mL, 0.1 M) for 3.5 h. The reaction was monitored by TLC and quenched with saturated NH_4Cl (5 mL) and taken up in EtOAc (50 mL). The organic layer was washed with water (15 mL) and brine (15 mL) before drying over $MgSO_4$. The solvent was evaporated and the crude was purified by column chromatography using 5% EtOH/$CHCl_3$ to give a non UV-active compound **13b** (0.04 g, 85%). υ_{max} (Nujol): 3407, 3076, 2929, 2853, 1640, 1464, 1377, 1226, 1176, 1070, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.75 (1H, ddt, *J* = 6.8, 10, 17 Hz), 4.92 (1H, dd, *J* = 3.2, 17 Hz), 4.86 (1H, dd, *J* = 2, 10 Hz), 4.39–4.35 (1H, m), 3.78–3.68 (1H, m), 3.60 (1H, dd, *J* = 4; 9.6 Hz), 2.31–2.24 (1H, m), 1.97 (2H, q, *J* = 6.8 Hz), 1.86 (1H, bs), 1.69–1.24 (22H, m); δ_C (100 MHz, $CDCl_3$): 139.24, 114.05, 79.25, 75.35, 72.59, 41.47, 36.19, 33.78, 29.60, 29.55, 29.47, 29.12, 28.91, 26.27.The reaction of the *anti*-1,2,4-triol **12a** (0.104 g, 0.363 mmol) was carried out under exactly the same conditions, but two products were isolated after column chromatography: a UV active compound **14a** (0.12 g, 75%) and a non-UV active **14b** (0.02 g, 12%).Compound **14a**: υ_{max} (Nujol): 3359, 2917, 2855, 1602, 1464, 1376, 1338, 1187, 1168, 1096, 975, 907, 835, 813, 721, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.73 (2H, d, *J* = 8 Hz), 7.25 (2H, d, *J* = 8 Hz), 5.74 (1H, ddt, *J* = 6.8, 10, 17 Hz), 4.92 (1H, dd, *J* = 2, 17 Hz), 4.86 (1H, dd, *J* = 2, 10 Hz), 4.11–4.07 (1H, m), 3.98 (1H, dd, *J* = 4.4, 10 Hz), 3.89 (1H, dd, *J* = 7.2, 10.4 Hz), 3.81−3.78 (1H, m), 2.39 (3H, s), 2.21 (2H, bs), 1.96 (2H, q, *J* = 7.2 Hz), 1.60–1.19 (22H, m); δ_C (100 MHz, $CDCl_3$): 145.06, 139.25, 132.62, 129.91, 128.94, 127.98, 127.93, 114.05, 73.59, 68.91, 67.01, 38.37, 37.55, 33.78, 29.58, 29.56, 29.53, 29.47, 29.33, 29.12, 28.91, 25.57, 21.66.Compound **14b**: υ_{max} (Nujol): 3400, 2923, 2858, 1641, 1462, 1376, 1260, 1097, 910 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 5.78 (1H, ddt, *J* = 6.8, 10, 17 Hz), 5.01–4.88 (2H, m), 4.42 (1H, bs), 3.84–3.74 (2H, m), 3.64 (1H, dd, *J* = 4.5, 10 Hz), 2.37–2.28 (1H, m), 2.05–1.98 (3H, m), 1.8–1.24 (22H, m); δ_C (75 MHz, $CDCl_3$): 139.25, 114.05, 79.19, 75.36, 72.60, 41.43, 36.23, 33.78, 29.56, 29.11, 28.89, 26.27.

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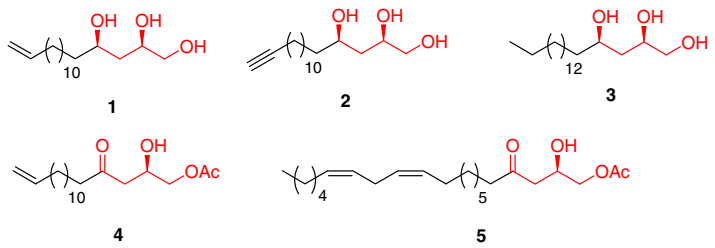
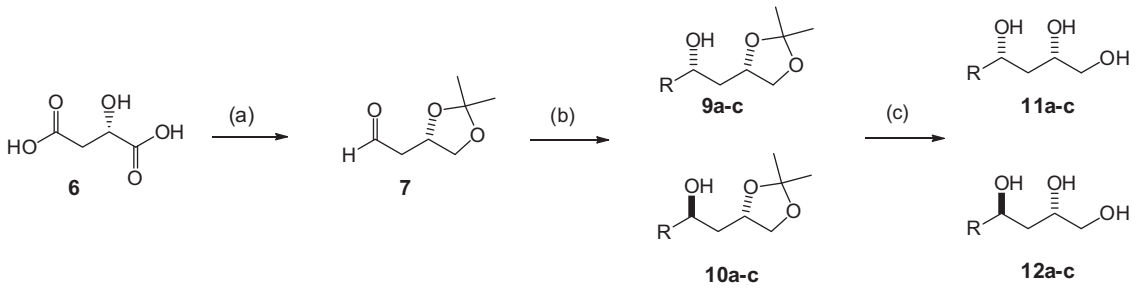
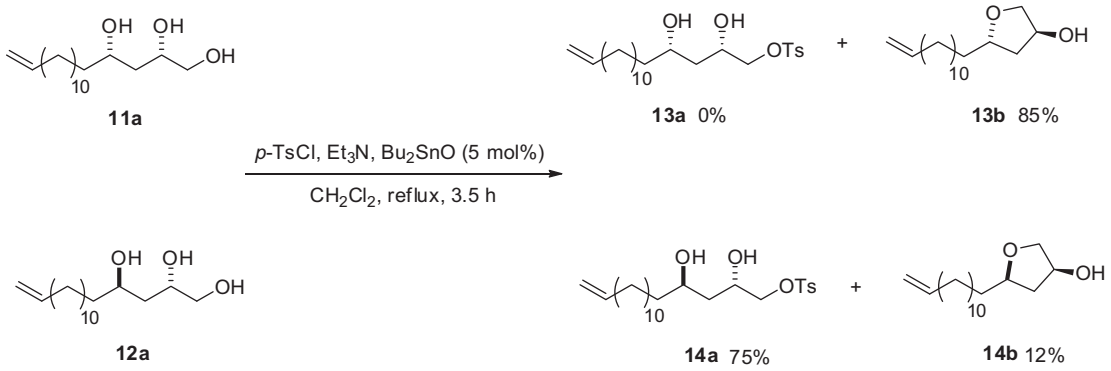


Figure 1. Some highly oxygenated components of avocado oil.



Reagents: (a) 15% overall yield over 5 steps; (b) RMgBr (**8a-c**), Et_2O, rt, 24 h, 67%; (c) 80% AcOH (aq), rt, 24 h, 64-99%

Scheme 1. Synthesis of substrate 1,2,4-triols.



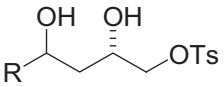
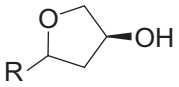
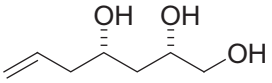
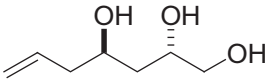
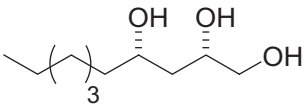
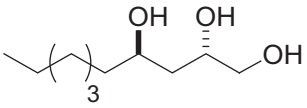
Scheme 2. Sulfonylation of *syn*- and *anti*-1,2,4-triols.

was identified and characterized as 3-hydroxy tetrahydrofuran. The reaction of the *syn*-1,2,4-triol was even more surprising since the reaction exclusively, and efficiently, produced only the 3-hydroxy tetrahydrofuran **13b** (85%). Similar results were observed for other 1,2,4-triols (**11b**, **11c**, **12b**, and **12c**) as shown in Table 1.

While the formation of the tetrahydrofurans from 1,2,4-triols was unexpected under these conditions, what was more intriguing to us was the apparent stereo dependence of the cyclization reaction. Why should one diastereomer favour cyclization, while the other favored tosylation? We thus turned our attention to the mechanistic possibilities that could explain these observations and made the following four postulations: Firstly, the chelation and derivatization of the 1,2-diol is the fastest reaction in both diastereomers since it is generally accepted that the formation of five-membered rings is kinetically more favored than the formation of six-membered rings.[15] Thus C1-*O*-tosylation should be favored over C4-*O*-tosylation. Secondly, the formation of the THF must arise from the internal displacement of the tosylate by the C4-hydroxyl group in a 5-*exo*-*tet* cyclization. Thirdly, the cyclization reaction is still under the mediation of tin chelation to enhance the nucleophilicity of the C4-hydroxyl group since no additional (strong) base was added;[16,17] this type of double activation of polyols by stannylene acetals has precedence in the work of the Simas and Grindley groups.[18,19] Lastly, we postulated that the better stability of formation of the six-membered chelate for the *syn*-1,3-diol is responsible for the faster reaction of the intermediate **(I)** versus intermediate **(II)** which experiences larger 1,3-diaxial steric repulsive interactions (Fig. 2). The reactive transition states are more likely the boat conformations (**Ia**) and (**IIa**).

Indeed the approximately 7:1 ratio of THFs from the *syn* and *anti* triols (**13b**/**14b**; **15b**/**16b**; and **17b**/**18b**) corresponds closely to that predicted by molecular modeling: ab initio (HF/3-212G)

Table 1
Tin catalyzed sulfonylation reaction of 1,2,4-triols

Entry	Substrate				
					
1		**15a**	0%	**15b**	82%
	11b				
2		**16a**	66%	**16b**	12%
	12b				
3		**17a**	0%	**17b**	56%
	11c				
4		**18a**	83%	**18b**	5%
	12c				

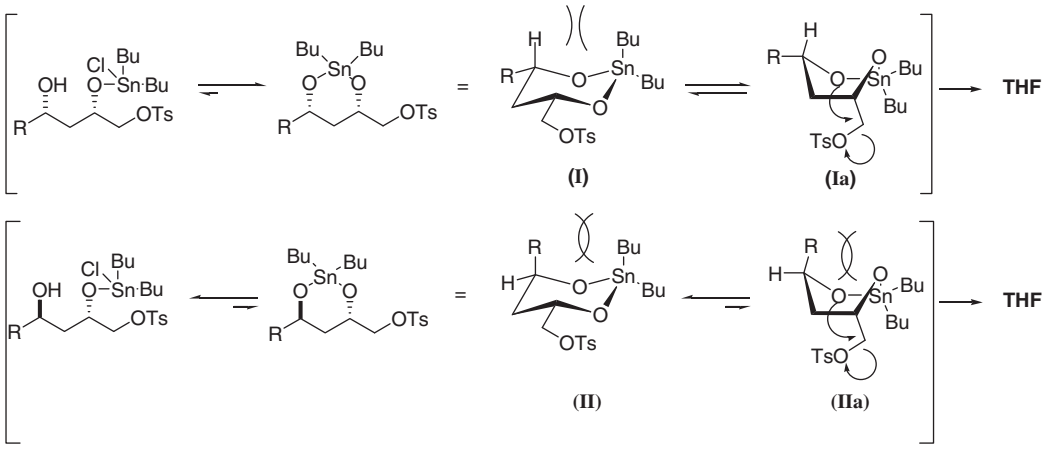


Figure 2. Rationale for the observed stereo differentiation in reactivity.

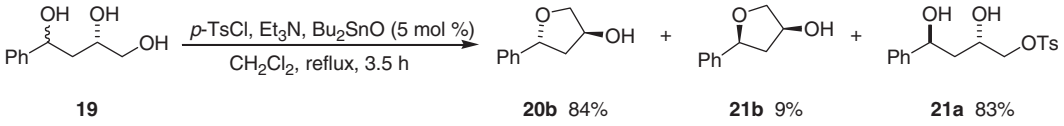
optimization $\Delta\Delta G$ = 1.15 kcal/mol; DFT (B3LYP/LACVP//HF/3-212G) $\Delta\Delta G$ = 1.43 kcal/mol.[§]

We then applied this derivatization method to the mixed diastereomers of phenyl-1,2-4-triols (**19**) to synthesize the known THFs **20b** and **21b**.[20,21] Indeed we observed diastereoselectivity in the reaction whereby after 3.5 h the *syn*-triol was converted to THF compound **20b**, while the *anti*-triol formed the sulfonyl derivative **21a** in excellent yields of 84% and 83%, 'respectively' (Scheme 3); the THF **21b** was formed in only 9% yield.[¶] When the reaction was left to proceed for 24 h, the combined yield of the THFs (**20b** + **21b**) was 70%, but still **21a** persisted at 20%.

In summary, we have observed that the tin-catalyzed regioselective sulfonylation of 1,2-diols leads to the cyclization of *syn*-1,2,4-triols to form 3-hydroxy tetrahydrofurans, while *anti*-1,2,4-triols are efficiently and regioselectively tosylated. While we are continuing our investigation of the scope of this method as a truncated route for the synthesis of functionalized THFs, we are also intrigued by the possibility that the method may be used to distinguish between mixed diastereomers of 1,2,4-triols since the *anti*-triols preferentially give sulfonylation, while the *syn*-triols exclusively give cylization products.[22] The results of these investigations will be reported shortly.

[§] We acknowledge the assistance of Professor Richard Johnson at the University of New Hampshire (USA) for the molecular modeling results.

[¶] The characterization of compounds **20b** and **21b** (Supplementary Data) showed that they were identical to those previously reported.[20,21]



19 **20b** 84% **21b** 9% **21a** 83%

Scheme 3. Diastereoselective derivatization of phenyl-1,2,4-triols.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.110.

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