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Cyclization of Unsaturated Monoterpenic Alcohols Mediated by Thallium (III) Salts

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Abstract: The reaction of thallium triacetate and thallium trinitrate with four monoterpenic unsaturated alcohols (isopulegol, neo-isopulegol, cis-carveol and α-terpineol), in AcOH:H_2O (1:1, vol/vol) as solvent, led to the corresponding β-hydroxy-cyclic ethers with high regio- and stereoselectivity, in moderate to good yields. A mechanism of ring-contraction or ring-expansion of the oxythallated adduct is proposed, based on the substitution patterns of each double bond.

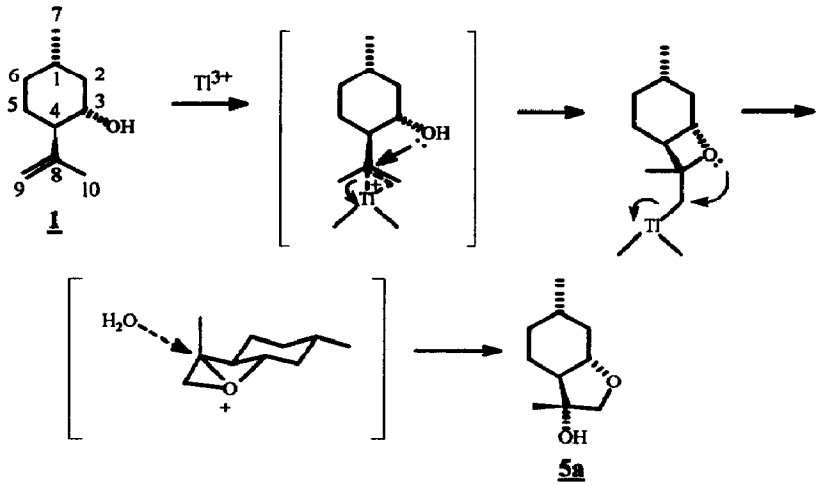
In a previous paper,[1] we reported our preliminary results on cyclization of some diterpenic alcohols, as well as the monoterpenes isopulegol (1) and neo-isopulegol (2), promoted by thallium triacetate. More recently, we have described the results of thallium (III) salt induced lactonizations of a series of unsaturated carboxylic acids.[2]

A paper by Kocovsky et al.[3] prompted us to reinvestigate the thallium (III) salt promoted cyclization of 1 and 2, to verify the influence of experimental conditions on the stereochemical course of the reactions. The cyclization of two other monoterpenic alcohols, namely cis-carveol (3) and α-terpineol (4), was also carried out.

We initially investigated the behaviour of thallium triacetate (TTA) and thallium trinitrate (TTN) in the cyclization of isopulegol (1), using different solvent systems (glacial acetic acid or a 1:1 mixture of AcOH:H_2O). The use of glacial AcOH as solvent furnished the β-acetoxy-ether **5b** together with minor amounts of the corresponding β-hydroxy- derivative **5a**, probably due to the water of hydration present in the commercial thallium salts.[4] On the other hand, the use of a 1:1 mixture of AcOH:H_2O provides exclusive formation of the β-hydroxy-ether **5a**, in very good yields. The latter conditions were then employed in the cyclization of 2, 3 and 4, using both TTA and TTN. Results are summarized in Table 1.

The most probable mechanism for explaining the high stereoselectivity observed in the cyclization of the 3-alkenols **1** and **2** involves the initial formation of the four-membered cyclic oxythallated adduct, which undergoes dethallation with concomitant oxygen migration. Solvolysis of the bridged oxonium ion by a rear-side attack leads to the ring-expanded product, as shown in Scheme I for isopulegol (**1**). The intermediate with a carbocation at C-8, proposed by Kocovsky et al.[3] does not account for the high stereocontrol observed.

Scheme I



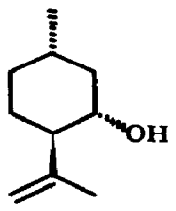
These mechanistic approaches were proposed by Michael et al.[5] in their work on cyclization of several 4-alkenols with thallium (III) salts.

Accordingly, cis-carveol (**3**) led almost exclusively to the six-membered cyclic ether **7**, through a ring-expansion of the oxythallated adduct, while α-terpineol (**4**) led to the ether **8**,[6] resulting from a ring-contraction process.

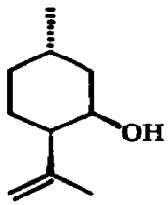
Regarding the behaviour of the two thallium salts employed, it is well known[7] that TTN reacts faster than TTA with olefinic substrates, and this was actually the only significant difference observed, as can be seen in Table 1.

We believe that these results could be of interest in the important field of cyclic ether synthesis, due to the high regio- and stereoselectivity of the thallium (III) salt - mediated cyclizations here described.

Table 1 - Reaction of 1 - 4 with thallium (III) salts in AcOH:H_2O, at room temperature



1



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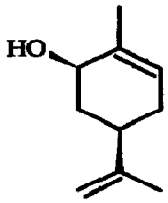
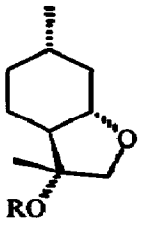
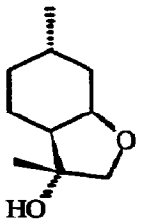


3

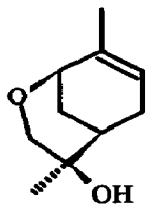
4



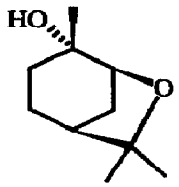
5a (R=H)
5b (R=Ac)



6



7



8

Entry	Substrate	Tl^{3+} salt	Time	Product	Yield
1	1	TTA	40 min	5a	85%
2	1	TTN	5 min	5a	85%
3	2	TTA	40 min	6	92%
4	2	TTN	5 min	6	80%
5	3	TTA	6h	7	55%
6	3	TTN	40 min	7	60%
7	4	TTA	1 h	8	86%
8	4	TTN	45 min	8	84%
9[a]	1	TTA	6 h	5a + 5b (1:9)[b]	64%[c]
10[a]	1	TTN	5 min	5a + 5b (1:9)[b]	74%[c]

a) Entries 9 and 10 were performed using glacial AcOH as solvent.
b) Ratio estimated by ^{1}H-NMR.
c) Yields refer to 5b product after purification by column chromatography.

Experimental

General procedure:

To a solution of the monoterpene (1mmol) in aqueous AcOH (50% vol/vol) (3ml), was added the thallium salt (1.2mmol). The mixture was stirred at room temperature, for the time indicated in table 1, and then poured into a diluted solution of sodium bicarbonate. The resulting brown mixture was filtered through Celite and the filtrate was extracted three times with ethyl acetate. The organic layer was washed with water, then with saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was evaporated and the crude product was purified by column chromatography on silica-gel, using hexane:ethyl acetate as eluent. All the obtained ethers gave spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR and MS) consistent with the assigned structures.

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