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THE STEREOSELECTIVE SYNTHESIS OF TERPENE TETRAHYDROFURANS USING THALLIUM TRIACETATE

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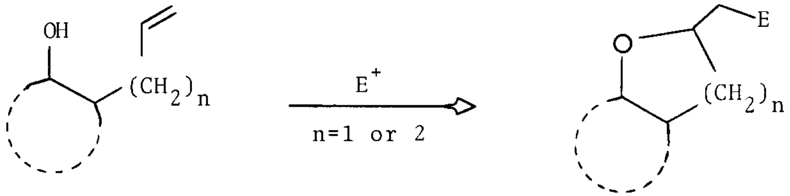
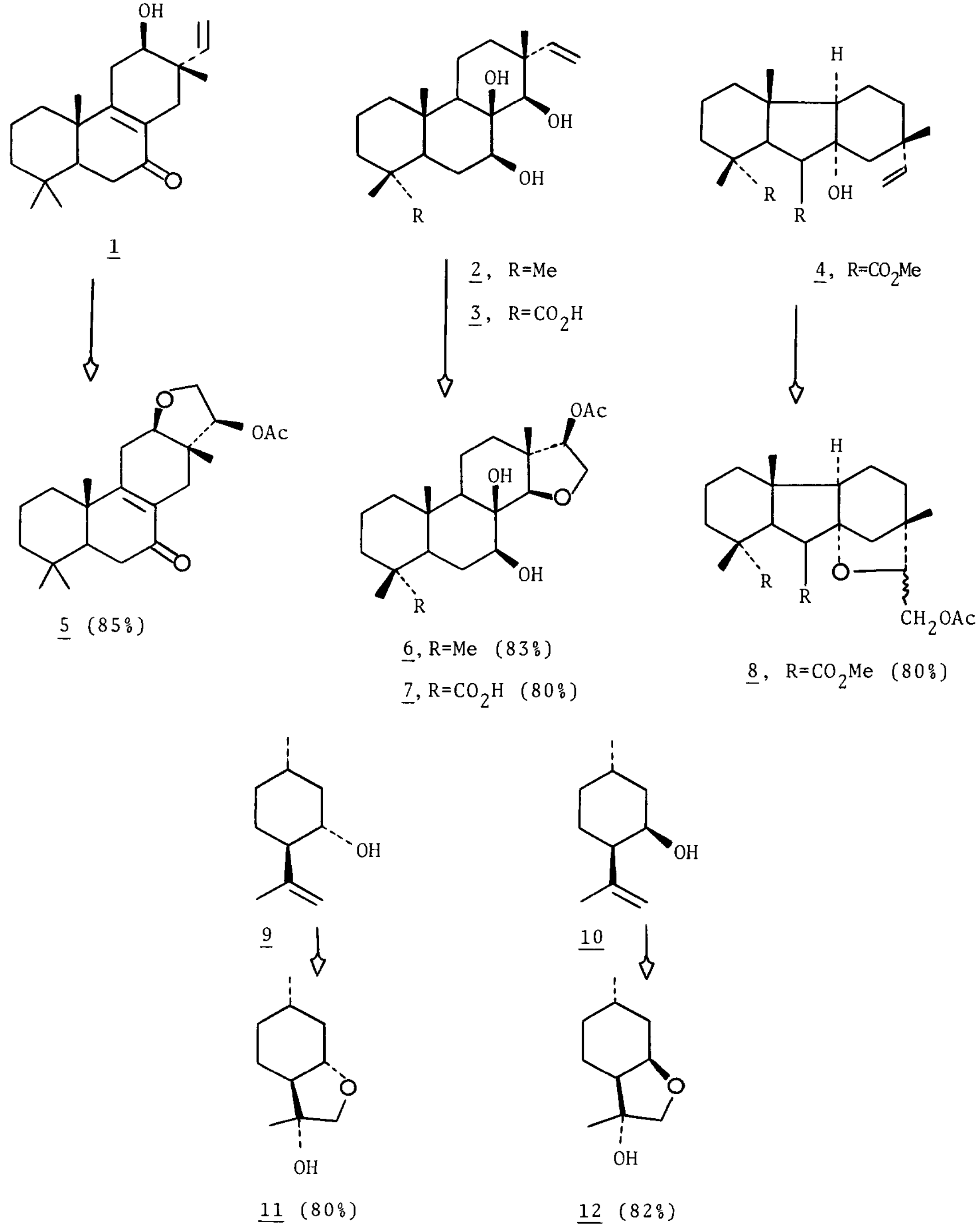
Abstract: The reaction of diterpenes 1-3 and monoterpenes 9, 10 with thallium triacetate leads stereoselectively to the tetrahydrofuran products 5-7 and 11, 12 respectively, by 5-Endo-Trig cyclisation of the 3-alkenol system.

The stereoselective synthesis of tetrahydrofurans and tetrahydropyrans is of current interest owing to their occurrence in biologically active natural products such as polyether antibiotics and prostacyclins. An important synthetic strategy is based on the electrophilic attack on alkenes followed by intramolecular oxygen nucleophile capture, and works well with 4- and 5-alkenols.



These two substrate reactions are formally 5- and 6-Exo-Trig, and are favoured according to Baldwin's rules.[1] We would like to report a series of nominally 5-Endo-Trig disfavoured reactions of 3-alkenols, mediated by thallium triacetate, which greatly expands the application of this synthetic strategy. Furthermore these reactions lead to 3-oxygenated tetrahydrofurans in a completely stereoselective manner.



1

2, R=Me

3, R=CO_2H

4, R=CO_2Me

5 (85%)

6, R=Me (83%)

7, R=CO_2H (80%)

8, R=CO_2Me (80%)

9

10

11 (80%)

12 (82%)

ISOLATED YIELDS ARE QUOTED IN PARENTHESIS

Recently Pinto and coworkers proposed the structures of three novel diterpenes, isolated from Vellozia compacta (compound 1)[2] and Vellozia variabilis (compounds 2 and 3)[3]. All three structures contain *trans*-vicinal hydroxyl and vinyl groups, and as part of the structure confirmation it was decided to test the action of electrophiles. Treatment of the three diterpenes 1-3, and the synthetic derivative 4, with an excess of thallium triacetate in acetic acid at room temperature led to the cyclised products 5-8 in high yields. The structures 5-8 were determined by conventional spectroscopic methods,[4] and demonstrate the exclusive formation of one epimer of the 3-acetoxy-*trans*-fused tetrahydrofuran system on reaction of the 3-alkenols 1-3.

These important results prompted a study with simple substrates, and isopulegol 9 and neoisopulegol 10 were therefore reacted in the same conditions leading to products 11 and 12 in high yields. The structures 11 and 12 were determined by conventional spectroscopic methods,[4] and again demonstrate the exclusive formation of one epimer of the 3-hydroxy tetrahydrofuran system.

Although the reaction of 4-alkenols with thallium triacetate has been studied previously,[5] we believe that our results represent the first successful experiments with 3-alkenols. In all five cases studied we obtain consistently high yields of tetrahydrofurans, irrespective of other functionalities present in the molecules, suggesting important synthetic applications without the need for protection/deprotection sequences. The reactivity of *trans*-disposed substrates 1-3, 9 is pleasingly surprising in view of the known kinetic problems associated with their cyclisations. The stereoselectivity demonstrated for the incorporation of acetoxyl or hydroxyl groups certainly reflects upon the mechanism of these disfavoured 5-Endo-Trig cyclisations, although we are presently unable to justify the incorporation of an acetoxyl group at primary and secondary carbon atoms (products 5-8) and a hydroxyl group at the tertiary carbon atom (products 11 and 12). Experiments designed to elucidate the mechanism (see ref.5 for an interesting discussion certainly applicable to our reactions) and investigate further the generality of this reaction are planned.

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GENERAL EXPERIMENTAL PROCEDURE

1 mmol of the substrate was dissolved in 2 ml of acetic acid, and 2 mmol (816 mg) of thallium triacetate sesquihydrate were added. The reaction mixture was stirred at room temperature for 1 to 2 hours (monitored by TLC) and then poured into water. The product was extracted three times with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution until neutral, and then washed with saturated sodium chloride solution, dried over magnesium sulfate and filtered through Celite. The solvent was evaporated and the crude product was purified by passing through a short silica gel column, using dichloromethane for elution.

REFERENCES AND NOTES

1. Baldwin, J.E., J. Chem. Soc. Chem. Comm., 1976, 734.
2. Pinto, A.C. and Borges, C., Phytochemistry, 1983, 22, 2011.
3. Pinto, A.C., unpublished results.
4. The products 5-8, 11 and 12 gave spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR and MS) consistent with the assigned structures. The stereochemistries of the 3-oxygenated carbon atoms were proposed on the basis of conventional NMR arguments.
5. Michael, J.P., Ting, P.C. and Bartlett, P.A., J.Org.Chem., 1985, 50, 2416, and references cited.

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