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Article

Syntheses of Chiral Intermediates. Hydrolysis of Terpene Epoxy-Tosylates

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Neste artigo é apresentado um estudo da hidrólise de quatro epoxi-tosilatos derivados da (-)-R-carvona. Esse estudo levou a produzir intermediários sintéticos com três e quatro centros quirais de maneira controlada.

This article presents hydrolytic studies on four diastereoisomeric epoxy-tosylates derived from (-)-R-carvone. This study led to preparation of ten-carbon synthetic quiral intermediates with three and four stereocontrolled centers.

Keywords: *terpenoid quirons, beta,gama-epoxy-tosylates, ring contraction*

Introduction

Wurtz[1], in 1859, prepared ethylene oxide and since then all compounds derived from oxiranes (1,2- epoxy) have proven to be versatile precursors in organic synthesis[2-5]. In the second half of the present century many papers have shown that the participation of *n*-oxygen electrons could be responsible for stereoeselectivity in reactions[6-12].

Hartshorn[13], in 1968, published the first example showing the participation of C-C bond of the oxirane group in the elimination of a tosyl group from a cholestane derivative heated in collidine to produce a dieno-ether (Fig. 1).

A series of papers from different authors demonstrated that steric relations between epoxy group and leaving group were of critical importance in determining the final product structure[14-18] (Fig. 2).

Here, we report the studies of hydrolysis of the four possible epimeric epoxy-tosylates derived from (-)-R- carvone.

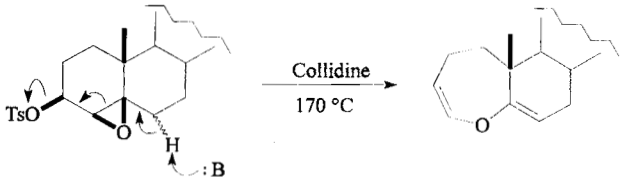


Figure 1.

Discussion and Results

The synthesis of epoxy-tosylates **1a**, **1b**, **1c** and **1d** from (-)-R-carvone has been previously reported by us[19] (Fig. 3).

Initially, the hydrolysis was carried out in a mixture of water/dioxane (1:2). The observation of the formation of the ketone **2** in 50% yield from the epoxy-tosylate **1a**[20] led us to propose Scheme 1 for its formation.

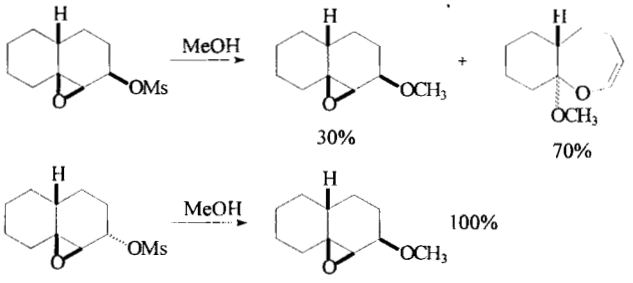


Figure 2.

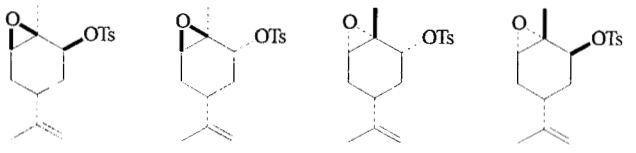
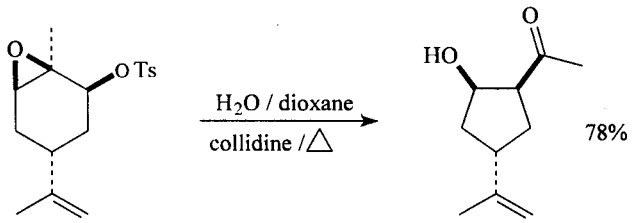


Figure 3.

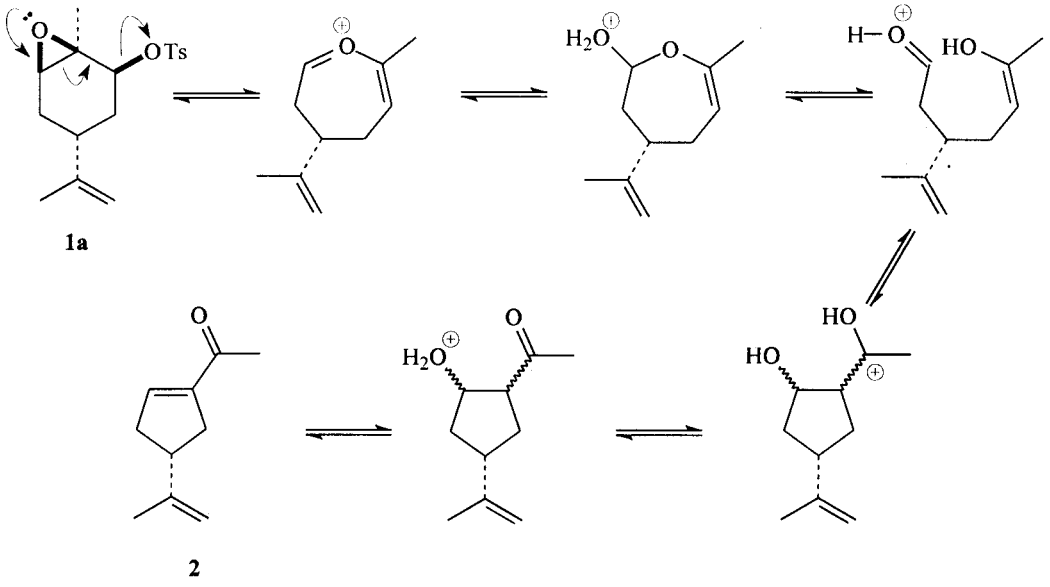
Analysis with CG/MS showed the presence of a small quantity of a second product with the characteristics to be expected for a hydroxy - ketone, a logical by-product to be according to Scheme 1. Probably, this compound was the precursor of **2** , being unstable in the presence of the TsOH formed *in situ*. Collidine was added to function as a proton scavenger. This procedure produced only one diastereoisomer, **3a** in 78% yield (Scheme 2).

To explain this result we proposed a new scheme for the formation of **3a** in which there is participation of the C-C bond of the oxirane leading to a carbocyclic ring contraction product (Scheme 3).



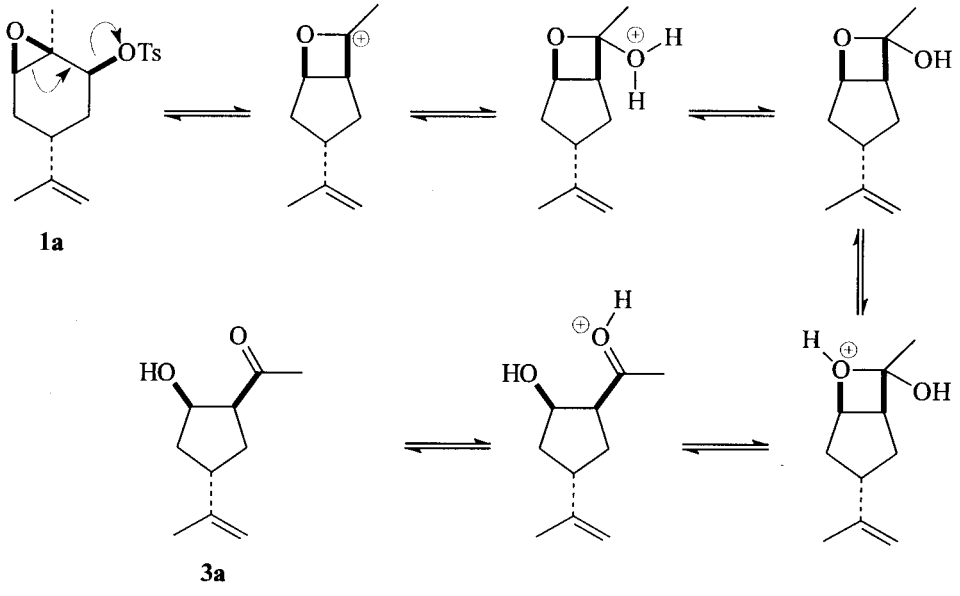
1a **3a**

Scheme 2.



1a **2**

Scheme 1.



1a **3a**

Scheme 3.

The structure proposed for 3a was confirmed by ^{1}H-NMR which suggests a intramolecular hydrogen bridge between the hydroxyl hydrogen and the ketone (Scheme 4).

When **1b** was hydrolyzed in the same solvent containing collidine, two products **3a** and the epoxy alcohol **4**[19,21] were isolated in 70% overall yield, in a proportion of 4 to 6 (Scheme 5).

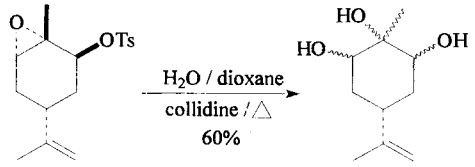
This result can be explained with different reactions occuring in each of the two conformations of **1b**. In one conformation we have a nucleophilic attack of water producing **4,** in the other the oxirane C-C bond is participating to produce **3a** as shown in Scheme 6.

In agreement with the results above, the hydrolysis of **1c** produced, stereospecifically, the hydroxy ketone **3b** in 60% yield. The explanation is similar to the one proposed for the formation of **3a** in Scheme 3 (Scheme 7).

The structure proposed for 3b was confirmed by ^{1}H-NMR and suggests a intramolecular hydrogen bridge between the hydroxyl hydrogen and the ketone (Scheme 8).

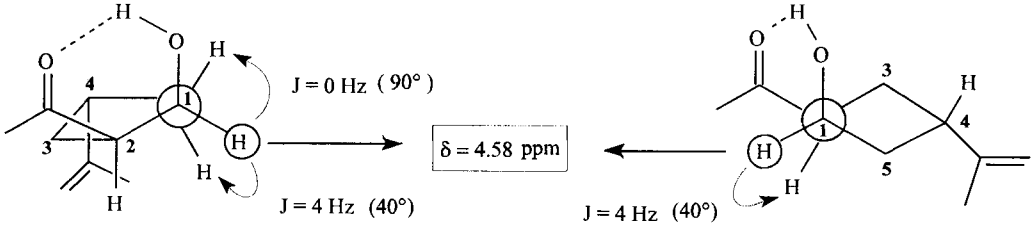
The epoxy tosylate **1d** behaved in an entirely different manner, the hydrolysis product was found to be a triol (Scheme 9).

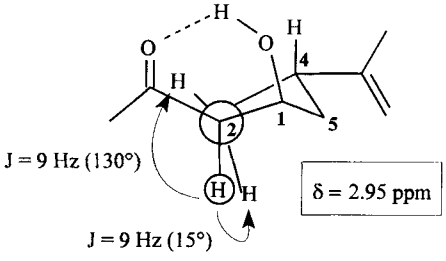
A reasonable explanation could be in terms of an initial nucleophilic attack of water on the tosyl carbon with the resulting alkyloxonium ion stabilizing the transition state for the epoxy ring-opening with an intramolecular hydrogen bond. The more difficult problem is to determine the true stereochemistry of the three new quiral centers formed. Our mechanism could explain either a *cis*, *trans* or a *trans*, *trans* relationship between the three hydroxyl groups. Consideration of Scheme 10 permits a better understanding of our deductions about the product structure.



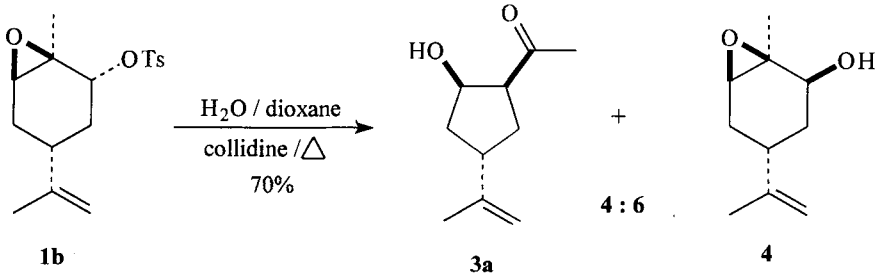
1d **4**

Scheme 5.



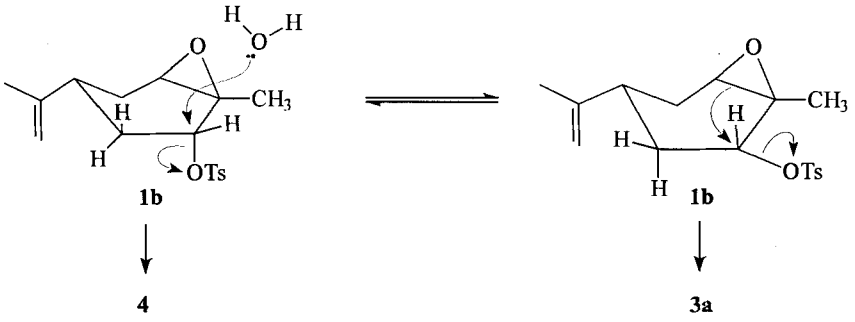


Scheme 4.

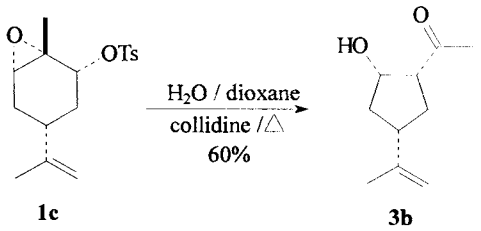


1b **3a** **4**

Scheme 6.



Scheme 7.



Scheme 8.

During our work, we encountered clear evidence that epoxy alcohols are intermediates in our hydrolyses of the epoxy-tosylates. In a previous paper we prepared authentic samples of the epoxy alcohols **5** and **6**[19,22]. The epoxy alcohol **5** potentially could give triols **4a** and **4b,** whereas **6** could give the triols **4c** and **4d**. When **5** and **6**[19] were submitted to the hydrolysis conditions each produced only one triol with melting points of 138-40 °C and 56-8 °C, respectively. The melting point of the triol obtained from **5** was identical to that of the triol produced from **1d**, thereby **4c** and **4d** were eliminated from consideration. The decision between **4a** and **4b** was also simple, since **4b** is a *meso* compound and would not present optical activity. All epoxy tosylates (**1a-d**) were shown to have optical activity.

We isolated the triol obtained from the hydrolysis of **1d** and found it to have a specific rotation of $[\alpha]_{25}^{D}$ = -29,8°, thus eliminating **4b**. The ^{1}H-NMR is perfectly coherent with the structure **4a** proposed (Scheme 11).

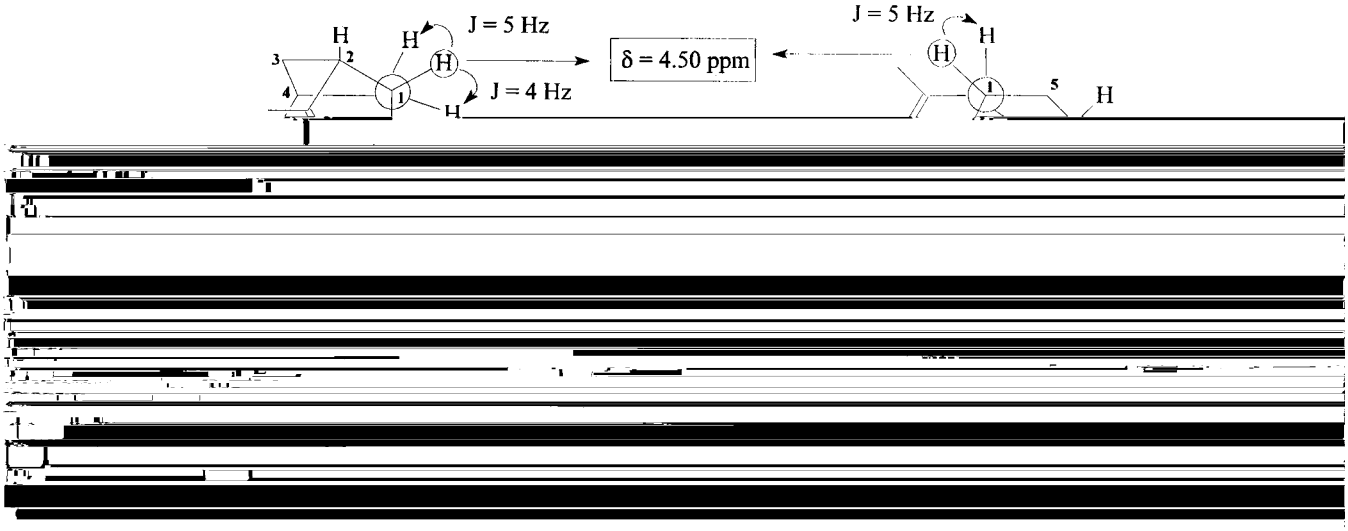
To summarize, we have found reasonably efficent pathways to two new quiral hidroxy-ketones and a new triol of known stereochemistry, as well a second new triol of as yet undetermined stereochemistry which can be viewed as derivatives of the limonene skeleton. Even though the four potentially useful quirons obtained here were prepared from (-)-R-carvone, the same quirons can theoretically be obtained from (+)-R-limonene via reaction with NOCl[23]. The enantiomeric products , in theory, could be prepared via the quiral *trans*-carveol obtained in the photooxygenation of (+)-R-limonene[24].

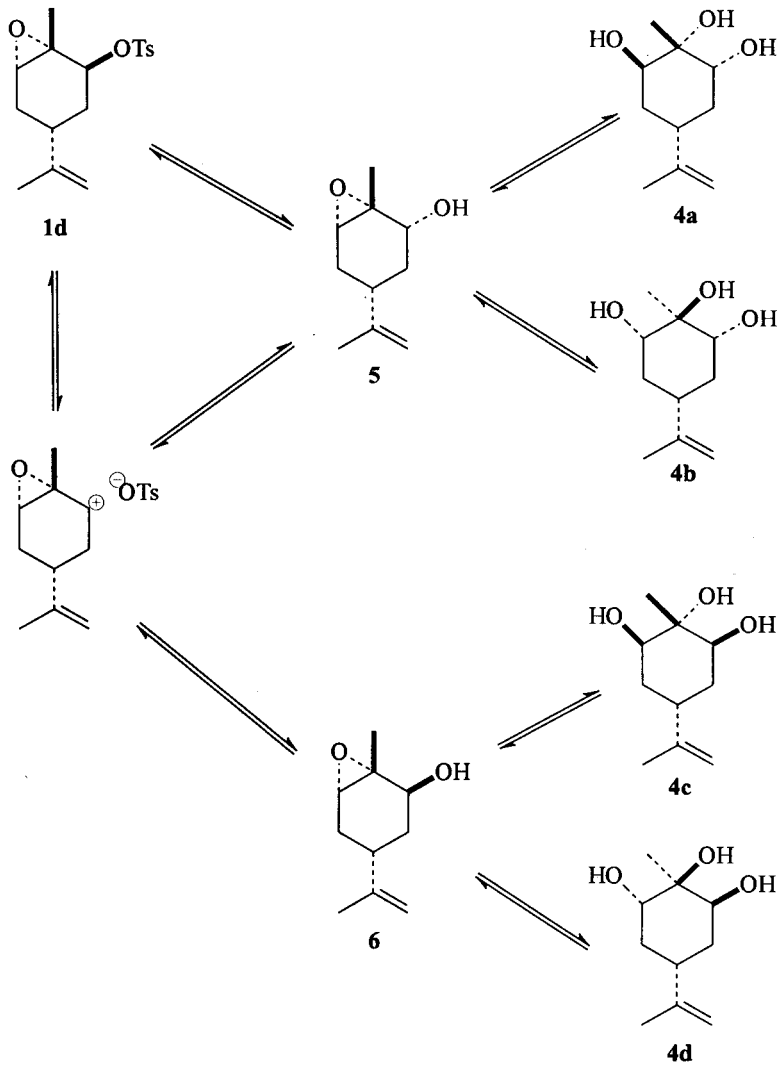
Experimental

The solvents were distilled prior to use and other chemicals were used without further purification.

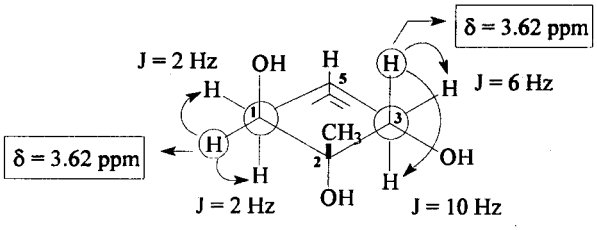
The reactions were monitored by TLC using Merck silica gel 60 HF_{254}. Flash chromatography (as described by Still[25]) used Merk silica gel 60, 400-230 mesh.

Melting points were determined on Kofler apparatus and are corrected.





Scheme 10.



Scheme 11.

^{1}H- and ^{13}C-NMR spectra of $CDCl_3$ solutions (TMS as internal standard) were recorded on Varian XL-100 (100 MHz).

HRGC analysis were performed on a HP 5890 gas chromatograph with FID by using a 20 m, 0.25 (i.d.), and 0.25 μm (phase thickness) OV-31 (OH) glass capillary column and H_2 (rate flow: 50 cm/s) as carrier gas (split: 1/20). Oven temp.: 60 °C (2 min) to 230 °C (5 min), rate: 10 °C / min; injector temp.: 200 °C; detector temp.: 220 °C.

Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

IR spectra were obtained using a Perkin-Elmer 257 spectrometer.

MS spectra were determined on HP 5987-A HRGS-MS and Micromass LTD, Micromass 12, Winford England spectrometers using electron impact (70 eV).

(4R)-1-acetyl-4-isopropenyl-ciclopentene (2)

In a 200-mL flask, were placed 1.5 g (4.66 mmol) of **1a** in 38 mL of water and 75 mL of dioxane. The solution was refluxed for 1.5 h, cooled, neutralized with sodium bicarbonate power, salting out with sodium chloride, the organic phase was separated and joined to the ether extract (2 x 25 mL) of the aqueous phase. All organic phases were combined and washed with brine, then dried over anhydrous Na_2SO_4, and evaporated to give yellow oil, distilled at

105-10 °C / 2 torr to give 370 mg (53% yield) of **2**. 2,4-DNPH derived m.p.= 177-9 °C [lit. 176-7 °C].

IV (neat) ν: 3060, 2960, 2900, 1660, 1610, 1440, 1370, 1230, 890, 810 cm^{-1}.

^{1}H-NMR (TMS, $CDCl_3$), δ 1.74 (S, 3H); 2.34 (s, 3H); 2.45-3.15 (m, 5H); 4.74 (s, br 2H); 6.68 (s,br, 1H).

^{13}C-NMR (TMS, $CDCl_3$): 196.4, 147.0, 144.9, 143.1, 109.2, 44.7, 38.5, 35.2, 26.3, 20.6 ppm.

MS (%): m/z: 150 (72), 135 (100), 107 (75), 93 (44), 91 (100), 79 (70), 77 (28), 65 (25), 43 (34).

U.V. (EtOH) - 238.3 nm.

*(1R, 2S, 4S)-2-acetyl-4-isopropenyl-ciclopentanol (**3a**)*

In a 125-mL flask, were placed 1.0 g (3.11 mmol) of **1a** and 0.38 g of collidine in 25 mL of water and 50 mL of dioxane. The solution was refluxed for 30 min., cooled, salting out with sodium chloride, the organic phase was separated and joined to the ether extract (2 x 25 mL) of the aqueous phase. All organic phases were combined and washed with brine, then dried over anhydrous Na_2SO_4, and evaporated to give yellow oil, distilled at 122-25 °C / 1 torr to give 410 mg (78% yield) of **3a**.

IV (neat) ν: 3420, 3070, 2960, 2940, 1710, 1640, 1440, 1360, 1180, 1100, 1140, 890, 820 cm^{-1}.

^{1}H-NMR (TMS, $CDCl_3$), δ 1.74 (s, 3H); 1.80 (m, 1H); 1.4 - 2.6 (m, 4H); 2.24 (s, 3H); 2.70 - 3.20 (m, 2H, J = 9 Hz , J = 9 Hz and J = 5 Hz), 4.78 (t, 1H, J = 4 Hz), 4.70 (s,br, 2H).

MS (%): m/z: 150 (3) 135 (5), 107 (100), 91 (50), 79 (50), 71 (60), 55 (30), (molecular ion, m/z 168, not found).

*(1S, 2R, 4S)-2-acetyl-4-isopropenyl-ciclopentanol (**3b**)*

In a 200-mL flask, were placed 1.5 g (4.66 mmol) of **1c** and 0.56 g of collidine in 38 mL of water and 75 mL of dioxane. The solution was refluxed for 3 h, cooled, salting out with sodium chloride, the organic phase was separated and joined to the ether extract (2 x 25 mL) of the aqueous phase. All organic phases were combined and washed with brine, then dried over anhydrous Na_2SO_4, and evaporated to give yellow oil ,distilled at 120-25 °C / 1 torr to give 460 mg (60% yield) of **3b**.

IV (neat) ν: 3440, 3070, 2960, 2930, 1700, 1640, 1440, 1360, 1240, 1180, 1100, 1000, 890 cm^{-1}.

^{1}H-NMR (TMS, $CDCl_3$), δ 1.76 (s, 3H); 1.4 - 2.6 (m, 4H); 2.22 (s, 3H); 2.60 (s, br 1H); 2.60 - 3.00 (dt, 2H, J = 3 Hz and J = 5 Hz), 4.50 (td, 1H, J = 5 Hz and J = 4 Hz), 4.72 (d, 2H).

MS (%): m/z: 168 (2), 150 (15), 135 (18), 125 (7), 107 (65), 91 (35), 79 (40), 71 (68), 55 (20), 43 (100).

*(1R, 3R)-1,2-trans-1,5-trans-5-isopropenyl-2-methyl-1,2, 3-ciclohexantriol (**4a**)*

In a 100-mL flask, were placed 0.5 g (2.98 mmol) of **5**, 30 mg of TsOH in 15 mL of water and 30 mL of dioxane. The solution was refluxed for 1,5 h, cooled, neutralized with sodium bicarbonate power, salting out with sodium chloride, the organic phase was separated and joined to the ether extract (1 x 55 mL) of the aqueous phase. All organic phases were combined and washed with brine, then dried over anhydrous Na_2SO_4, and evaporated to give a white solid , recrystalized from chloroform to give 210 mg (72% yield) of **4a**. m.p.=138-40 °C, $[\alpha]_{25}^{D}$ = -29,8° (c. 1.00, dioxane).

IV (2% KCl) ν: 3445, 3340, 3060, 2980, 2930, 2850, 1660, 1460, 1370, 1260, 1150, 1050, 1030, 1000, 930, 890, 860, 830 cm^{-1}.

^{1}H-NMR (TMS, $CDCl_3$), δ 1.29 (s, 3H); 1.2 - 2.0 (m, 7H); 1.71 (s, 3H); 2.32 (m, br 1H); 2.62 (dd, 1H, J = 6 Hz and J = 10 Hz), 2.62 (t, 1H, J = 2 Hz), 4.68 (s, br, 2H).

^{13}C-NMR (TMS, $CDCl_3$): 150.2, 109.0, 75.6, 73.8, 72.4, 38.4, 35.8, 34.4, 23.5, 20.9 ppm.

MS (%): m/z: 186 (2), 171 (4), 161 (8), 151 (15), 133 (18), 125 (25), 109 (25), 107 (45), 88 (40), 81 (28), 71 (98), 55 (25), 43 (100).

Acknowledgments

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References

1. Wurtz, A. *Beilstein Organische Chemie* **1859**, *17* (3), 4.
2. Smith, J.G. *Synth.* **1984**, *8*, 629-56.
3. March, J.; *Advanced Organic Chemistry: Reactions, Mechanism and Structure*; Wiley: New York, 1992, p 387-88.
4. Kocovsky, P.; Pour, M. *J. Org. Chem.* **1990**, *55* 5580-89.
5. Hartshorn, M.P.; Lane, G.A.; Goxon, J.M.; Garland, R.P. *J. Chem. Soc., Chem. Commun.* **1968**, *2*, 1056.
6. Winstein, S.; Marshall, H. *J. Am. Chem. Soc.* **1952**, *74*, 1120.
7. Richey, H.G.; Kinsman, D.V. *Tet. Lett.* **1969**, *30*, 2505.
8. Morita, H; One, S. *Tet. Lett.* **1969**, *17*, 1347.
9. Danen, W.C. *J. Am. Chem. Soc.* **1972**, *94*, 4835.
10. Santelli, M. Viala, J.; *Tetrahedron* **1978**, *34*, 2327.
11. Whalen, D.L. *J. Am. Chem. Soc.* **1970**, *92*, 7619.
12. Whalen, D.L.; Vitullo, V.P.; Cooper, J.D. *J. Am. Chem. Soc.* **1971**, *93*, 6294.

13. Hartshorn, M.P.; Lane, G.A.; Goxon, J.M.; Garland, R.P. *J. C. S. Chem. Comm.* **1968**, *2*, 1056.
14. Clark, G.R. *Tet. Lett.* **1984**, *25* (27), 2839-42.
15. Santelli, M.; Viala, J. *Tetrahedron* **1978**, *34*, 2327.
16. Whalen, D.L. *Tet. Let.* **1978**, *50*, 4973.
17. Whalen, D.L.; Russel, H.M.; Ross, A.M.; Brown, S. *J. Org. Chem.* **1978**, *43*, 428.
18. Whalen, D.L.; Cooper, J.D. *J. Org. Chem.* **1978**, *43*, 432.
19. Jones Jr, J.; Kover, W.B. *Synth. Comm.* **1995**, *25* (23), 3907-21.
20. Wolinsky, J.; Barber, W. *J. Am. Chem. Soc.* **1960**, *82*, 636.
21. Rao, A.S.; Tadwalker, V.R.; Narayanaswany, M. *Indian J. Chem.* **1971**, *9*, 1223-6.
22. Geneste, P.; Accrombessi, G.; Olivé, J.L.; Pavio, A.A. *Tetrahedron* **1981**, *37 (18)*, 3135-40.
23. Beckham, L.J.; Fessler, W.A.; Kisc, M.A. *Chem. Rev* **1951**, *48*, 324.
24. Schenck, G.O.; Gollnick, K.; Buchwald, G.; Schroeter, S.; Ohloff, G. *Ann.* **1964**, *93*, 674.
25. Still, W.C.; Kahn, M.; Mitra, A.J. *J. Org. Chem.* **1978**, *43*, 2923.