

Unexpected dimerization reaction of 5-methyl-6,7-methylenedioxy-1-tetralone in the presence of TMSCl-ethylene glycol

Gema Esteban and Joaquín Plumet*

Universidad Complutense. Facultad de Química. Departamento de Química Orgánica. E-28040, Madrid. Spain

E-mail: plumety@quim.ucm.es

Dedicated to Professor Joan Bosch on his 60th birthday

Abstract

Unprecedented dimerization reactions of the title compound using TMSCl as reagent and ethylene glycol as solvent has been observed and rationalized.

Keywords: Dimerization, tetralone, trimethylsilyl chloride, ethylene glycol, Mukaiyama reaction

Introduction

During our approach to the synthesis of the hydrophenalene ring system of pseudopterisines,¹ it was necessary to protect the 1-tetralone derivative **1** as cyclic acetal **5** or dithiane **6**. Thus, the reaction of **1** with 1,2-ethanedithiol in presence of $\text{BF}_3 \cdot \text{OEt}_2$ afforded **6** (88% isolated yield).² In contrast, when **1** reacts with ethylene glycol (benzene, reflux) in the presence of TsOH, compound **5** was isolated with maximum (and difficult to reproduce) 47% yield (Figure 1).

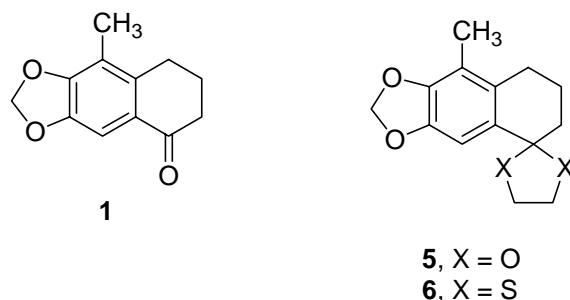
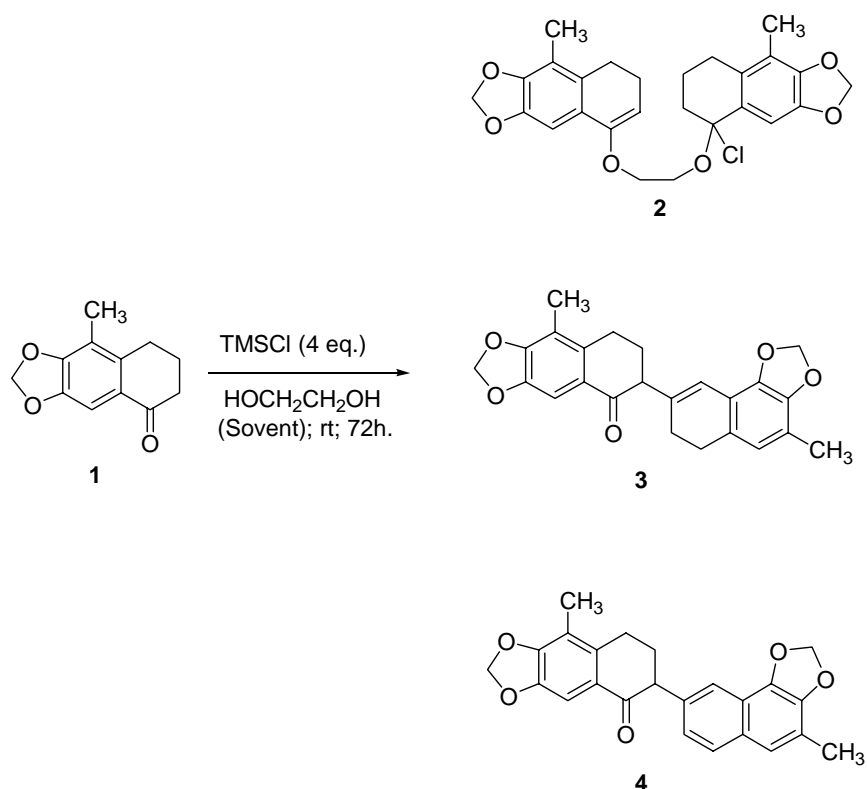


Figure 1

During the search for an alternative method for the preparation of **5**, the use of ethylene glycol as solvent in the presence of trimethylsilyl chloride³ was considered as an appealing

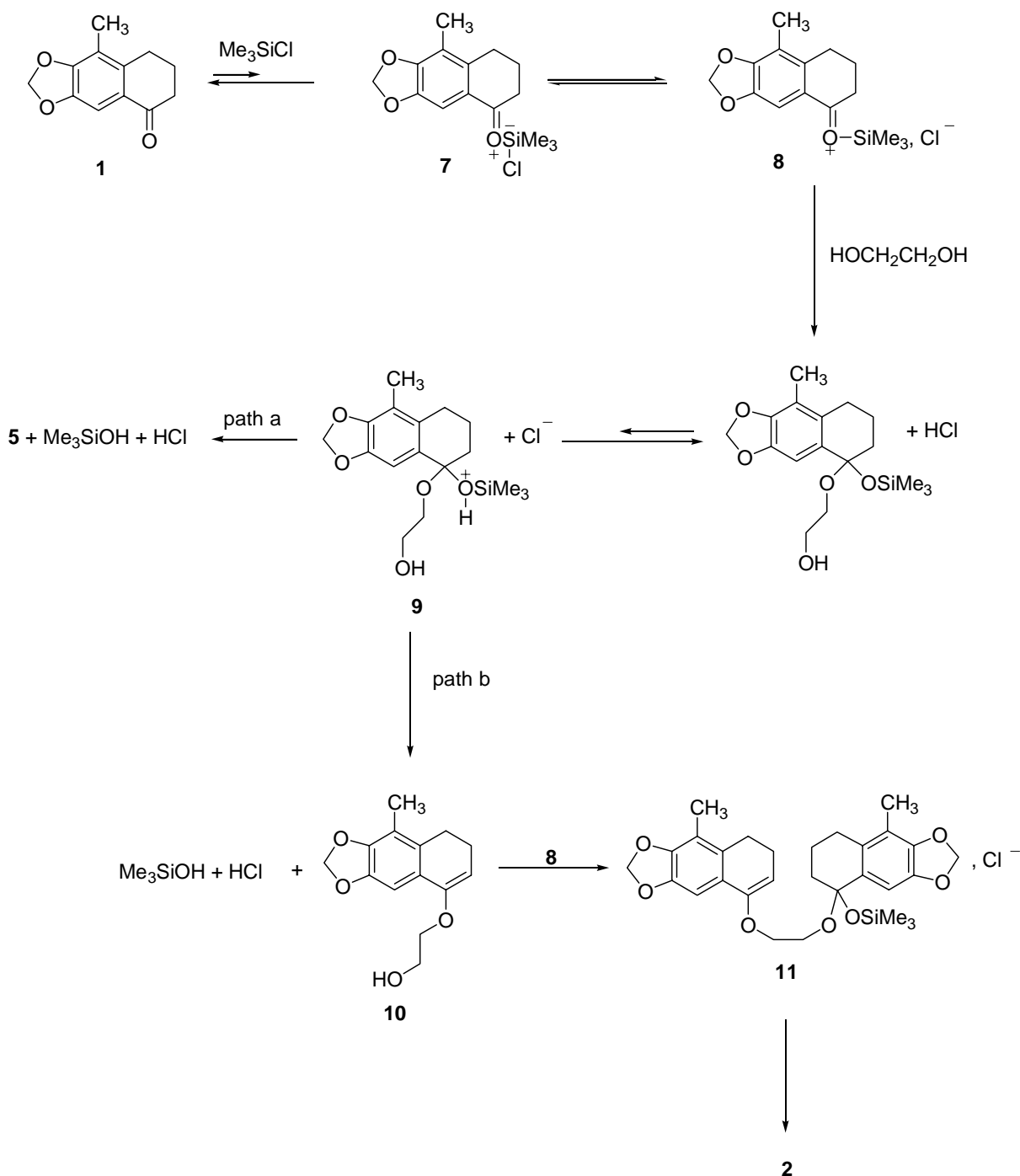
possibility. In this way, when **1** (2,0 mmol) was subjected to reaction with 8,2 mmol of TMSCl in 10 ml of ethylene glycol (rt, 72h), no traces of compound **5** were observed and instead a mixture of compounds **2**, **3** and **4** were isolated by column chromatography (SiO₂, hexane-AcOEt, 20:1). (Scheme 1)



Scheme 1

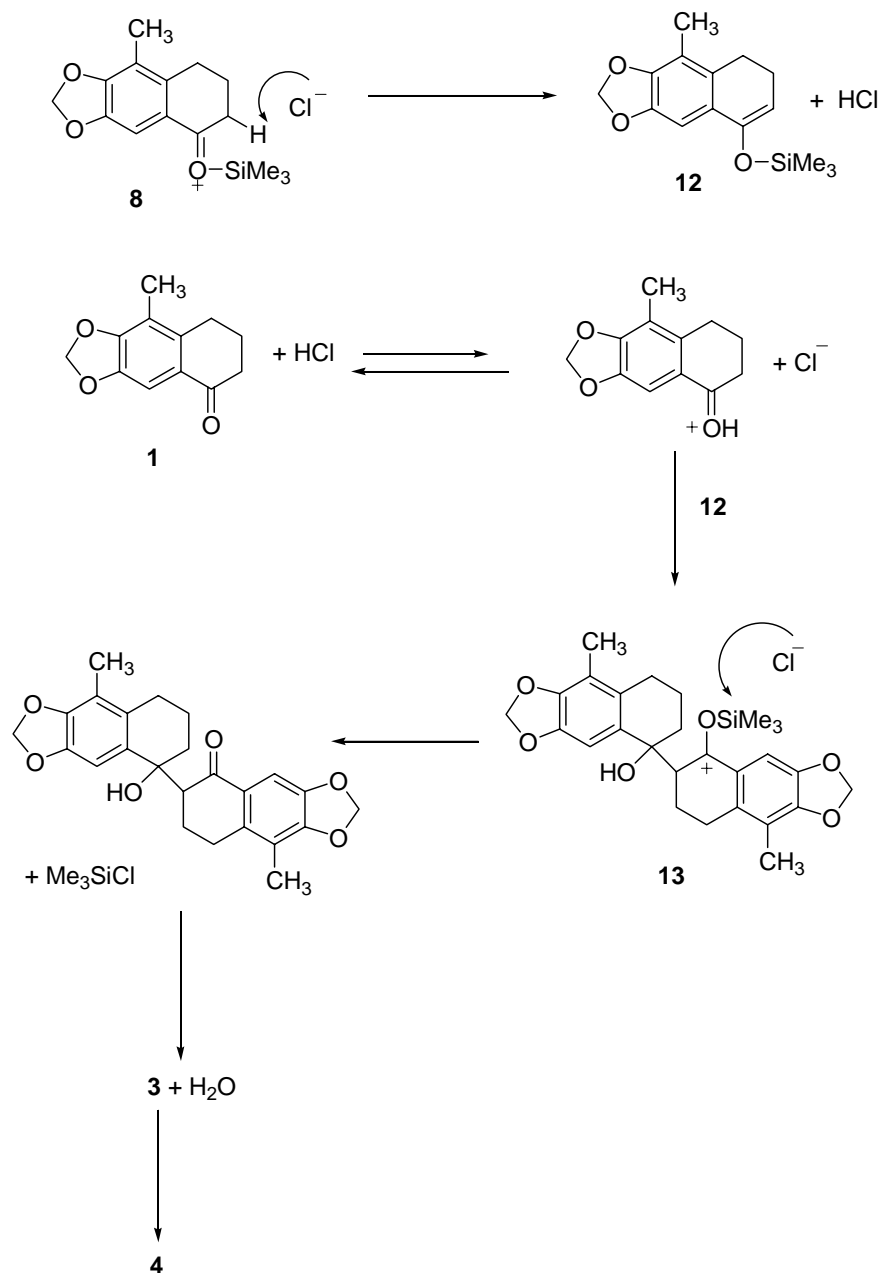
The structures of these new compounds were established on the basis of their spectroscopic (¹H-, ¹³C-NMR, MS) and analytical data. Thus, in all cases the ¹H- and ¹³C-NMR spectra show double signals which suggest the dimeric nature of these compounds. That was confirmed by MS as well as by the presence of chlorine in compound **2**.

A probable reaction for the formation of the major product **2** is depicted in Scheme 2. Reaction of **1** with Me₃SiCl⁴ should afford five-coordinate complex **7** which can exist in equilibrium with cation **8**.⁵ The nucleophilic attack of ethylene glycol on **8** should give intermediate **9**. Now two possible reaction paths are conceivable for **9**. Path a) involves the intramolecular addition of the remaining OH group to give the expected and not observed compound **5**. Alternatively, chloride ion may act as basic reagent inducing β-elimination reaction (path b) giving intermediate **10** which, by intramolecular reaction with **8** (nucleophilic addition to carbonyl-activated group) of **1** afforded **11**. Final nucleophilic substitution reaction of chlorine anion on **11**, should give **2**.



Scheme 2

Regarding the formation of compounds **3** and **4**, these may be formed *via* a Mukaiyama-type aldol reaction⁶ between silylenolether **12** (arising from **8** *via* Cl^- induced enolization) and protonated ketone **1**, to give intermediate **13** which, after recovering of catalyst (Me_3SiCl) and dehydration should afford compound **3**. Further aromatization of **3** (probably during the work-up of the reaction) gave **4** (Scheme 3).



Scheme 3

In summary, the results here presented constitute a convenient procedure for the synthesis of dimeric structures of tetralone derivatives avoiding the use of any organometallic catalytic reagent.

Experimental Section

General Procedures. The reaction was carried out under a positive pressure of dry Ar using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by

using standard syringe techniques. Ethylene glycol and TMSCl were commercial and used as received. 5-Methyl-6,7-methylenedioxy-1-tetralone (**1**) was synthesized as previously described.⁷ IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ¹H-NMR and ¹³C-NMR were obtained on Varian XL-300 and Bruker AM-300 spectrometers. Silica gel Merck (230-400 mesh) and Merck 60F₂₅₄ plates were used for conventional and analytical (TLC) chromatography respectively.

Reaction of 5-Methyl-6,7-methylenedioxy-1-tetralone with ethylene glycol and TMSCl (1**)**

190 mg. Trimethylsilyl chloride (1.04 ml; 8.2 mol) was added to a suspension of **1** (408 mg; 2,0 mmol) in ethylene glycol (10 ml) at room temperature (22-24 °C) under Ar. After stirring the resulting mixture at rt for 72 h, dilution with Et₂O (20 ml), addition of a solution of NaHCO₃ (5%) and decantation of the organic phase, the aqueous layer was extracted with Et₂O (3 x 5 ml). The combined organic extracts were washed with H₂O, a saturated solution of NaCl and dried over MgSO₄. After removing the solvent *in vacuo*, 382 mg of an orange oil was isolated and chromatographed twice (SiO₂, hexane-AcOEt 20:1). The following fractions were isolated and characterized.

8-{2-[(5-chloro-9-methyl-5,6,7,8-tetrahydronaphto [2,3 [1,3]dioxol-5-yl)oxy] ethoxy}-4-methyl-5,6-dihydronaphto [2,3-d] [1,3]dioxole (2**)**

87 mg as a pale yellow oil. ¹H-NMR (CDCl₃, ppm): δ 1.60-1.75 (m, 2H, CH₂); 2.13 (s, 3H, CH₃); 2.21 (s, 3H, CH₃); 2.10-2.25 (m, 2H, CH₂); 2.49 (t, 2H, J=7.5Hz, CH₂); 2.58 (t, 2H, J=7.8 Hz, CH₂); 2.95 (m, 2H, CH₂); 3.76 (t, 2H, J=5.9Hz, OCH₂); 4.47 (t, 2H, J=5.9 Hz, OCH₂); 5.79 (t, 1H, J=4.5 Hz, =CH); 5.89 (s, 2H, OCH₂O); 5.95 (s, 2H, OCH₂O); 6.73 (s, 1H, CH); 7.35 (s, 1H, CH). ¹³C-NMR (CDCl₃, ppm): δ 11.4 (CH₃); 11.7 (CH₃); 22.9 (CH₂); 23.9 (CH₂); 29.6 (CH₂); 33.7 (CH₂); 41.8 (CH₂); 64.2 (OCH₂CH₂O); 100.3 (OCH₂O); 101.2 (OCH₂O); 109.9 (CH); 108.2 (CH); 116.7 (C); 118.5 (C); 122.2 (C); 122.6 (C); 128.8 (C); 129.6 (C); 136.3 (C); 139.8 (C); 144.4 (C); 147.7 (C); 144.8 (C); 149.6 (C); 166.8 (C). IR (CHCl₃, cm⁻¹) ν max: 2780; 1590; 930 (C-O-C); 750 (C-Cl). MS 437(1); 472(3); 471(3, M⁺); 470(10); 221(10); 215(19); 213(27); 201(30); 202(100); 199(25); 193(28); 189(26); 187(35); 149(37); 115(22). Elem. Anal: Calcd. for C₂₆H₂₇ClO₆: C, 66.31; H, 5.78. Found: C, 66.56; H, 5.88.

9,9'-dimethyl-7,7',8,8'-tetrahydro-5,6'-binaphto[2,3-d][1,3]-dioxol-5'(6'H)-one (3**)**

16 mg as pale yellow oil. ¹H-NMR (CDCl₃, ppm) δ 2.17 (s, 6H, 2xCH₃); 2.10-2.82 (m, 8H, 4xCH₂); 3.69 (dd, 1H, J=7.2 and 4.5 Hz, CH); 5.66 (t, 1H, J=4.5 Hz, =CH); 5.89 (d, 2H, J=1.1 Hz, OCH₂O); 6.00 (s, 2H, OCH₂O); 6.56 (s, 1H, CH); 7.45 (s, 1H, CH). ¹³C-NMR (CDCl₃, ppm): δ 11.5 (CH₃); 11.9 (CH₃); 23.0 (CH₂); 23.8 (CH₂); 24.7 (CH₂); 28.2 (CH₂); 50.1 (C); 100.5 (OCH₂O); 101.4 (OCH₂O); 102.3 (CH); 104.5 (CH); 116.6 (C); 117.9 (C); 124.6 (CH); 127.9 (C); 128.0 (C); 130.0 (C); 135.3 (C); 139.7 (C); 145.0 (C); 146.0 (C); 150.7 (C); 198.9 (C=O). IR (CHCl₃, cm⁻¹) ν max: 3040; 1720 (C=O); 1660 (C=C); 930 (C-O-C). MS: 391 (10); 390(37, M⁺); 388 (19); 205(13); 204 (67); 203 (27); 202 (44); 199 (19); 190 (19); 189 (64); 187 (38); 186

(24); 177 (30); 175 (25); 174 (17); 149 (100); 148 (86). Elem. Anal: Calcd. for C₂₄H₂₂O₅: C, 78.83; H, 5.69. Found: C, 73.46; H, 5.32.

9,9'-dimethyl-7',8'-dihydro-5,6'-binaphto [2,3-d] [1,3]-dioxol-5'(6'H)-one (4)

8 mg as reddish oil. ¹H-NMR (CDCl₃, ppm) δ 2.20 (s, 3H, CH₃); 2.48 (s, 3H, CH₃); 2.20-2.92 (m, 4H, 2 x CH₂); 4.32 (m, 1H, CH); 5.99 (s, 2H, OCH₂O); 6.02 (s, 2H, OCH₂O); 6.73 (s, 1H, CH); 7.03 (d, 1H, CH); 7.32 (dd, 1H, CH); 7.50 (s, 1H, CH); 7.78 (s, 1H, CH). IR (CHCl₃, cm⁻¹) ν max 2980, 1720 (C=O); 940 (C-O-C). MS: 389 (2); 388 (6, M⁺); 386 (2); 220 (7); 189 (22); 167 (15); 148 (27); 113 (12); 111 (12); 96 (12); 91(16). Elem. Anal: Calcd. for C₂₄H₂₀O₅: C, 74.21; H, 5.19. Found: C, 74.40; H, 5.12.

Acknowledgements

This research was supported by PharmaMar S.A.

References and Notes

1. Benoit-Marquie, F.; Csáký, A. G.; Esteban, G.; Martínez, M. E.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 3355.
2. Esteban, G.; López, B.; Plumet, J.; del Valle, A. *Heterocycles* **1997**, *45*, 1921.
3. Chan, T. H.; Brook, M. A.; Chaly, Y. *Synth. Comm.* **1983**, 203.
4. For recent reviews on the use of silicon Lewis Acids in organic synthesis, see:
(a) Dilman, A. D.; Joffe, S. L. *Chem. Rev.* **2003**, *103*, 733. (b) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (c) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391.
5. Prakash, G. K. S.; Bae, C.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 1297.
6. For recent uses of cyclohexanone derivatives in Mukaiyama Aldol reactions, see:
(a) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593. (b) Han, L. B.; Zhao, C. Q. *J. Org. Chem.* **2005**, *70*, 10121. (c) Sarabèr, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1717, and references quoted in these papers.
7. Esteban, G.; López-Sánchez, M. A.; Martínez, M. E.; Plumet, J. *Tetrahedron* **1998**, *54*, 197.