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Detailed Studies of Perezone Rearrangements

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Summary. The isomerization of perezone (**1**) into isoperezone (**2**) by means of 3,4,5,6-tetrahydro-2-pyrimidinethiol afforded 6-methoxyperezone (**6**), the sulfide **7**, and the heterocycle **8** as by-products. Addition of a small amount of water to the reaction system increased the yield of **2** from 45 to 65%. The pathway for the formation of **6**, **7**, and **8** is discussed. The reaction of **2** with silica gel or with *p*-TsOH regioselectively yielded β-isopipitzol (**3**) or dihydroisoperezinone (**4**) in 72 and 82% yield, respectively.

Keywords. Perezone; Isoperezone; Rearrangement.

Detaillierte Untersuchung von Perezon-Umlagerungen

Zusammenfassung. Die Isomerisierung von Perezon (**1**) zu Isoperezon (**2**) mit 3,4,5,6-Tetrahydro-2-pyrimidinthiol ergab 6-Methoxyperezon (**6**), das Sulfid **7** und den Heterocyclus **8** als Nebenprodukte. Zugabe einer geringen Menge Wasser zum Reaktionsgemisch erhöhte die Ausbeute an **2** von 45 auf 65%. Der Mechanismus der Bildung von **6**, **7** und **8** wird diskutiert. Reaktion von **2** mit Kieselgel oder *p*-TsOH führte regioselektiv mit 72 bzw. 82% Ausbeute zu β-Isopipitzol (**3**) oder Dihydroisoperezinon (**4**).

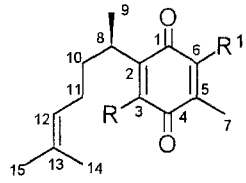
Introduction

Perezone (**1**), the first natural product isolated in crystalline form in the New World [1], has been the subject of fascinating chemical studies for almost one and a half centuries [2]. Its rearrangement into pipitzol acetate (in fact a mixture of α- and β-pipitzol acetate) by treatment with acetic anhydride was achieved as early as 1885 [3]. This rearrangement was better understood when the structures of α- and β-pipitzol were elucidated some 30 years ago [4] and when a further mechanistic study [5], using isotopically labeled compounds, was carried out. Subsequently, it became clear that changes in the reaction conditions of perezone (**1**) [5–7] and of several simple derivatives [8–10] allowed to manipulate the stereoselectivity and the regioselectivity of the reaction outcome, thus providing the opportunity to generate a variety of new polycyclic molecules.

In continuation of a series of investigations on the molecular rearrangements of perezone, a recent publication [11] accounts for its transformation into isoperezone (**2**), a molecule with a structure erroneously ascribed to perezone some 60 years ago [12] based on extensive chemical transformations. The remarkable trans-

formation of **1** into **2** is claimed [11] to occur in a moderate yield (58%) by means of 3,4,5,6-tetrahydro-2-pyrimidinethiol in absolute methanol; no further reaction by-products were reported.

On the other hand, when the NMR shift reagent Eu(*fod*)$_3$ was added to an isoperezone solution, a mixture of *β*-isopipitzol (**3**) and dihydroisoperezinone (**4**) was obtained [13] in 13 and 51% yield, respectively. This motivated the use of other *Lewis* acids [13]. The treatment of **2** with $ZnBr_2$ afforded *β*-isopipitzol (**3**), dihydroisoperezinone (**4**), and perezinone (**5**) in 20, 2, and 29% yield, respectively, whereas the reaction of **2** with $BF_3{\cdot}Et_2O$ [11] gave dihydroisoperezinone (**4**) in 32% yield.



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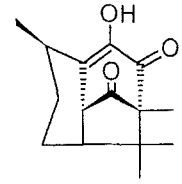
1	OH	H
2	H	OH
6	OH	OMe
9	OMe	OH
10	OH	OH
11	OMe	OMe



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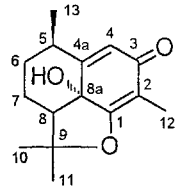

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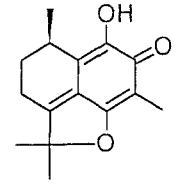

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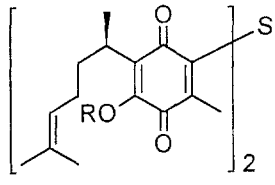
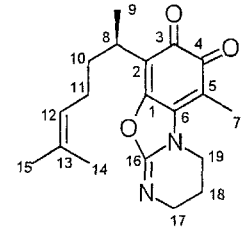


	R
7	H
12	Ac



8

In this paper, we report the isolation of 6-methoxyperezone (**6**) the sulfide **7**, and the heterocycle **8** as by-products of the perezone → isoperezone rearrangement, as well as the regioselective transformation of isoperezone into β-isopipitzol or into dihydroisoperezinone in high yields.

Results and Discussion

The reaction of perezone (**1**) with 3,4,5,6-tetrahydro-2-pyrimidinethiol was carried out using the same reaction conditions as reported by *Rodríguez et al.* [11]. The MeOH was evaporated, and the residue was triturated with hexane, yielding 45% of **2** as yellow crystals instead of the previously described yield of 58% [11]. The hexane-insoluble solid residue was dissolved in EtOAc and chromatographed over silica gel.

The first fractions of the chromatography afforded 6-methoxyperezone (**6**, 1%) whose spectroscopic data were in agreement with those reported in the literature [10]. Presumably, **6** was obtained by addition of MeOH to **1**. The medium polarity fractions of the chromatography gave **7**, a red oil whose MS showed the M^+ at $m/z = 526$, suggesting the empirical formula $C_{30}H_{38}O_6S$. The ^1H NMR spectrum of this oil showed similar signals as diperezone [14]. The only significant change is due to the chemical shift of Me-7, found at 2.27 ppm. This corresponds to a low-field shift in comparison with 6-methoxyperezone (**6** [10]), O-methyl-6-hydroxy-perezone (**9** [10]), 6-hydroxyperezone (**10** [15]), O-methyl-6-methoxyperezone (**11** [15]), and diperezone [14] (1.93, 1.90, 1.93, 1.93, and 1.88 ppm, respectively). On the other hand, H-8 in **7** appears as a multiplet at 2.94 ppm, slightly different from the respective signals of **6** [10], **9** [10], **10** [15], **11** [15], and diperezone [14] (3.09, 3.09, 3.0, 3.0, and 3.07 ppm, respectively). Furthermore, the ^{13}C NMR chemical shifts of Me-7 in **1** [16, 17] and in diperezone [14] appear at 14.6 and 12.8 ppm, respectively, whereas in those related quinones in which Me-7 is adjacent to two oxygen bearing carbons it is shifted to higher field (near 8 ppm; **6** [10], **9** [10], **10** [16, 17], and **11** [17]: 8.0, 7.7, 7.6, and 8.0 ppm, respectively). The ^{13}C NMR chemical shift of Me-7 in **7** appears at 13.8 ppm. These data permitted to conclude that the S atom is located on the same double bond as Me-7, thus completing the structural elucidation of **7**. On the other hand, the acetylated derivative **12** of the sulfide **7** was prepared. The MS of this compound showed the M^+ at $m/z = 610$, whereas the ^1H NMR spectrum exhibited one additional singlet at 2.34 ppm, corresponding to the acetyl methyl groups. In the ^{13}C spectrum of **12** only 17 signals were observed, thus confirming the presence of a symmetrical molecule.

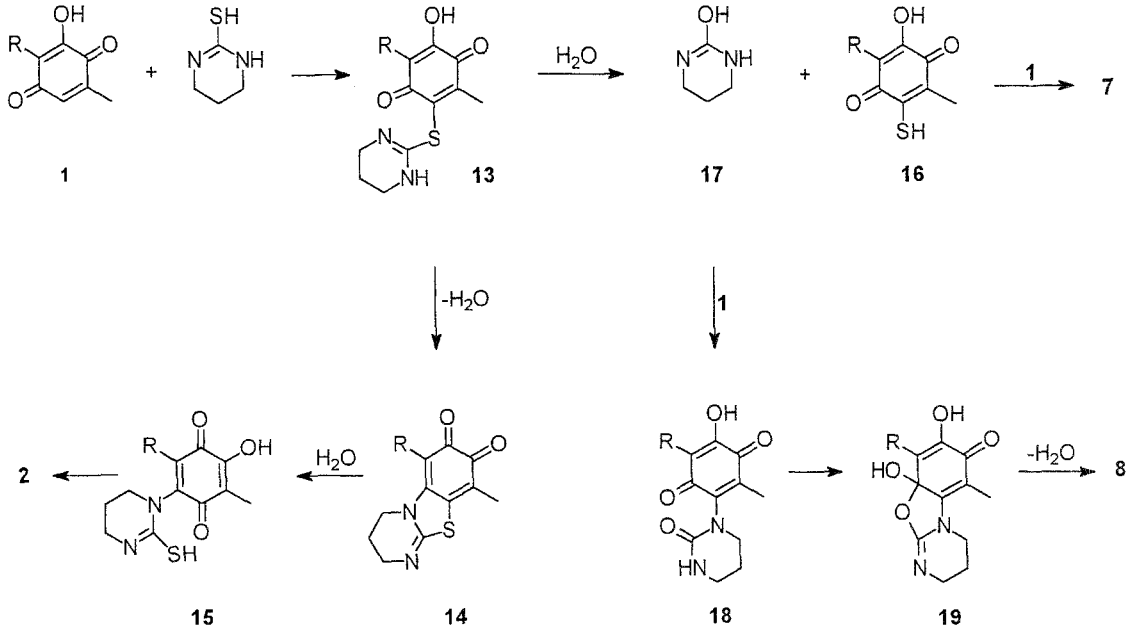
Finally, from the more polar fractions of the chromatography, **8** was isolated as a red oil. Its MS showed the M^+ at $m/z = 328$ which corresponds to $C_{19}H_{24}N_2O_3$, and ion fragments at $m/z = 246$ (100), 218 (33), and 217 (18) due to $[M\text{-}C_4H_6N_2]^+$, $[M\text{-}C_4H_6N_2\text{-}CO]^+$, and $[M\text{-}C_8H_{15}]^+$, respectively. The ^1H NMR spectrum of this compound contained signals for the side chain and no evidence for a vinylic quinone ring proton. In consequence, the Me-7 signal appears now as a singlet at 2.11 ppm. In addition, two triplets at 4.16 and 3.68 ppm and a quintet at 2.08 ppm coupled with the triplets were observed, corresponding to methylenes 17, 19, and 18, respectively. The ^{13}C NMR spectrum of **8** showed 19 signals whose

assignment is based on a comparison with related quinones, heteronuclear long-range spin-spin couplings, and on a heteronuclear correlation experiment. Assignment of the side-chain signals is trivial based on comparison with related molecules [16, 17], and the assignment of the quinone ring signals was possible from the corresponding long-range couplings obtained from a gated decoupling experiment. The carbonyl groups resonate at 177.9 and 177.7 ppm. The lower field signal, which appears as a doublet due to a long-range coupling with H-8, is ascribed to the C-3 carbonyl, whereas the C-4 carbonyl appears at 177.7 ppm as a quartet due to a long-range coupling with the Me-7 protons. The other quinone ring carbons also appear long-range coupled as a doublet at 154.5 ppm, a quartet at 142.0 ppm, a multiplet at 120.4 ppm, and a quartet at 105.2 ppm and were therefore assigned to C-1, C-6, C-2 and C-5, respectively. The chemical shifts of C-1 and C-6 are in agreement with the five-membered heterocycle ring junction to the quinone ring. Finally, a HETCOR plot showed cross-peaks between H-17, H-18, and H-19 and the ^{13}C signals at 43.8, 20.5, and 43.4 ppm. They were assigned to C-17, C-18, and C-19, respectively.

The reaction of perezone (**1**) with 3,4,5,6-tetrahydro-2-pyrimidinethiol [11] to afford isoperezone (**2**) involves the conjugate addition of the thiol, followed by oxidation to generate **13** (Scheme 1). Intramolecular attack of a nitrogen atom on the adjacent carbonyl carbon atom, followed by H_2O elimination, leads to an *o*-quinone fused with a thiazole ring (**14**, Scheme 1). The latter is hydrolyzed by a water molecule which splits the sulfur-to-quinone bond affording the *N*-addition product **15** whose leucoanalogue undergoes a *retro-Michael* elimination of 3,4,5,6-tetrahydro-2-pyrimidinethiol to produce **2**. This mechanistic pathway on the one hand shows that a water molecule is important for the transformation of **1** into **2**. On the other hand, it suggests that a plausible pathway for the formation of **7** and **8**, shown in Scheme 1, involves the hydrolysis of **13** to afford **16** and **17** which lead to **7** and **8**, respectively, by reaction with another molecule of **1**. Intermediates **13–19** have not been isolated up to now, but the isolation of **6–8** explains the moderate yield reported [11] for the rearrangement of **1**→ **2**.

When the above rearrangement is performed in the presence of a small amount of H_2O, it affords **2** and **8** in 65 and 8% yield, respectively. This proved that the presence of H_2O is effectively important for the carbonyl transposition reaction and suggests that the reported yield of 58% [11] was probably caused by the presence of moisture in the methanol. In our hands, the reaction gave 45% yield of **2** when performed in absolute methanol.

In previous papers [11, 13] it was reported that intramolecular cycloaddition reactions of **2** induced by *Lewis* acids follow different pathways thus affording mixtures of **3**, **4**, and **5**. Perezinone (**5**) is readily available [6, 8] from hydroxyperezone (**10**), and therefore no further studies for its obtention are required. In contrast, the isoperezone (**2**) into *β*-isopipitzol (**3**) rearrangement is a rare example of a [4+2] intramolecular cycloaddition through a 2-substituted cyclopentadienyl cation [13], whereas the isoperezone (**2**) into dihydroisoperezinone (**4**) rearrangement involves an intramolecular electrophilic attack on the side chain double bond by the *Lewis* acid polarized *o*-quinone [11] (formed by tautomeric equilibrium), followed by cyclization. These two reactions deserve further studies for their optimization, since it can be assumed that a mild treatment



Scheme 1. The transformation of **1** into **2**, **7**, and **8**

would favor the formation of **3**, whereas a hard acid would lead mainly to the formation of **4**.

Indeed, when the cyclization of **2** was carried out in a CH_2Cl_2 solution at room temperature with silica gel, **3** was regioselectively obtained in 72% yield after 14 days. However, when the reaction was carried out in CH_2Cl_2 under reflux for 8 days, **3** and **4** were obtained in 68 and 14% yield, respectively. On the other hand, the cyclization of **2** in a CH_2Cl_2 solution catalyzed by a hard acid (*p*-TsOH) at room temperature afforded **4** as the only product in 82% yield after 5 days.

The ^{13}C NMR assignments of **2**, given in the experimental section, were derived similarly to those of **8**. The assignment of the quinone ring carbons is further based on a comparison with reported values for 6-hydroxythymoquinone [17], those of the side chain signals on comparison with related molecules [16, 17]. The ^{13}C NMR spectrum of **4** was assigned based on heteronuclear one-bond and long-range couplings, COSY and HETCOR experiments, and by comparison with model compounds [8]. The assignments of the *gem*-dimethyl methyl groups are tentative.

Experimental

Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were performed at room temperature on a Perkin Elmer 241 polarimeter in $CHCl_3$. UV spectra were determined on a Perkin Elmer UV/Vis is Lambda 12 spectrophotometer using EtOH. IR

spectra were recorded in $CHCl_3$ solutions on a Perkin Elmer 16F PC FT-IR spectrophotometer. ^1H and ^{13}C NMR measurements were carried out at 300 and 75.4 MHz, respectively, on a Varian XL-300GS spectrometer in $CDCl_3$ solutions containing *TMS* as internal standard. The mass spectra were obtained on a Hewlett Packard 5989-A spectrometer at 20 eV. For gravity CC, Merck silica gel 60 (230–400 mesh ASTM) was used.

Reaction of perezone (**1**) *with 3,4,5,6-tetrahydro-2-pyrimidinethiol*

A solution containing **1** (1.0 g, 4.03 mmol) and 3,4,5,6-tetrahydro-2-pyrimidinethiol (0.515 g, 1.1 eq.) in 60 ml of absolute methanol was heated under refluxed for 12 h. After evaporation of the solvent, the residue was triturated with hexane, filtered, and the hexane was evaporated. The solid residue was recrystallized from hexane to yield **2** (450 mg, 45%). The hexane-insoluble residue was dissolved in EtOAc and adsorbed on silica gel for CC. Elution was performed with hexane-EtOAc mixtures of increasing polarity. The first fractions of the chromatography yielded **6** as a red oil (10 mg, 1%), identified by direct comparison with an authentic sample [10]. The medium polarity fractions of the chromatography afforded 200 mg (19%) of **7** as a red oil which could not be purified completely by successive rechromatographies. Finally, from the more polar fractions of the chromatography, **8** was isolated as a red oil (38 mg, 3%). When a solution of **1** (100 mg, 0.4 mmol) and 3,4,5,6-tetrahydro-2-pyrimidinethiol (51.5 mg, 1.1 eq) in absolute methanol was treated with one drop of H_2O, heated under reflux for 12 h, and worked up as described previously, it yielded **2** (65 mg, 65%) and **8** (11 mg, 8%).

Isoperezone (**2**)

Yellow crystals; m.p.: 107–109°C (Ref. [11]: m.p.: 108–109°C); ^1H NMR: $\delta = 7.03$ (s, interchangeable with D_2O, 1H, OH), 6.45 (d, $J_{3,8} = 1.0$ Hz, 1H, H-3), 5.04 (t septet, $J_{11,12} = J_{11',12} = 7.1$ Hz, $J_{12,14} = J_{12,15} = 1.4$ Hz, 1H, H-12), 2.90 (m, 1H, H-8), 1.94 (s, 3H, Me-7), 1.66 (br s, 3H, Me-14), 1.55 (s, 3H, Me-15), 1.14 (d, $J_{8,9} = 7.0$ Hz, 3 H, Me-9) ppm; ^{13}C NMR: $\delta = 188.1$ (s, C-4), 183.2 (s, C-1), 151.4 (s, C-6), 149.6 (s, C-2), 133.1 (d, C-3), 132.2 (s, C-13), 123.8 (d, C-12), 116.7, (s, C-5) 35.7 (t, C-10), 31.5 (d, C-8), 25.8 (t, C-11), 25.6 (q, C-15), 19.4 (q, C-9), 17.7 (q, C-14), 7.8 (q, C-7) ppm.

6,6'-Thiobis-perezone (**7**)

Red oil; ^1H NMR: $\delta = 7.19$ (br s, 1H, OH), 5.04 (m, 1H, H-12), 2.94 (m, 1H, H-8), 2.27 (s, 3H, Me-7), 1.63 (br s, 3H, Me-14), 1.54 (s, 3H, Me-15), 1.13 (d, $J_{8,9} = 7.0$ Hz, 3H, Me-9) ppm; ^{13}C NMR: $\delta = 182.2$ (s, C-1), 180.9 (s, C-4), 151.2 (s, C-3), 146.7 (s, C-6), 135.1 (s, C-5), 131.4 (s, C-13), 125.4 (s, C-2), 124.4 (d, C-12), 34.1 (t, C-10), 30.3 (d, C-8), 26.7 (t, C-11), 25.7 (q, C-15), 18.2 (q, C-9), 17.6 (q, C-14), 13.8 (q, C-7) ppm; EIMS (20 eV): $m/z = 526$ (36, $[M]^+$), 248 (98), 247 (91), 167 (57), 166 (100), 69 (81).

Heterocycle (**8**)

Red oil; $[\alpha]_D^{25} = -15°$ ($c = 0.6$, $CHCl_3$); UV (EtOH): $\lambda_{max}(\log \varepsilon) = 222$ (4.14), 349 (3.95), 469 (3.26) nm; IR: $\nu_{max} = 1730$, 1656, 1616, 1414 cm^{-1}; ^1H NMR: $\delta = 5.04$ (t septet, $J_{11,12} = J_{11',12} = 7.0$ Hz, $J_{12,14} = J_{12,15} = 1.4$ Hz, 1H, H-12), 4.16 (t, $J_{17,18} = 6.0$ Hz, 2H, CH_2-17), 3.68 (t, $J_{18,19} = 6.0$ Hz, 2H, CH_2-19), 3.01 (m, 3H, H-8), 2.11 (s, 3H, Me-7), 2.08 (quintet, $J_{17,18} = J_{18,19} = 6.0$ Hz, 2H, CH_2-18), 1.64 (s, 3H, Me-14), 1.53 (s, 3H, Me-15), 1.20 (d, $J_{8,9} = 7.0$ Hz, 3H, Me-9) ppm; ^{13}C NMR: $\delta = 177.9$ (s, C-3), 177.7 (s, C-4), 154.5 (s, C-1), 149.5 (s, C-16), 142.0 (s, C-6), 131.6 (s, C-13), 124.1 (d, C-12), 120.4 (s, C-2), 105.2 (s, C-5), 43.8 (t, C-17), 43.4

(t, C-19), 34.2 (t, C-10), 29.7 (d, C-8), 26.5 (t, C-11), 25.6 (q, C-14), 20.5 (t, C-18), 18.4 (q, C-9), 17.6 (q, C-15), 8.6 (q, C-7) ppm; EMS (20 eV): $m/z = 328$ (29, $[M^+]$), 246 (100), 218 (33), 217 (18).

6,6′-Thiobis-(3,3′-di-O-acetyl-perezone) (**12**)

Acetylation of **7** with AcCl and pyridine for 15 min at room temperature afforded **12** as a yellow oil which was purified by chromatography. $[\alpha]_D^{25} = -18.6°$ ($c = 0.65$, $CHCl_3$); UV(EtOH): $\lambda_{max}(\log \varepsilon) = 216$ (3.43), 280 (3.09) nm; IR: $\nu_{max} = 1774$, 1658, 1178 cm^{-1}; ^1H NMR: $\delta = 5.0$ (t septet, $J_{11,12} = J_{11',12} = 7.0$ Hz, $J_{12,14} = J_{12,15} = 1.4$ Hz, 1H, H-12), 2.89 (m, 1H, H-8), 2.34 (s, 3H, Me-Ac), 2.27 (s, 3H, Me-7), 1.64 (br s, 3H, Me-14), 1.55 (s, 3H, Me-15), 1.11 (d, $J_{8,9} = 7.0$ Hz, 3H, Me-9) ppm; ^{13}C NMR: $\delta = 182.0$ (s, C-1), 177.6 (s, C-4), 167.8 (s, Ac), 149.3 (s, C-3), 143.2 (s, C-6), 140.8 (s, C-2), 139.1 (s, C-5), 132.0 (s, C-13), 123.9 (d, C-12), 34.6 (t, C-10), 31.2 (d, C-8), 26.5 (t, C-11), 25.7 (q, C-15), 20.4 (q, Ac), 18.5 (q, C-9), 17.7 (q, C-14), 14.3 (q, C-7) ppm; EIMS (20 eV): $m/z = 610$ (1, $[M^+]$), 568 (1), 289 (6), 166 (79), 43 (100).

Reaction of **2** *with silica gel*

A solution of **2** (100 mg) in 7.0 ml of CH_2Cl_2 in the presence of 0.5 g of silica gel (230–400 mesh ASTM) was stirred at room temperature for 14 days. The solution was filtered, and the silica gel was washed with acetone. The combined solvents were evaporated to dryness, and the residue was chromatographed on silica gel using hexane-EtOAc (99:1) as eluent to yield 72 mg (72%) of **3** as white crystals (m.p.: 146–148°C; Ref. [13]: m.p.: 146–148°C). In another experiment, a solution of **2** (100 mg) in 7 ml of CH_2Cl_2 was heated under reflux for 8 days in the presence of silica gel (0.5 g). After work up as described previously, the residue was chromatographed on silica gel, eluting with hexane-AcOEt (95:5). The first fractions afforded 68 mg (68%) of **3**, whereas the last fractions yielded 14 mg (14%) of **4** whose physical data are in agreement with those reported [11].

^1H NMR: $\delta = 5.73$ (d, $J_{4,5} = 2.4$ Hz, 1H, H-4), 3.33 (s, 1H, OH), 2.85 (m, 1H, H-5), 2.12–1.96 (m, 2H, H-6 and H-7), 1.67 and 1.42 (s each, 3H, Me-10 and 11), 1.66 (s, 3H, Me-12), 1.63 (m, 1H, H-6′), 1.59 (dd, $J_{7,8} = 11.8$ Hz, $J_{7',8} = 3.5$ Hz, 1H, H-8), 1.18 (m, 1H, H-7′), 1.12 (d, $J_{5,13} = 7.0$ Hz, 3H, Me-13) ppm; ^{13}C NMR: $\delta = 189.8$ (s, C-3), 173.5 (s, C-1), 158.5 (s, C-4a), 120.9 (d, C-4), 106.9 (s, C-2), 93.8 (s, C-9), 71.6 (s, C-8a), 55.0 (d, C-8), 36.3 (t, C-7), 31.1 (d, C-5), 30.0 and 24.0 (q each, C-10 and C-11), 19.2 (t, C-6), 16.0 (q, C-13), 7.1 (q, C-12) ppm.

Reaction of **2** *with p-TsOH*

A solution of **2** (100 mg) and *p*-TsOH (10 mg) in 7 ml of CH_2Cl_2 was stirred at room temperature for 5 days, diluted with 30 ml of EtOAc, washed with H_2O, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was chromatographed over silica gel, eluting with hexane-AcOEt (95:5) to yield 82 mg (82%) of **4**, identical with the product obtained above.

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