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SYNTHESIS OF AN ALLYLIC SPIRO-LACTONE

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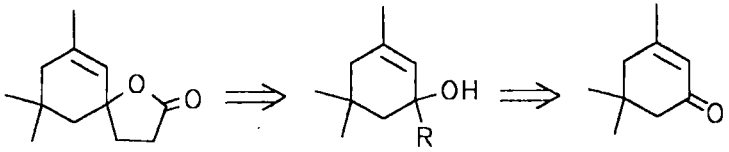
ABSTRACT: A synthesis of an allylic spiro-lactone (**1**) is described. Compound **1** is obtained in 5 steps from dimedone with an overall yield of 8.8%. The main feature of the synthesis is the transformation of compound **3** in **1**, which involves an water elimination accompanied by allylic rearrangement and lactonization.

Compound **1**, an allylic spiro-lactone, was required in our laboratory for studies on the ozonation reaction of substrates of unusual structures. Contrary to our expectations, the synthesis of compound **1** presented some very interesting problems. In fact, our first approach, based on the retrosynthetic route below (equation 1), was useless because of the marked tendency towards elimination presented by alcohols which are both tertiary and allylic such as in structure **2**.



1 **2** (1)

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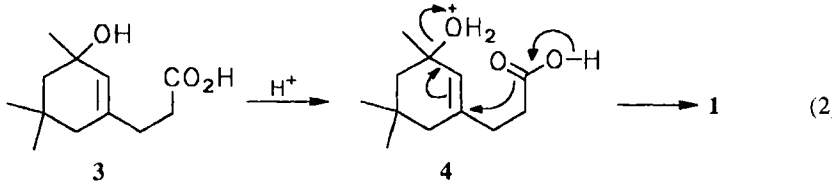
The particular structure of lactone **1**, however, allowed us to use in our profit this readiness of elimination through a modified approach (equation 2).

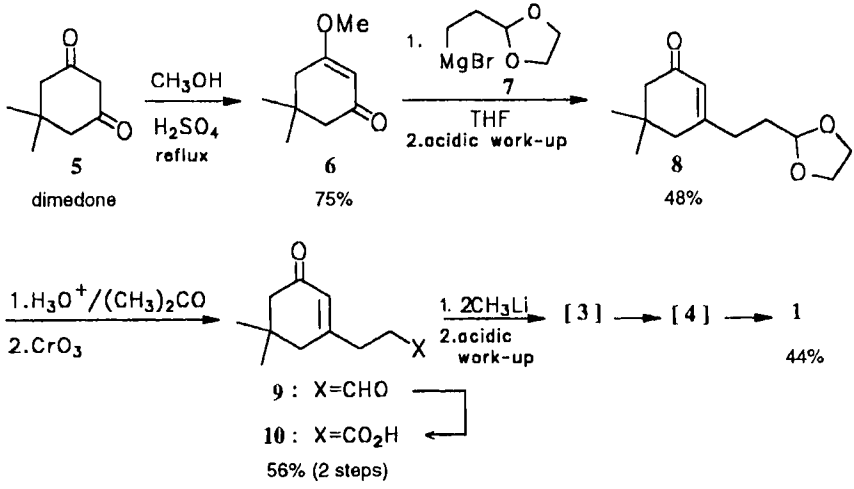


3 **4** (2)

Presumably, the favorable entropy contribution to the stability of lactone **1** is decisive for the feasibility of this synthesis.

In Scheme 1, the complete synthesis of compound **1** is depicted .

Scheme 1



In the first step, one of the keto groups of dimedone **5** is protected as its enol ether by treatment with methanol and acid.[1] The resultant compound **6** is then reacted with the Grignard reagent **7**;[2] the acid work-up of the reaction product promotes hydrolysis of the enol ether and elimination of the tertiary hydroxyl group in β to the ketone, affording directly product **8**. This Grignard reaction must be effected at relatively low temperature[3] (23°C) in order to avoid extensive transformation of the reagent **7** in cyclopropane derivatives.[4] Acidic hydrolysis of

the acetal group[5] of **8** gave aldehyde **9** which was oxidized with Jones reagent[6] to the acid **10**. The transformation of the keto acid **10** in compound **3** could not be carried out by a Grignard reaction in THF, probably because the formation of an insoluble salt of **10** prevented the completion of the reaction. With methyllithium in THF, instead, a soluble salt is formed and product **3** could be obtained. Compound **3**, however, was not isolated because of its sensitivity to the acidic work-up conditions, leading directly to lactone **1**. The desired lactone **1** was then obtained in 8,8% overall yield from dimedone.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 80MHz. The ^{13}C NMR spectra were recorded at 20MHz. A capillary containing C_6D_6 was used for field-frequency lock in NMR measurements for samples dissolved in CCl_4. Analytical gas chromatography (GLC) separations were performed on a 6ft x $^1/_8$ in. stainles steel column packed with 3% OV-17 silicone on Chromosorb W, operating at temperatures in the range 50-200°C. GC-MS spectra were obtained by EI ionization at 70eV. Given yields correspond to materials with the same purity as the samples used in the subsequent steps.

3-Methoxy-5,5-dimethyl-2-cyclohexen-1-one (6). A solution of concentrated H_2SO_4 (1.0mL) and dimedone (10.5g, 75mmol) in absolute methanol was heated to reflux for 6h. After cooling to room temperature, the solution was alkalized with some pellets of KOH and most of the methanol was removed by evaporation under vacuum. The residue was diluted with ethyl ether and water. The organic phase was separated and washed with saturated NaCl solution and dried with anhydrous K_2CO_3. The solution was concentrated under vacuum and the residue distilled to yield 8.5g (75%) of compound **6**: bp 120°C (10mmHg); IR (film) 1655, 1608, 1226, 1155 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.20 (br. s, 1H), 3.69 (s, 3H), 2.20 (s, 2H), 2.07 (s, 2H), 1.07 (s, 6H) ; ^{13}C NMR (CCl_4) δ 196.0, 175.0, 101.0, 55.3, 50.6, 42.6, 32.2, 28.2; MS *m/e* (rel intensity) 154 (M^+, 20), 139 (5), 111 (4), 98 (100), 79 (4), 68 (65), 55 (4).

5,5-Dimethyl-3-[2-(1,3-dioxolan-2-yl)-ethyl]-2-cyclohexen-1-one (8). Magnesium (turnings) (1.6g) was activated, in dry THF (40mL), with iodine and 1,2-dibromoethane. After starting of the reaction, a solution of 2-(2-bromoethyl)-1,3-dioxolane (10.9g, 60mmol) in dry THF (15mL) was added dropwise while the temperature of the reaction mixture was maintained below 23°C by external cooling. When the addition was complete, stirring at the same temperature was continued for a further 1h. Then a solution of compound **6** (4.6g, 30mmol) in THF (9mL) was added in the course of 1.5h and the mixture was allowed to stand overnigth, always below 23°C and under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl, the product was extracted with ethyl ether and the organic solution was dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel eluting with ether-hexane (8:2), giving compound **8** (3.2g, 48%) as a colorless liquid: IR (film) 1666, 1625, 1138cm^{-1}; ^1H NMR (CCl_4) δ 5.75 (br. s, 1H), 4.80 (t, 1H, J=4.0Hz), 3.97-3.68 (m, 4H), 2.43-2.10 (m, 2H), 2.18 (s, 2H), 2.10 (s, 2H), 1.95-1.60 (m, 2H), 1.05 (s, 6H); ^{13}C NMR (CCl_4) δ 196.3, 160.1, 124.7, 103.2, 64.6, 50.7, 43.8, 33.3, 31.7, 31.0, 28.2.

5,5-Dimethyl-3-oxo-1-cyclohexene-1-propanaldeyde (9). Compound **8** (3.2g, 14mmol) was added to a solution of 2M aqueous HCl (20mL) in acetone (150mL). After stirring at room temperature for 40h, the reaction mixture was neutralized by addition of saturated $NaHCO_3$ solution. Acetone was removed under vacuum and the resultant aqueous solution was extracted with ether. The organic phase was washed with saturated brine and dried with $MgSO_4$. The crude product was purified by column chromatography in silica gel eluting with ether-hexane (8:2), giving compound **9** (1.8g, 69%) as a colorless liquid: IR (film) 2731, 1725, 1666, 1650cm^{-1}; ^1H NMR (CCl_4) δ 9.75 (s, 1H), 5.74 (s, 1H), 2.80-2.35 (m, 4H), 2.22 (s, 2H), 2.12 (s, 2H), 1.02 (s, 6H); ^{13}C NMR (CCl_4) δ 199.1, 197.4, 160.6, 124.5, 50.8, 43.8, 40.5, 33.4, 29.7, 28.2; MS *m/e* (rel intensity) 180 (M^+, 7), 165 (6), 152 (18), 147 (24), 123 (18), 109 (4), 96 (53), 82 (100), 67 (34), 53 (15).

5,5-Dimethyl-3-oxo-1-cyclohexene-1-propanoic acid (10). To a solution of compound **9** (2.3g, 13mmol) in acetone[7] (15mL), maintained under stirring in on ice bath, was added dropwise a solution CrO_3 (2.9g, 29mmol) and concentrated

H_2SO_4 (4.6g, 2.5mL) in water (to complete 14mL), until the orange color of the Jones reagent was no longer discharged. The mixture was then stirred at room temperature for a further 2h period. The acetone was then removed under vacuum, the residue was diluted with ether and water, the organic phase was separated and the aqueous phase was extacted twice with ether. The combined organic phases were extracted with a saturated aqueous $NaHCO_3$ solution and discarded, The aqueous solution of the organic salt was then acidified with dilute HCl (1 volume of concentrated HCl to 1 volume of water), and extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum to give product **10** as a colorlees liquid (2.1g, 81%): IR (film) 3060, 1737, 1660, 1631cm^{-1}; ^{1}H NMR (CCl_4) δ 10.14 (br s, 1H), 5.85 (br s, 1H), 2.50 (s, 4H), 2.18 (s, 4H), 1.03 (s, 6H); ^{13}C NMR (CCl_4) δ 198.6, 175.8, 160.9, 124.5, 50.5, 43.9, 33.4, 32.3, 31.0, 28.2,; MS *m/e* (rel intensity) 181 (M^+,20), 163 (75), 151 (12), 135 (31), 121 (51), 112 (100), 94 (54), 67 (41), 55 (27).

7,9,9-Trimethyl-1-oxaspiro-[4.5]-6-decen-2-one (1). To a solution of compound **10** (0.208g, 1.06mmol) in dry THF (4.0mL) maintained at 0°C under nitrogen atmosphere was added a 1.51M solution of methyllithium in ether (1.45mL, 2.2mmol). After stirring for 1h at room temperature, saturated aqueous NH_4Cl solution (3mL) was added. The reaction mixture was diluted with ether and saturated NH_4Cl solution, the organic phase was separated and washed once and again with saturated NH_4Cl until the aqueous phase remained slighthy acidic. The organic solution was then dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate-hexane (7:3) to yield compound **1** (91.1mg, 44%) as a colorless liquid: IR (film) 1766, 1673, 1178cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.45-5.34 (m, 1H), 2.72-1.93 (m, A_2B_2 system, 4H), 1.82-1.45 (m, 7H), 1.01 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.9, 139.3, 121.4, 85.2, 47.5, 44.1, 35.7, 30.4, 30.2, 28.7, 27.7, 23.8; MS *m/e* (rel intensity) 194 (M^+, 20), 179 (8), 161 (19), 139 (77), 121 (53), 119 (100), 91 (65), 77 (45), 55 (28).

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References and Notes

1. Beringer, M.; Kuntz, I. *J. Am. Chem. Soc.* **1951**, *73*, 364-366.

2. (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122-1123.
(b) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409-435.

3. Sworin, M.; Neumann, W.L. *Tetrahedron Lett.* **1987**, *28*, 3217-3220.

4. *Methoden der Organischen Chemie* (Houben-Weyl), vol. XIII/2a, 1973, p 118.

5. Cummins, W.J.; Drew, M. G. B.; Mann, J.; Markson, A. J. *Tetrahedron* **1980**, *44*, 5151-5160.

6. Haines, A. H. *Methods for the Oxidation of Organic Compounds* ; Academic Press: London, 1988.

7. Acetone was destilled from potassium permanganate.

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