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A NEW METHOD FOR METHYLENEATION OF BUTYROLACTONES

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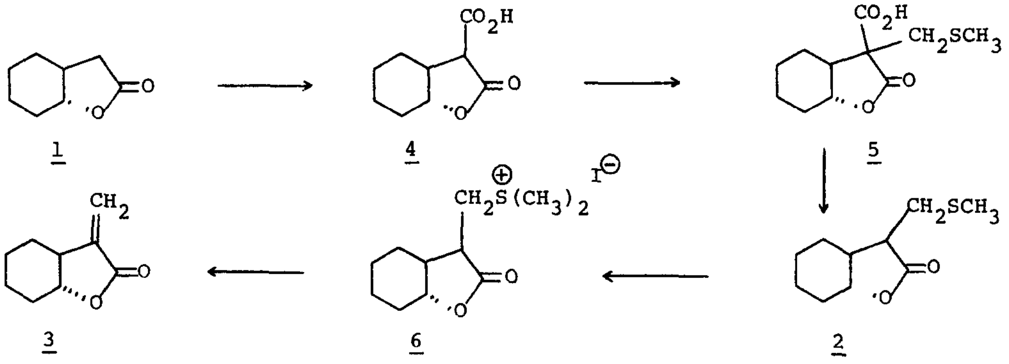
The frequent occurrence of α-methylene lactones in sesquiterpenes of biological interest has resulted in a continued interest in methods for their synthesis. Although a number of syntheses have been developed,[2] a method which would allow construction of the α-methylene moiety in a stable, protected form would be very useful in the synthesis of some of the highly functionalized sesquiterpenes.

Recently, Kupchan and co-workers devised a method for protection of the α-methylene group of α-methylene lactones by thioether formation.[3] These β-thioethers are quite stable and the methylene group is easily regenerated by alkylation to give the sulfonium salt, followed by mild base catalyzed β-elimination. The stability and facile removal of these thioethers suggested that they could be applied to a synthesis of α-methylene lactones in masked form.

Lactones, when treated with strong amide bases, can be converted to the corresponding enolate anions and efficiently alkylated or acylated.[4] It was envisioned that an α-halosulfide could be used to alkylate a lactone enolate; however, when the lithium enolate of lactone 1 in tetrahydrofuran (THF) was treated with either chloro- or iodomethyl methylsulfide, with or without, hexamethylphosphoramide (HMPA) cosolvent at temperatures varying from -78° to 25° no more than a trace (<5%) of the desired thiomethyl methyl lactone 2 was obtained. The majority of the material appeared to be condensation products. The results of Posner and Loomis[4a] suggested that with simple unhindered lactones the rate of condensation is competitive with alkylation and that good yields of mono-alkylation products are obtained only when there is sufficient excess base present to convert these mono-alkylated lactones to their stable enolate anions. This, of course, is not practical with lactone 2 as excess strong base results in β-elimination of methyl mercaptide and formation of the α-methylene lactone 3 which is an efficient Michael acceptor.

In order to activate the lactone towards alkylation and to remove any possibility of enolization after alkylation, lactone 1 was converted to the corresponding malonic acid derivative by carboxylation of the enolate anion with dry CO_2 at -78°. Thus, lactone 1 (1-4mmoles) was added slowly to a solution containing an equivalent amount of lithium N-isopropylcyclohexylamide[5] in THF at -78°. After 40 minutes at -78° dry CO_2 (Matheson) was bubbled in as the solution was allowed to warm to room temperature. Upon acidification an oily mixture of acids 4 was obtained in >95% yield. The nmr spectrum of this mixture showed two doublets for the α-methine proton, 3.35 δ (J=13Hz) minor isomer, and 3.50 δ (J=8Hz) major isomer. Recrystallization of the crude product from water converted the mixture completely to the 3.35 δ isomer which was identical with the acid obtained by Newman and VanderWerf[6] from hydrolysis of the product from reaction of cyclohexene oxide and diethyl sodiomalonate.

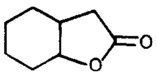


Treatment of acid 4 with two equivalents of lithium diisopropylamide in THF at -78° resulted in rapid precipitation of the dianion. The mixture was allowed to warm to room temperature, then HMPH was added to give a 10% solution in THF followed by an equivalent of iodomethyl methyl sulfide.[7] The dianion rapidly reacted producing a clear yellow solution, acidification of which gave the desired acid 5 in >95% yield. Recrystallization from CCl_4- hexane produced white plates mp 101-104°.[8]

The protecting carboxylate group was smoothly removed by refluxing acid 5 in xylene. The (methylthio)-methyl lactone 2 was obtained in 86% yield, after chromatography on Silica Gel to separate the xylene followed by "short-path" distillation (100°/0.01mm). Direct distillation of the reaction mixture resulted in lower yields (ca. 50%) and some elimination to form the methylene lactone 3.

The methylthio group of lactone 2 was removed liberating the methylene lactone 3 in a simple two step procedure. The lactone 2 was refluxed in excess methyl iodide under a nitrogen atmosphere for 36 hours. The sulfonium iodide 6 slowly precipitated as an amorphous cream colored solid which was separated by filtration, triturated with ether, and dried *in vacuo* (>95% yield). The crude salt was then suspended in 5% aqueous sodium bicarbonate overlaid with ether. When the salt had all dissolved (5 hours) the ether layer was dried and concentrated yielding the methylene lactone 3 as a crystalline solid (95% yield). An analytical sample, mp 39-41°, was obtained after two recrystallizations from hexane, and was shown to be identical (ir, nmr, tlc, vpc, mixed mp, elemental analysis) to an authentic specimen.[9]

This same sequence of reactions was also applied to the *cis*-lactone 7, because sesquiterpenoid butenolides occur frequently with both the *cis* and *trans* fusion of the lactone ring. Thus the *cis*-methylene lactone 8 was obtained as an oil ("short-path" distillation, 90°/0.05mm) in comparable overall yield and it had the same physical and spectral characteristics as those reported.[2b,c]



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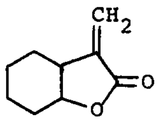

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5. Prepared by adding standardized butyllithium to excess amine.
6. M. S. Newman and C. A. VanderWerf, JACS, 67, 233 (1945).
7. Generated in situ from chloromethyl methyl sulfide (Aldrich) and anhydrous lithium iodide.
8. Analytical and spectral data consistent with the expected structures were obtained for all new compounds.
9. The author thanks Prof. R. B. Miller (University of California-Davis) for a sample of the trans-methylene lactone 3.