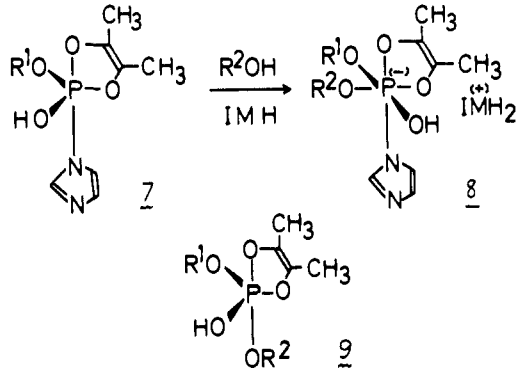
mary vs. the secondary hydroxyl functions of the diol is 98:2; the previous synthesis[4a] of **6**, without triethylamine, involved a 90:10 selectivity.

The best results in these procedures are obtained when the bulkier alcohol is introduced first (R^1OH), whenever possible. Although many alcohol pairs have been used successfully, some combinations of steric and electronic features in R^1 and R^2 result in the formation of some symmetrical acyclic triesters. Another limitation is the formation of some alkyl (1-methylacetonyl) phosphates in the hydrolysis of **3**.

We speculate that the amine catalysis of the phosphorylation involves intermediates with penta- and hexacoordinate[6] phosphorus, **7** and **8**, the former being involved in the rate-controlling step. Decomposition of **8** generates the phosphorane intermediate **9**, which is assumed to be formed in the uncatalyzed reaction. Triethylamine could act in



the same manner, but via dipolar ions[6] analogous to **7** and **8**. The selectivity and the lower efficiency of triethylamine (pK_B = 3.0) vs. imidazole (pK_B = 6.9) may be due in part to the higher steric requirements of the former; quinuclidine (pK_B = 2.9), in fact, resembles imidazole, rather than triethylamine, in catalytic pattern. Tetramethylguanidine (pK_B = 0.4) is also an effective catalyst in these reactions. The presence of histidine, arginine, and lysine residues in hydrophobic active sites of enzymes that catalyze reactions of phosphates could facilitate the addition of nucleophiles to tetracoordinate phosphorus by similar mechanisms.

The techniques described here, and others recently introduced,[4] provide considerable flexibility in approaches to complex biological phosphodiesters, such as oligonucleotides and phospholipids; the latter, in high degree of purity, are required for studies on membrane structure.

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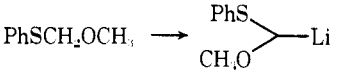
New Synthetic Methods. A Ring Expansion Approach to α-Methylene δ-Lactones

Sir:

Attention has been focused on the synthesis of α-methylene γ-butyrolactones because of their importance as a structural unit of many antitumor agents.[1] The presence of an α-methylene δ-lactone in the growth inhibitory elemanolide sesquiterpenes vernolepin, vernodalin, and vernomenin[2] has led to several approaches to this system too,[1,3] but most commonly by cleavage of cycloalkanone rings. Our interest in these terpenes, as well as related biologically important natural products like pentalenolactone[4] and the quassinoids,[5] led us to consider new approaches based upon the ring expansion of the easily accessible γ-butyrolactones. This work delineates three such approaches as well as demonstrates the utility of lithiated methoxymethyl phenyl thioether as an acyl anion equivalent.[6]

The γ-butyrolactone **1a** was readily available by the metal hydride reduction of the Diels–Alder adduct of 2,3-dimethylbutadiene and maleic anhydride[7] (see Scheme I). Methylation of the corresponding enolate utilizing lithium diisopropylamide in THF (−78°) and methyl iodide[8] provided **1b**, mp 30–31°.[9] Addition of bis(phenylthio)methyllithium[10] to **1a** in THF at 0° caused mainly enolization, but **1b** gave the adduct **2b**[9] (X = PhS) quantitatively. Conversion of the latter to **3b**[9] was effected with silver nitrate and *N*-chlorosuccinimide in methanol buffered with collidine at 0° (40%).[11a] *p*-Toluenesulfonic acid monohydrate (PhH, 50°) rearranged **3b** to **4b**,[9] mp 74–75° (ir 1735 cm^{-1}; NMR two methines at δ 4.30 and 4.34 and two CH_3O at δ 3.36 and 3.39, 36%). Methylenation to **5b** via the Wittig reaction (DME, room temperature), hydrolysis (5% aqueous HCl:THF 1:4, room temperature), and oxidation (manganese dioxide, methylene chloride, room temperature) completed the sequence in 54% overall yield of pure isolated product[9] (**6b**, ir 1733 cm^{-1}; NMR CH_2O at δ 4.24 and $=CH_2$ at δ 5.54 and 6.38).

The use of methoxyphenylthiomethyllithium (**7**), available by treatment of methoxymethyl phenyl thioether[12] with *n*-butyllithium in THF at −30°, proved superior.[13] It added in 88% yield to **1a** and in quantitative yield to **1b** to give **2a**[9] and **2b**[9] (X = OCH_3), respectively. Mercuric chloride–red mercuric oxide[11] in methanol at room temperature transacetalized the latter to give **3b** (60%) identical with the material obtained by the previous route.

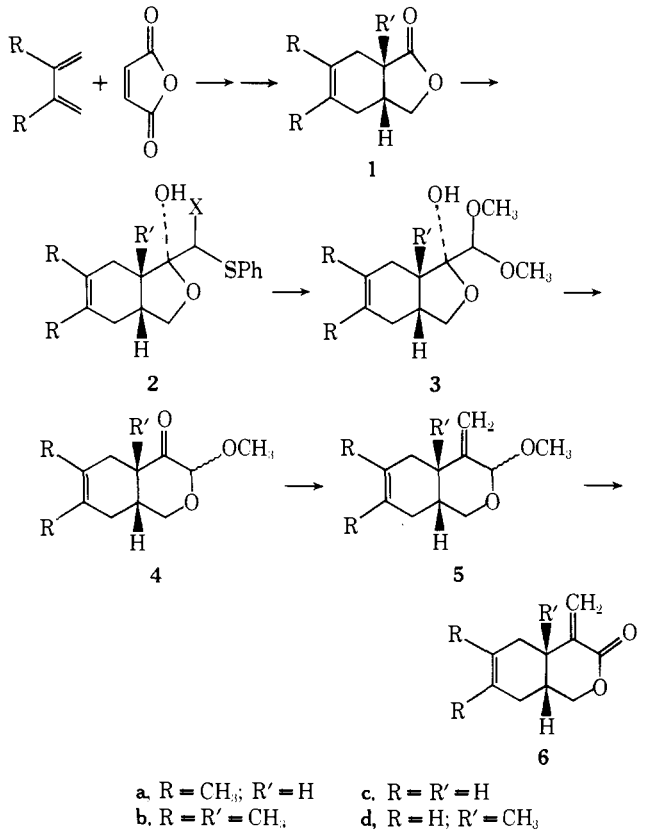


7

Addition of **7** to **1d**[9] (mp 43–47°), available from **1c** by a sequence analogous to that for **1b**,[7] gave **2d**[9] (X = OCH_3) in 91% yield. Heating a solution of the latter in methanol containing iodine at 50° gave **3d**[9] in 71% yield.[14] Ring expansion as above gave the key tetrahydropyran-3-one (**4d**)[9] in 69% yield (ir 1735 cm^{-1}; NMR two methines at δ 4.32 and 4.35 and two methoxyls at δ 3.39 and 3.37). Conversion of **4d** to **6d**[9] proceeded in identical fashion to the preparation of **6b** in an overall yield of 56% (**6d**, ir 1733 cm^{-1}; NMR CH_2O at δ 4.20 and $=CH_2$ at δ 5.52 and 6.31).

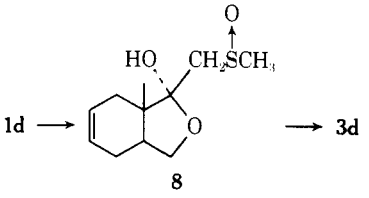
An alternative approach makes use of the Pummerer reaction[15] as the key step. Dimsyllithium, prepared by the addition of *n*-butyllithium to a solution of DMSO in THF,[16] adds to **1d** in THF at 10°. Treatment of this adduct **8**[9] with iodine in refluxing methanol gives **3d** which, when subjected to a catalytic amount of TsOH in benzene at 50°, is converted into the key tetrahydropyran-3-one (**4d**) exclu-

Scheme I. Approach A for the Synthesis of α-Methylene δ-Lactones

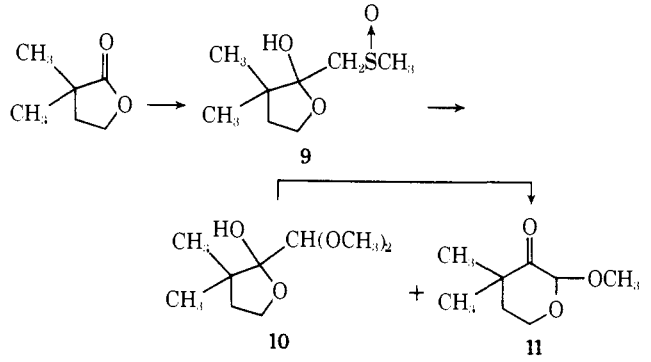


a, R = CH_3; R′ = H c, R = R′ = H
b, R = R′ = CH_3 d, R = H; R′ = CH_3

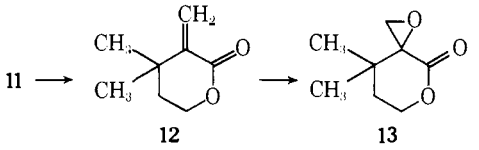
sively in 49% overall isolated yield from **1d**. The latter is identical with the sample prepared from **2d** (X = OCH_3).



The Pummerer sequence was also applied to the conversion of 2,2-dimethyl-γ-butyrolactone to 3,3-dimethyl-2-methylene-δ-lactone. In this case, the Pummerer rearrangement of the adduct **9**[9] utilizing iodine in methanol gave a 1:1 mixture of **10** and **11**. Brief treatment of this mixture



with neat trifluoroacetic acid at 0° followed by immediate rotoevaporation in vacuo converted the mixture into the desired tetrahydropyran-3-one (**11**)[9] exclusively (ir 1730 cm^{-1}; NMR methine at δ 4.38 and methoxyl at δ 3.41) in 40% overall isolated yield based on γ-butyrolactone. The standard sequence of methylenation, hydrolysis, and oxidation completed the conversion to the desired α-methylene δ-lactone **12**[9] (ir 1725 cm^{-1}; NMR CH_2O at δ 4.28 and $=CH_2$ at δ 5.54 and 6.25). The reactivity of this system was demonstrated by the facile nucleophilic epoxidation (sodium carbonate, hydrogen peroxide, methanol, 0°) to give the epoxy lactone **13**.



These sequences provide convenient methods for the conversion of the readily available γ-butyrolactones to α-alkoxy or α-methylene δ-lactones found in the previously mentioned cytotoxic agents especially with respect to control of stereochemistry based on the Diels–Alder reaction.

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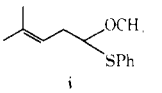

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