71564-05-1; **4a**, 71516-94-4; **4b**, 71516-95-5; **4c**, 71516-96-6; **5a**, 71549-35-4; **5b**, 71516-97-7; **5c**, 71516-98-8; **5d**, 71516-99-9; **6a**, 71517-00-5; **6b**, 71517-01-6; **6c**, 71517-02-7; **6d**, 71517-03-8; **6e**, 71517-04-9; **7a**, 71517-05-0; **7b**, 71517-06-1; **7c**, 71517-07-2; **7d**, 71517-08-3; **7e**, 71517-20-9; **8a**, 71517-09-4; **8b**, 71517-10-7; **8c**, 71517-11-8; **8d**, 71517-12-9; **8e**, 71517-13-0; **9a**, 71517-14-1; **9b**, 71517-15-2; **9c**, 71517-16-3; **9d**, 71517-17-4; **9e**, 71517-18-5; **11**, 67495-99-2; **12**, 71517-19-6; $(C_6H_5)_3PCHCO_2CH_3$, 2605-67-6.

Supplementary Material Available: Full spectroscopic data for compounds **2a,b**, **3a,b**, **4a**, **5a,b**, **7a,b**, **8a,b**, and **9a,b** and a brief discussion of pertinent structural data (2 pages). Ordering information is given on any current masthead page.

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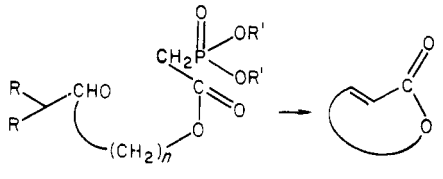
Large-Ring Lactones by Internal Ketophosphonate Cyclizations

Summary: The intramolecular cyclization of phosphonoacetates of hydroxycarbonyl compounds is a useful method for the construction of macrocyclic α,β-unsaturated lactones of 13 and more carbon atoms and of varying degrees of substitution.

Sir: The existence of a variety of macrocylic lactones in natural products had led to a number of methods for their construction. These methods almost always use the lactonization step itself, by suitable activation of the carboxyl group, for the construction of the lactone ring.[1]

We have examined the possibility of forming macrocylic lactones by closing the ring at the carbon α to the ester



linkage by an internal version of the phosphonoacetic ester method.[2] The process would, of course, be especially useful when, as in many of the cytochalasins,[3] the desired system actually is a trans α,β-unsaturated lactone, since this should be the primary result of this type of cyclization.[4] It should be valuable in the construction of lactones involving particularly hindered hydroxyl groups, since the cyclization step is effected at a distance from that function.

The use of ketophosphonates in intramolecular cyclization has been demonstrated previously for the synthesis of five- and six-membered lactams,[5] lactones,[6] and cyclenones.[7] A very recent publication actually describes the use of the reaction in the construction of a 26-membered ring lactone.[8] This particular case, reported after our own work had been completed, involved a precursor in which the substitution pattern imposed considerable rigidity, thereby facilitating ring closure, and the conditions which were effective in that instance were not suitable, in our hands, for the general case. It is important to note that the most difficult cyclizations will, in general, involve the least-substituted precursors (more degrees of freedom). Our aim was, therefore, to find conditions which would give reasonable yields with most precursors.

We now report that the phosphonoacetate cyclization is indeed a viable method for the construction of lactones with rings of 13 or more members. Considerable experimentation was necessary before reasonably satisfactory conditions could be defined; in particular, it was surprising to find that, in a number of instances, appreciable quantities of cyclic dilactones were formed via intermolecular condensation of the aldehydophosphonates. This was true even when high dilution conditions supposedly had been achieved by the very slow introduction (see below) of the aldehydophosphonate to the cyclizing medium.

It was eventually found that lithium bases (either as lithium hexamethyldisilazane or as lithium isopropoxide) in tetrahydrofuran (THF) containing ~1% of hexamethylphosphoramide (HMPA) were able to bring about the desired formation of cyclic lactones.[9,10] Under these conditions, the amount of (dimeric) dilactones formed was usually 1% or less. By this process, the aldehydophosphonoacetate **1** gave the 13-membered ring α,β-unsaturated lactone **2**,[11] while the apposite phosphonates led to **3**[12] and **4** all in 60–70% yields. The 14-membered *tertiary* lactone **5** (a ~7:1 mixture of *E* and *Z* isomers) and the 15-membered lactone **6** were similarly obtained in 40–50% yields.

A detailed experimental procedure is given below for the cyclization of **1** to **2**.

To a stirred solution of HMPA (0.5 mL) in 50 mL of THF kept under argon at room temperature were added simultaneously, by means of motor-driven syringes, a 5-mL solution of the phosphonate **1** (175 mg, 0.5 mM) in 1:1 THF–benzene and a 5-mL THF solution containing 0.55

(1) For recent reviews, see Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683–710. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585–613. Back, T. G., *Tetrahedron* **1977**, *33*, 3041–3059.
(2) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, Chapter 2.
(3) For synthesis and references see Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775–7777.
(4) Another noteworthy approach to α,β-unsaturated macrolides is illustrated by the recent work of Takahashi, T.; Hahiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424–7425.
(5) Matthews, R. S. Ph.D. Thesis, Columbia University, 1967. Stork, G.; Matthews, R. S. *Chem. Commun.* **1970**, 445–446.
(6) Lehmann, H. G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 300–301.
(7) Henrick, C.; Bohme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.*, **1968**, *90*, 5926–5927.
(8) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071. A ketophosphorane has been used to make a 12-membered unsaturated lactone: Wilson, K. E. Ph.D. Thesis, University of Alberta, 1973, as quoted by S. Masamune, ref 1. Some of our results were communicated at the Leermakers Symposium on Synthesis, Wesleyan University, 1977.
(9) The use of a hindered silicon base (Kuwajima, I.; Soto, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817–1820) did not give significantly higher yields than simpler bases.
(10) The following general observations were made: the use of sodium or potassium counterions was much less satisfactory than lithium; the (desirable) presence of HMPA made the reaction rather insensitive to the bulk solvent; satisfactory results were obtained with benzene as well as with tetrahydrofuran.
(11) All compounds gave mass spectra and NMR spectra ($CDCl_3$) in accord with indicated structures.
(12) In this case, the lactone was obtained as a 3:2 mixture of *E* and *Z* isomers. The *E* compound had the longer retention time on 1.5% OV-101. Particularly characteristic was the NMR of the vinyl hydrogen β to the carbonyl: δ 6.96 (dt, J = 8, 15.5 Hz) for the *E* and δ 5.98 (dt, J = 8, 11 Hz) for the *Z* isomer. The *E* compound was also made by the method of Yamamoto: Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705–7707.

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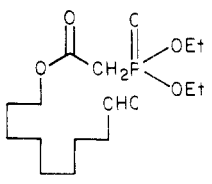

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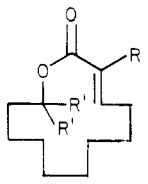
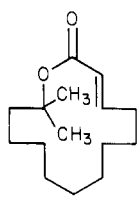


2, R = R' = H
3, R = CH_3; R' = H
4, R = H; R' = CH_3



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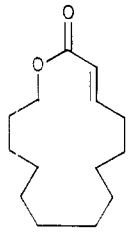

6

mmol of lithium isopropoxide.[13] The addition was carried out over a 15-h period. After an additional hour, 0.5 mL of acetic acid was added, and the bulk of the solvent was removed on a rotary evaporator. The residual oil was diluted with 25 mL of 20% ether in petroleum ether, washed with water (3 × 5 mL), saturated bicarbonate, and salt solutions, dried, and concentrated to give, after purification by chromatography on 0.8 g of silica gel (petroleum ether/benzene), 64.5 mg (66% yield) of the lactone **2**: R_f (benzene) 0.42; IR ($CHCl_3$) 1710, 1645 cm^{-1}; mass spectrum 196 (M^+); NMR δ 4.30 (t, J = 5 Hz, CH_2O), 5.82 (dt, J = 1, 16 Hz, COCH=CH), 7.04 (dt, J = 8, 16 Hz, COCH=CH). The structure was further confirmed by hydrogenation to the saturated lactone, identical in all respects with authentic tridecanolide.

The aldehydophosphonoacetates were prepared by three different methods: the precursors of the 13-membered lactones **2**, **3**, and **4** were made by transformation of 10-undecenol, or its 2,2-dimethyl homologue (CH_3MgBr on ethyl 10-undecenoate), into the diethylphosphonoacetate (esterification with the appropriate α-bromo acid bromide, in the presence of dimethylaniline in the case of the tertiary alcohol,[14] followed by Arbuzov reaction with triethylphosphite), which could then be ozonized (Zn–acetic acid workup) to the desired aldehydophosphonate of **1**.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for supporting this work and Dr. Y. Nakahara for some early experiments on this approach.

Registry No. 1, 71518-32-6; 2, 71518-33-7; (*E*)-3, 71518-34-8; (*Z*)-3, 71518-35-9; 4, 71518-36-0; (*E*)-5, 71518-37-1; (*Z*)-5, 71518-38-2; 6, 69008-83-9; 10-oxodecyl 2-(diethoxyphosphinyl)propanoate, 71518-39-3; 1,1-dimethyl-10-oxodecyl (diethoxyphosphinyl)acetate, 71518-40-6; 1,1-dimethyl-11-oxoundecyl (diethoxyphosphinyl)acetate, 71518-41-7; 12-oxododecyl (diethoxyphosphinyl)acetate, 71518-42-8.

(13) Yields fell rapidly when the cyclizations were run in more concentrated solutions.

(14) Abramovitch, B.; Shivers, J. C.; Hudson, B. E.; Hauser, C. R. *J. Am. Chem. Soc.*, **1943**, *65*, 986.

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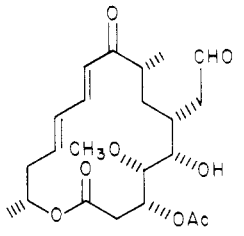
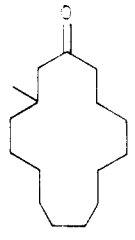
Synthesis of Macrocycles by Intramolecular Ketophosphonate Reactions. Stereoselective Construction of the "Left-Wing" of Carbomycin B and a Synthesis of *dl*-Muscone from Oleic Acid

Summary: Macrolides and macrocarbocycles are formed in good yields by intramolecular ketophosphonate reactions. The method is applied to the synthesis of the "left-wing" of carbonolide B and *dl*-muscone.

Sir: We have recently described a stereoselective construction of the "right-wing" of the 16-membered ring macrolide antibiotics carbomycins A and B and leucomycin A_3.[1] In connection with this and other projects, we initiated a program directed toward the synthesis of macrocycles by C–C bond formation.[2,3] Previous isolated examples[4d,e] indicated that internal Wittig type reactions might be useful and general procedures for forming unsaturated macrocycles. In this communication we wish to report our results on the synthesis of macrolides[2] and macrocarbocycles by an intramolecular ketophosphonate reaction,[4] including the successful and stereoselective construction of the "left-wing" of carbonolide B (**1**)[5] and a synthesis of *dl*-muscone (**2**)[6] from oleic acid.



carbonolide B (1)



muscone (2)

Ozonolysis (O_3, AcOH–CH_2Cl_2, $(CH_3)_2S$) of oleic acid methyl ester provided the aldehyde **3**[7] (70%) from which the ketal acid **5** was obtained (90% overall) by sequential ketalization (ethylene glycol, TsOH, benzene, reflux), to afford **4**, and saponification (LiOH, aqueous MeOH). This carboxylic acid provided a simple "right-wing" model support onto which the "left-wing" of carbonolide B (**1**) was built as follows. 2-Hydroxybutyraldehyde was condensed with (carbethoxymethylene)triphenylphosphorane to afford the hydroxy ester **6** (80%), protection of which with dihydropyran under acidic conditions provided the tetrahydropyranyl ether **7** (86%). Reduction of **7** with

(1) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327–2330.

(2) For reviews on the synthesis of macrolides see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683–710. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585–607. Back, T. G. *Tetrahedron* **1977**, *33*, 3041–3059.

(3) For some recent macrolide syntheses involving C–C bond formation see: (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867–3868. (b) Trost, B. M.; Verhoeven, T. R. *Ibid.* **1979**, 101, 1595–1597. (c) Maruaka, K.; Hashimoto, S.; Kitagawa, Y.; Yamomoto, H.; Nozaki, H. *Ibid.* **1977**, *99*, 7705–7707. (d) Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *Ibid.* **1978**, *100*, 7424–7425.

(4) For previous ring-forming reactions involving ketophosphonates see: (a) Stork, G.; Matthews, R. *Chem. Commun.* **1970**, 445–446. (b) Henrick, C.; Bohme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926–5927. (c) Lehmann, H. G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 300–301. (d) Reference 2b, pp 591 and footnote 69. (e) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071. See also Stork, G.; Nakamura, E. *J. Org. Chem.*, preceding paper in this issue.

(5) Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826–5827.

(6) For previous syntheses of muscone see: (a) Stork, G.; McDonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264–1265, and references cited therein. (b) Fristad, W. E.; Dime, D. S.; Bailey, T. R.; Paquette, L. A. *Tetrahedron Lett.* **1979**, 1999–2002, and references cited therein.

(7) Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1926**, *48*, 1074–1080.

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