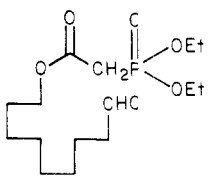
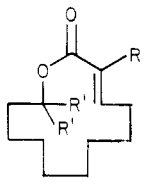
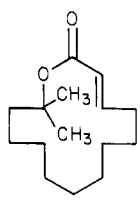


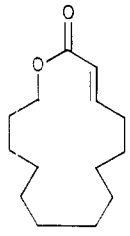
1



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



5



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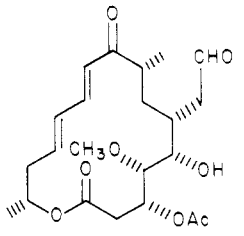
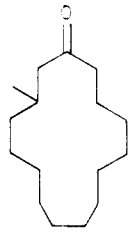
Synthesis of Macrocycles by Intramolecular Ketophosphonate Reactions. Stereoselective Construction of the "Left-Wing" of Carbomycin B and a Synthesis of *dl*-Muscone from Oleic Acid

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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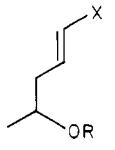
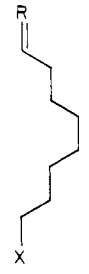
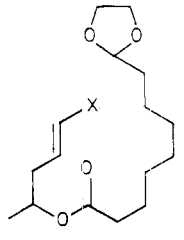
excess DIBAL led to the alcohol **8** (100%), which was protected as the *tert*-butyldiphenylsilyl ether **9** (Ph_2-*t*-BuSiCl–imidazole–DMF, 88%) before liberation of the secondary hydroxy group (AcOH–THF–H_2O, 3:2:2, 45 °C) to give **10** (75%).



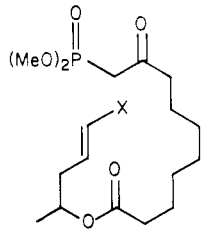
6, R = H; X = COOEt
7, R = THP; X = COOEt
8, R = THP; X = CH_2OH
9, R = THP; X = CH_2OSi-*t*-$BuPh_2$
10, R = H; X = CH_2OSi-*t*-$BuPh_2$



3, R = O; X = $COOCH_3$
4, R = $-OCH_2CH_2O-$; X = $COOCH_3$
5, R = $-OCH_2CH_2O-$; X = COOH
16, R = $-OCH_2CH_2O-$; X = CHO



11, X = CH_2OSi-*t*-$BuPh_2$



12, X = CH_2OSi-*t*-$BuPh_2$
13, X = CH_2OH

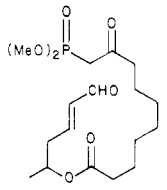
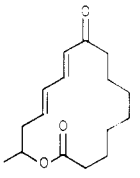
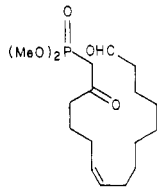
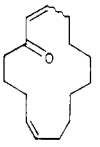
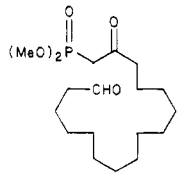
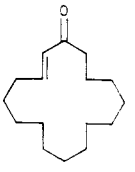
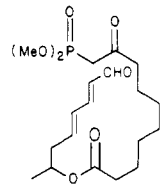
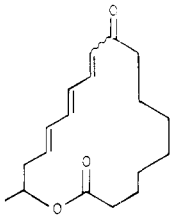
Combination of **5** and **10** with DCC in the presence of *N*,*N*-dimethylaminopyridine[8] in ether produced the ester **11** in 93% yield. Liberation of the aldehyde from **11** proceeded quantitatively (AcOH–THF–H_2O, 3:2:2, 45 °C) and was followed by reaction with the lithium derivative of dimethyl methylphosphonate (1.6 equiv, THF, −78 °C) and pyridinium chlorochromate oxidation to furnish the ketophosphonate **12** (40% overall). The requisite α,β-unsaturated aldehyde **14** (Table I) was obtained via the allylic alcohol **13** by desilylation (pyridinium hydrofluoride–THF) followed by oxidation (pyridinium chlorochromate) in 50% overall yield from **12**.

Cyclization of **14** to **15** (Table I) proceeded smoothly in DME with NaH under high dilution conditions (syringe pump) at 25 °C. The dienone **15** obtained in 70% yield and containing the complete "left wing" of carbonolide B (**1**) was proven by ^1H NMR spectroscopy to be geometrically homogeneous (trans,trans) [360 MHz, $CDCl_3$, τ 2.98 (dd, J = 15.5, 10.5 Hz, 1 H, H_β), 3.80 (d, J = 15.5 Hz, 1 H, H_α), 3.83 (dd, J = 15.5, 10.5 Hz, 1 H, H_γ), 3.94 (ddd, J = 15.5, 9.2, 5.3 Hz, 1 H, H_δ)].

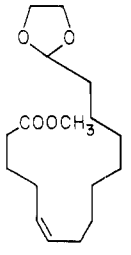
This ketophosphonate-based cyclization procedure can also be applied to the construction of macrocarbocyclic systems as demonstrated by a short and efficient synthesis of *dl*-muscone (**2**) starting from oleic acid. Thus the ketal

(8) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524. (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475–4478. (c) Ziegler, F. E.; Berger, G. D. *Synth. Commun.* **1979**, *9*, 539–543.

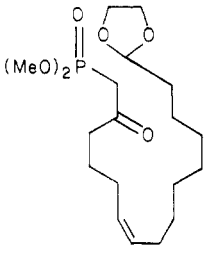
Table I. Synthesis of Macrocycles by Intramolecular Ketophosphonate Reaction

ketophosphonate	macrocycle	% yield
 14	 15	70
 19	 20	50
 21	 22	45
 23	 24	55

acid **5** upon reduction with excess diborane in THF followed by pyridinium chlorochromate oxidation yielded the aldehyde **16**, which was condensed with the sodium salt of (4-carboxybutyl)triphenylphosphorane in Me_2SO to afford, after diazomethane treatment, the methyl ester **17** (80% overall yield from **5**). Reaction of **17** with the lithium derivative of dimethyl methylphosphonate led to the ketophosphonate **18** (85%), deprotection of which (AcOH–THF–H_2O, 3:2:2, 45 °C) afforded the aldehyde **19** (Table I) (95%). Cyclization of this ketophosphonate



17



18

aldehyde (**19**) with NaH in DME under high dilution conditions gave the carbocycle **20** (Table I, mixture of *E* and *Z* isomers) in ca. 50% yield together with considerable amounts (15–20%) of the corresponding cyclic dimer. Reaction of **20** with lithium dimethylcuprate (ether, 0 °C) followed by hydrogenation (10% Pd–C, EtOH) gave *dl*-muscone (**2**) in 90% overall yield.

Further examples supporting the generality and usefulness of this macrocyclization procedure are provided in Table I (**21** → **22** and **23** → **24**). Of particular interest is the formation of the 18-membered ring lactone **24**, suggesting the potential of this method to the construction

of the polyene macrolide antibiotics.[9,10]

Registry No. 1, 69734-27-6; 2, 956-82-1; 3, 1931-63-1; 4, 953-29-7; 5, 834-33-3; 6, 71519-26-1; 7, 71519-27-2; 8, 71519-28-3; 9, 71519-29-4; 10, 71519-30-7; 11, 71519-31-8; 12, 71519-32-9; 13, 71519-33-0; 14, 71519-34-1; 15, 71519-35-2; 16, 64810-60-2; 17, 71519-36-3; 18, 71519-37-4; 19, 71519-38-5; (*E*)-20, 71519-39-6; (*Z*)-20, 71519-40-9; 21, 71519-41-0; 22, 31446-88-5; 23, 71519-42-1; 24, 71537-28-5; oleic acid, 112-80-1; oleic acid methyl ester, 112-62-9; 2-hydroxybutyraldehyde, 37428-67-4; dihydropyran, 110-87-2; *tert*-butyldiphenylsilyl chloride, 58479-61-1; dimethyl methylphosphonate lithium derivative, 34939-91-8.

(9) All new compounds exhibited satisfactory analytical and spectral data.

(10) This work was financially supported by Merck Sharp and Dohme and the University of Pennsylvania.

(11) Fellow of the Alfred P. Sloan Foundation, 1979–1981.

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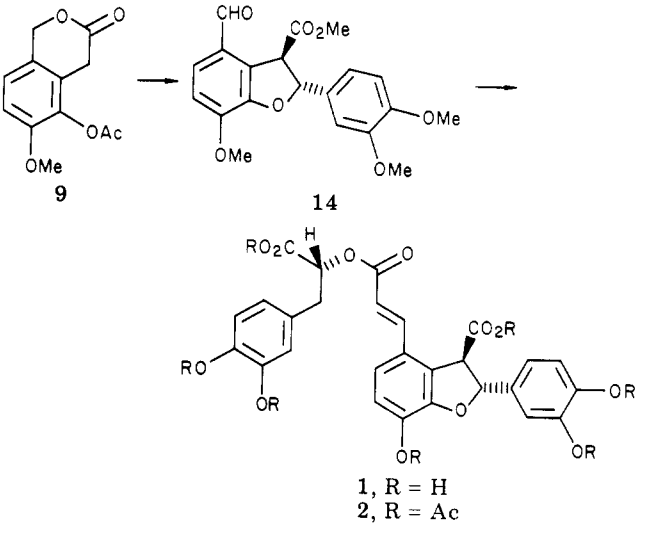
Total Synthesis of Heptamethyl Lithospermate

Summary: The total synthesis of *rac*-heptamethyl lithospermate (**2**) is described.

Sir: Extracts of several species of the genus *Lithospermum* have been shown to inactivate gonadotrophins.[1] They have proven capable of blocking the action of thyrotrophin and prolactin,[2] as well as LH, FSH, and TSH.[3] Lithospermic acid (**1**), the principal polyphenolic acid present in the roots of *Lithospermum ruderale* and *Lithospermum officinale*, has recently been isolated and characterized.[4,5] Out initial efforts toward developing a satisfactory synthetic access to **1** have resulted in the synthesis of the racemic permethylated derivative of lithospermic acid (**2**). The route described here involves three stages (Scheme I): (1) access to the 1,2,3,4 substitution pattern about the "central" aromatic ring; (2) conversion to the desired trans-substituted dihydrobenzofuran ring system; and (3) addition of the aryllactate/cinnamate side chain.

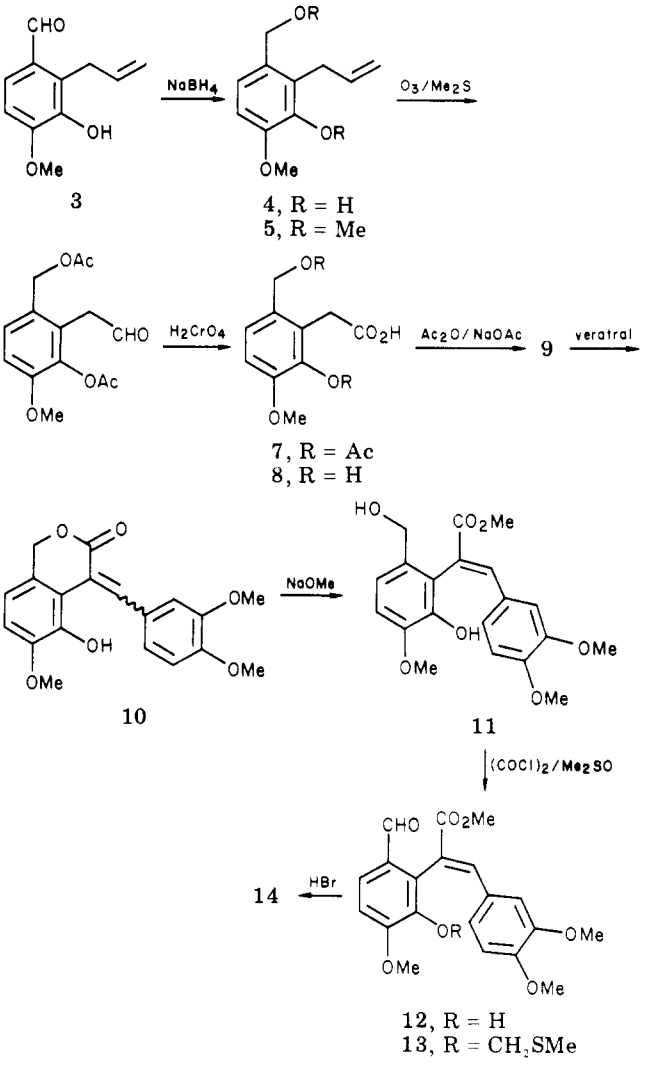
Our entry into the required 1,2,3,4 substitution pattern was found in the synthesis of the benzopyranone **9**. To this end (Scheme II), isovanillin was converted into 2-allylisovanillin (**3**) via the published procedure[6] involving Claisen rearrangement of *O*-allylisovanillin. Sodium borohydride reduction of **3** afforded the crystalline alcohol **4** in 90% yield: mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.6 (br s, 1 H), 3.53 (dt, J = 2 and 6 Hz, 2 H), 3.88 (s, 3 H), 4.60 (s, 2 H), 4.7–5.2 (m, 2 H), 5.77 (br s, 1 H), 5.6–6.4 (m, 1 H), 6.70 (d, J = 8 Hz, 1 H), 6.88 (d, J = 8 Hz, 1 H); MS

Scheme I



1, R = H
2, R = Ac

Scheme II



12, R = H
13, R = CH_2SMe

m/e 194.096 (M^+). The diol **4** was protected as the diacetate **5** (90%) by treatment with acetic anhydride and triethylamine in refluxing THF. Ozonolysis of **5**, followed by reduction with dimethyl sulfide, afforded the aldehyde **6** in 76% yield: mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.30 (s, 3 H), 3.65 (d, J = 2 Hz, 2 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 6.93 (d, J = 9 Hz, 1 H), 7.30 (d, J = 9 Hz, 1 H), 9.48 (t, J = 2 Hz, 1 H); IR 1770, 1745 cm^{-1}; MS m/e

(1) (a) E. M. Cranston, *J. Pharm. Exp. Ther.*, **83**, 130 (1945); (b) E. R. Plunkett and R. L. Noble, *Endocrin.*, **49**, 1 (1951); (c) E. M. Cranston and G. A. Robinson, *Proc. Soc. Exp. Biol. Med.*, **70**, 66 (1949); (d) W. R. Breneman, M. Carmack, D. E. Overack, R. O. Creek, and R. Shaw, *Endocrin.*, **67**, 583 (1960).

(2) (a) F. Kemper and A. Loeser, *Acta Endocrin.*, **29**, 525 (1958); (b) R. L. Noble, E. R. Plunkett, and R. C. B. Graham, *J. Endocrin.*, **10**, 212 (1954).

(3) (a) F. J. Zeller, W. R. Breneman, and M. Carmack, *Poul. Sci.*, **37**, 455 (1958); (b) W. R. Breneman, F. J. Zeller, M. Carmack and C. J. Kelley, *Gen. Comp. Endocrin.*, **28**, 24 (1976).

(4) C. J. Kelley, J. R. Mahajan, L. C. Brooks, L. A. Neubert, W. R. Breneman, and M. Carmack, *J. Org. Chem.*, **40**, 1804 (1975).

(5) H. Wagner, D. Wittman, and W. Schaffer, *Tetrahedron Lett.*, 547 (1975).

(6) F. Caesar and A. Mondon, *Chem. Ber.*, **101**, 990 (1968).

0022-3263/79/1944-4013$01.00/0