methanonaphtho[2,3-*b*:6,7-*b*']bisoxirene (0.10 g, 5.6%) (white needles, methanol); mp 218–219 °C (lit.[4] mp 218–220 °C).

(1aα,2aα,6aα,7aα)-1,1,8-Trichloro-1a,2,3,6,7,7a-hexahydro- and (1aα,2aα,4β,5β,6aα)-4-Hydroxy-5-iodo-1,1,8-trichlorooctahydro-2a,6a-methano-1*H*-cyclopropa[*b*]naphthalene (8 and 18). Deoxygenation of **7** (50–600 mg, 0.18–2.2 mmol) was effected with an excess of aluminum triiodide as described for **15** above, but with column in place of radial chromatography during workup.

A. At 30–32 °C for 20 h: **8** (0.52 g, 91%) as colorless needles (methanol); mp 106–107 °C ^{1}H NMR δ 1.40–1.50 (m, 4 H), 2.01 (bd, J = 16.7 Hz, 2 H), 2.26 (bd, J = 16.7 Hz, 2 H), 2.35–2.40 (m, 2 H), 2.93 (s, H8), 5.53 (bs, H4/H5); ^{13}C NMR δ 18.0 (C2a/C6a), 23.6 (C1a/C7a), 24.5/27.4 (C2/C3/C6/C7), 41.5 (C8), 67.2 (C1), 123.9 (C4/C5). Anal. Calcd for $C_{12}H_{13}Cl_3$: C, 54.7; H, 5.0; Cl, 40.3. Found: C, 54.7; H, 4.8; Cl, 40.2.

B. At 35 °C for 24 h (light petroleum ether/ethyl acetate, 6:1) in order of elution: **8** (11.8 mg, 25%) and **18** (36.5 mg, 50%) as colorless needles (CH_2Cl_2/light petroleum ether); mp 146–147 °C dec; ^{1}H NMR δ 1.50–1.77 (m, 5 H), 2.15 (dd, J = 5.4, 14.4 Hz, 1 H), 2.28 (dd, J = 4.5, 15.7 Hz, 1 H), 2.30–2.40 (m, 3 H), 2.52 (dd, J = 15.7, 4.5 Hz, 1 H), 2.95 (s, H8), 3.07 (bd, J = 7.13 Hz, H4), 4.40–4.48 (m, H5); ^{13}C NMR δ 19.5/19.9 (C2a/C6a), 23.9 (C1a/C7a), 25.4/25.6 (C2/C7), 35.0/36.3 (C3/C6), 36.3 (C2), 40.7 (C8), 40.8 (C5), 67.0 (C1), 69.2 (C4). Anal. Calcd for $C_{12}H_{14}Cl_3OI$: C, 35.4; H, 3.9; Cl, 26.10; I, 31.1. Found: C, 35.4; H, 3.6; Cl, 25.9; I, 31.0.

C. At 45 °C and 80 °C: **8** (10%) and **18** (60%), and only **18** (80%), respectively.

D. As in A above but with workup after 15 min: trans iodohydrin **19** (0.5 g, 95%) as colorless needles (CH_2Cl_2/light petroleum ether); mp 151–152 °C dec; ^{1}H NMR δ 1.25–1.75 (m, 5 H), 2.30–2.61 (m, 5 H), 2.86 (s, H8), 3.80–3.90 (m, H4/H5); ^{13}C NMR δ 22.1/22.9 (C2a/C6a), 23.3 (C1a/C7a), 24.2/25.2 (C2/C7), 35.0/39.7 (C3/C6), 39.5 (C5), 42.0 (C8), 66.7 (C1), 72.6 (C4). Anal. Calcd for $C_{12}H_{14}Cl_3OI$: C, 35.4; H, 3.9; Cl, 26.1; I, 31.1. Found: C, 35.4; H, 3.6; Cl, 26.1; I, 31.1.

Treatment of **19** with either AlI_3 or I^- under the same conditions gives the cis isomer **18** (92%); **19** is stable in the solvent at 36 °C.

Treatment of 18 and 19 with Sodium Hydroxide. Iodohydrin (20 mg, 0.05 mmol) and NaOH pellets (0.4 g, 10 mmol) in 1,4-dioxane (3 mL) were stirred at 30 °C for 1 h. The reaction mixture was partitioned between light petroleum ether/water (100 mL, 1:1). The organic phase was separated, washed (water, 2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to a solid.

A. From 18: unchanged starting material (85–93%) even after 24 h.

B. From 19: epoxide **7** (15 mg, 74%), identical with that described above, was obtained as a white solid.

Boord Reactions of 18 and 19. A mixture of the iodohydrin (100 mg, 0.25 mmol) and zinc dust (0.5 g, 7.7 mmol) was refluxed in methanol (6 mL) for 24 h, cooled to rt, CH_2Cl_2 (75 mL) was added, and the mixture was filtered. The organic phase was separated, washed with HCl (2 M, 10 mL) and water (2 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated under vacuum. Crystallization of the solid (methanol) gave **8** (58 mg, 90% from **18**) (60 mg, 90% from **19**).

Acknowledgment. We thank Dr. H. S. Rzepa (Imperial College, London) for his interest and the PM3 calculations and Professor E. Vogel (University of Cologne) for a generous gift of isotetralin. Financial assistance from the former NZ University Grants Committee (to S.G.G.R.) is gratefully acknowledged.

Registry No. **2**, 39623-22-8; **3**, 18963-51-4; **4**, 102618-60-0; **5**, 102618-68-8; **6**, 135257-80-6; **7**, 135257-81-7; **8**, 135356-60-4; **9**, 102680-43-3; **10**, 135257-82-8; **11**, 135257-83-9; **12**, 135356-61-5; **13**, 135356-62-6; **14**, 135356-63-7; **15**, 135257-84-0; **18**, 135257-85-1; **19**, 135356-64-8; aluminum triiodide, 7784-23-8; (1aα,2aα,3aα,4aα,5aα,6aα)-7,7-dichlorooctahydro-2a,5a-methanonaphtho[2,3-*b*:6,7-*b*']bisoxirene, 102618-62-2.

Supplementary Material Available: All X-ray data, including a PLUTO plot of **5** (7 pages). Ordering information is given on any current masthead page.

Reaction of Diethyl Phosphorochloridite with Enolates: A General Method for Synthesis of β-Keto Phosphonates and α-Phosphono Esters through C–P Bond Formation

Koo Lee and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

Received May 14, 1991 (Revised Manuscript Received July 8, 1991)

The reaction of ketone enolates with diethyl phosphorochloridite, followed by air oxidation of the immediate reaction products, has proven to be a general and convenient method for preparation of β-keto phosphonates. Fourteen β-keto phosphonates have been prepared by this method, in an average yield greater than 60%. This procedure also appears to be applicable to preparation of both α-phosphono aldehydes and α-phosphono esters. Although special precautions may be necessary to avoid aldol condensation during formation of aldehyde enolates, in two cases it was shown that the resulting enolates react readily with diethyl chlorophosphite. Finally, a set of five ethyl esters was converted to α-phosphono esters by this method. Yields of the α-phosphono esters are influenced by steric hindrance at the enolate carbon, but the average yield for this series was ca. 70%. Because this synthetic method relies upon an electrophilic phosphorus reagent for formation of the C–P bond, it is complementary to the traditional Arbuzov synthesis. On the basis of the 21 examples presented here, it appears to be more widely applicable.

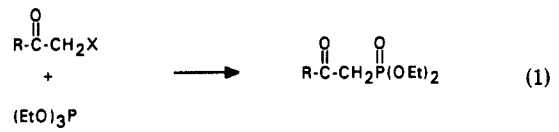
β-Keto phosphonates are commonly employed as synthetic reagents, particularly in the Horner–Wadsworth–Emmons reaction.[1] While there are many sequences that can be used to prepare them,[2] the classical Arbuzov reaction,[3] in which an α-halo carbonyl compound is treated with a trialkyl phosphite (eq 1), is by far the predominant choice. This reaction has been studied extensively, and its limits are well understood. Of prime importance for

(1) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. Horner, L.; Hoffman, H.; Wippell, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. Horner, L.; Hoffman, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber.* **1962**, *95*, 581. Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.

(2) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(3) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

0022-3263/91/1956-5556$02.50/0

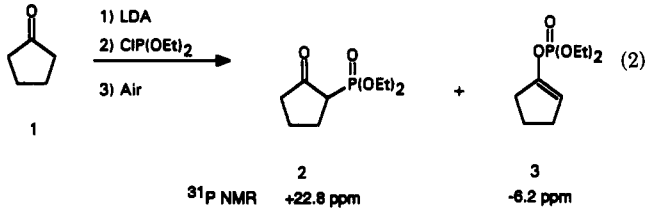


(1)

an Arbuzov synthesis of a β-keto phosphonate are two requirements: the α-halo ketone must be amenable to an S_N2 reaction, and the phosphite must be a good nucleophile. If these conditions are not met, an attempted reaction either fails or affords the isomeric vinyl phosphate.[4] To circumvent these limitations and broaden the range of readily accessible β-keto phosphonates, we have sought methods for C–P bond formation based on electrophilic phosphorus reagents.[5-7] In this paper, we report a convenient and general method for β-keto phosphonate synthesis from enolates. We also have shown that this general procedure is applicable to preparation of α-phosphono aldehydes and esters.

Both earlier literature[8] and our previous studies[6] indicate that dialkyl phosphochloridates react cleanly at the oxygen terminus of an enolate anion under many reaction conditions. With dialkyl phosphorochloridites as the electrophile, the reaction regiochemistry was more difficult to predict. Some limited studies suggested such reactions afford a complex mixture of O-, C-, and disubstituted products.[9]

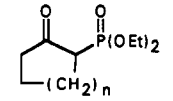
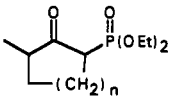
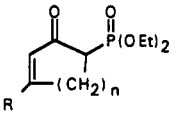
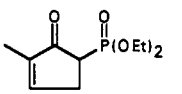
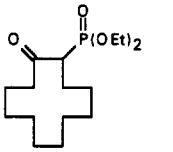
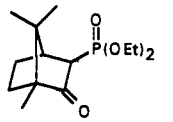
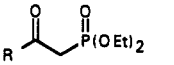
We have explored a variety of conditions for reaction of diethyl phosphorochloridite with ketone enolates, initially with the enolate of cyclopentanone (eq 2). Instead



(2)

of attempting isolation of phosphonite or phosphite intermediates, an in situ oxidation of the immediate products was accomplished by leaving the products open to air after reaction of the enolate and diethyl phosphorochloridite was complete. This approach makes it possible to identify both the direct C–P and O–P products simply by analysis of the ^{31}P NMR spectrum of the reaction mixture, because authentic samples of both phosphonate **2** and vinyl phosphate **3** are readily available.[6] On the basis of this approximation of the C–P/O–P ratio, it was possible to optimize formation of the desired isomer. With the lithium enolate of cyclopentanone, the best combination of a high C/O ratio (>12.5:1) and experimental ease was obtained with diethyl ether as solvent, conditions that gave an 80% isolated yield of phosphonate **2**. We also explored the effect of THF, ether/HMPA, and THF/HMPA solvents on the C–P/O–P ratio. For cyclopentanone, these different solvents have little effect on the C–P/O–P ratio, but with other ketones use of ether/HMPA improved the ratio in many cases. In a few cases, a THF/HMPA combination proved superior.

Table I. Conversion of Ketones to β-Keto Phosphonates

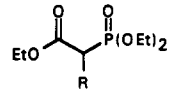
entry	solvent	structure	n (R)	no.	% yield
1	ether		1	2	79
2	ether/HMPA		2	4	70
3	ether		3	5	63
4	ether		1	6	64
5	THF/HMPA		2	7	39
6	THF/HMPA		1 (Me)	8	57
			2 (Me)	9	85
7	ether		3 (H)	10	32
8	ether/HMPA				
9	ether/HMPA			11	50
10	THF/HMPA			12	66
11	ether/HMPA			13	44
12	ether/HMPA		(Ph)	14	66
13	ether/HMPA		(t-Bu)	15	68
14	ether/HMPA		(Et)	16	72

A variety of ketones was converted to their respective β-keto phosphonates by application of this procedure, and isolated yields are generally attractive. Furthermore, many of the diethyl phosphonates described in Table I cannot be prepared in any other straightforward way. For example, this procedure gives reasonable to good yields with a variety of cyclic ketones (Table I, entries 1–10) where the Arbuzov reaction would be difficult to employ. Some of these keto phosphonates (entries 1, 2, and 7) have been prepared in comparable yields by rearrangement of the isomeric vinyl phosphate.[6] In other cases the vinyl phosphate rearrangement fails due to competing phosphate elimination (entries 3[6a] and 10[6b]), competing 1,2-phosphorus migration (entry 8[6c]), or formation of an unreactive anion (entries 6[10] and 9). With the bicyclic ketone camphor, standard conditions resulted in a modest yield of the desired C–P product (entry 11), suggesting that this keto phosphonate is still best prepared by the rearrangement route.[6]

On the basis of a limited number of examples, it appears that the phosphorochloridite/oxidation procedure provides an attractive method for preparation of phosphonate derivatives of acyclic ketones as well. For example, aceto-

(4) Perkow, W.; Ullerich, K.; Meyer, F. *Naturwissenschaften* **1952**, *39*, 353.
(5) Sampson, P.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 4342.
(6) (a) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185. (b) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *Ibid.* **1989**, *54*, 4750. (c) Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *Ibid.* **1990**, *55*, 2842.
(7) Roussis, V.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 627.
(8) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415. Borowitz, I. J.; Firstenberg, S.; Casper, E. W. R.; Crouch, R. K. *J. Org. Chem.* **1971**, *36*, 3282.
(9) Novikova, M. V.; Kurkin, A. N.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1978**, 271. Kurkin, A. N.; Novikova, M. V.; Lutsenko, I. F. *Ibid.* **1980**, 1183. Kurkin, A. N.; Novikova, M. V. *Vestn. Mosk. Univ., Ser. 2: Khim.* **1978**, *19*, 624; *Chem. Abstr.* *90*, 87853x. Grazizov, M. B.; Khairullin, R. A.; Moskva, V. V. *Russ. Chem. Rev.* **1990**, *59*, 251.
(10) Jacks, T.; Wiemer, D. F. Unpublished results.

Table II. Conversion of Esters to α-Phospho Esters[a]

entry	structure	R	no.	% yield
1		H	21	93
2		Me	22	79
3		Et	23	68
4		*i*-Pr	24	63
5		*t*-Bu	25	46

[a] All reactions were conducted in diethyl ether.

phenone (entry 12) was converted to the corresponding keto phosphonate in 66% yield through this approach. Entries 13 and 14 reflect comparable yields for other acyclic ketones. Of special significance is the observation that 2-butanone (entry 14) was converted to the primary phosphonate **16**,[11] with no trace of the regioisomer observed by ^1H or ^{31}P NMR, when the enolate was formed under conditions of kinetic control. While each of these acyclic keto phosphonates could be prepared by an Aubuzov synthesis, this new route is clearly more convenient, except perhaps for those few cases were the α-halo ketone necessary for an Arbuzov synthesis is commercially available. However, because it also can be used to prepare phosphonate derivatives of cyclic ketones, the phosphorochloridite/oxidation approach is more general.

All reactions reported in Table I were conducted on a 2.5 mmol scale, but preliminary experiments indicate much larger scale reactions should be feasible. For example, cycloheptanone was converted to phosphonate **5** on a 100 mmol scale with only a slight decrease in isolated yield (from 63% to 59%). The only significant difference in our procedure for larger scale reactions involves the oxidation protocol. For small-scale reactions, after concentration in vacuo the reaction vessel was simply left open to air and the crude oil was stirred overnight with a magnetic stirrer. For the large-scale reactions, faster oxidation can be accomplished by bubbling anhydrous air or O_2 through the crude oil. Comparison of product formation under these conditions (by ^{31}P NMR) showed no significant differences, except for faster oxidation under the latter conditions.

Although formation of aldehyde enolates can be more difficult,[12] we have had some success with preparation of phosphono aldehydes through this reaction sequence when KH was used for enolate formation. For example, phenylacetaldehyde (**17**) was converted to its diethyl phosphonate derivative **18** in 70% yield, while the more hindered 2-methylbutyraldehyde (**19**) was converted to phosphonate **20** in 41% yield. This reaction sequence shoud be applicable to other aldehydes if the enolates can be generated cleanly, but this may require procedures more complex than simple treatment of the aldehyde with base.[13]

Finally, we completed this phase of our study with a brief survey of the reactivity of ester enolates under these conditions. As shown in Table II, we chose to test a series of ethyl esters, where reaction at the carbon terminus of the enolate becomes progressively more difficult due to increasing steric hindrance. With the short-chain esters in this series, ethyl acetate and ethyl propionate, isolated yields of the corresponding phosphonates (**21** and **22**) are high. With ethyl butyrate and ethyl isovalerate, the expected phosphonates (**23** and **24**) are obtained in somewhat lower yields, and with ethyl *tert*-butylacetate the expected phosphonate **25** was obtained in 46% yield. In the earlier cases, ethyl acetate, propionate, and butyrate, the C–P/O–P ratio is very high (>20:1 by ^{31}P NMR). As steric hindrance near the carbon terminus of the enolate increases, i.e., with ethyl isovalerate and *tert*-butylacetate, vinyl phosphates[6b] become significant byproducts.

Comparison of this new synthesis of α-phosphono esters with previous approaches suggests that our method should prove to be popular for these compounds as well. The Arbuzov reaction can be used to prepare phosphono esters when the α-carbon is not hindered, but yields are dramatically decreased by steric hindrance. For example, preparation of phosphonate **24** by the Arbuzov reaction has been reported in ca. 20% yield.[14] Our previous synthesis of phosphono esters via vinyl phosphate rearrangement also is sensitive to steric hindrance; attempted preparation of phosphonate **24** by this method failed.[6b] Furthermore, this is apparently the first synthesis of the even more hindered phosphonate **25**. From this perspective, the yields reported in Table II are especially appealing. Once again, our new method is arguably more convenient than an Arbuzov synthesis, except perhaps for those few cases where the requisite α-halo esters are commercially available.

The 21 examples reported here suggest that this sequence is a general route to β-keto phosphonates and α-phosphono esters.[15] Thorough development of this route should make it possible to exploit the wealth of information on enolate chemistry in syntheses of a broad range of new phosphonates, including phosphonate analogues of complex, biologically important phosphates and phosphonates with varied ester substituents.

Experimental Section

Diethyl ether, THF, and DME were distilled from sodium/benzophenone immediately prior to use, and all reactions in these solvents were conducted under a positive pressure of an inert gas. Column chromatography was done on Merck grade 62A silica gel (100–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H and ^{13}C) were recorded with $CDCl_3$ as solvent and internal standard; ^{31}P chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Low-resolution electron impact (EI) mass spectra were obtained at 70 eV; only selected ions are reported here. High-resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility.

2-(Diethoxyphosphinyl)cyclopentanone (2). A solution of cyclopentanone (**1**, 0.21 mg, 2.5 mmol) in ether (0.5 mL) was added dropwise via syringe to a stirred solution of LDA (2.75 mmol, prepared in situ from diisopropylamine (0.38 mL) and *n*-BuLi (1.90 mL, 1.6 M in hexane)) in diethyl ether (6 mL) at −78 °C. After 40 min, diethyl phosphorochloridite (0.39 mL, 2.75 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 N, 3 mL), and the mixture was filtered through a Florisil pad (60–120 mesh). After concentration in vacuo, the resulting crude oil was magnetically stirred in a reaction vessel open to air overnight, and then purified by radial chromatography (silica gel, 1:1 EtOAc/hexane to afford phosphonate **2** (435 mg, 79%). This compound

(11) Mikolajczyk, M; Balczewski, P. *Synthesis* **1984**, 691.
(12) Ladjama, D.; Riehl, J. J. *Synthesis* **1979**, 504. (b) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**, 491.
(13) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791. Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.
(14) Wuts, P. G. M.; Putt, S. R.; Ritter, A. R. *J. Org. Chem.* **1988**, *53*, 4503.
(15) After submission of this manuscript, a similar strategy was reported for preparation of dioxinone phosphonates (cf. Boeckman, R. K.; Kamenecka, T. M.; Nelson, S. G.; Pruitt, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581). In that procedure, after reaction of a vinylogous ester enolate with diethyl chlorophosphite at relatively high temperature, aqueous peroxide was employed for the oxidation step. While their average yield is lower, since there are no common substrates in the two studies it may be premature to evaluate this alternative protocol.

was identical (by ^1H NMR, ^{31}P NMR, EIMS) with an authentic sample of phosphonate **2** prepared by rearrangement of the vinyl phosphate.[6a]

2-(Diethoxyphosphinyl)cyclohexanone (4). A solution of cyclohexanone (245 mg, 2.5 mmol) in ether (0.5 mL) was added to a solution of LDA (1.1 equiv) in ether (6 mL). After addition of HMPA (0.48 mL, 2.75 mmol) to the resulting ketone enolate, diethyl phosphorochloridate (0.369 mL, 2.75 mmol) was added. After workup and air oxidation according to the previous procedure, the resulting mixture was purified by radial chromatography (1:1 EtOAc/hexane) to give the desired phosphonate **5** (409 mg, 70%): ^1H NMR, ^{31}P NMR, and EIMS data are identical with those previously reported.[6a]

2-(Diethoxyphosphinyl)cycloheptanone (5). Cycloheptanone (11.22 g, 100 mmol) was added dropwise to a magnetically stirred solution of LDA in ether (1.1 equiv in 150 mL) at −78 to −50 °C. After 1.5 h, diethyl phosphorochloridite (14.83 mL, 102.5 mmol) was added dropwise, and then the reaction mixture was allowed to warm to rt. Anhydrous air was bubbled through the stirring solution via syringe needle at rt for 2 h. Acetic acid in ether (1 N, 120 mL) was added slowly, and the mixture was filtered through a Florisil pad. After evaporation of solvent, the resulting liquid was purified by column chromatography on silica gel (1:1 EtOAc/hexane) to give pure phosphonate **7** (14.63 g, 59%): ^1H NMR δ 4.13 (m, 4), 3.04 (ddd, 1, J_{HP} = 25.2 Hz, J = 12.1, 4.9 Hz), 2.81 (td, 1, J = 10.6, 1.4 Hz), 2.47 (dd, 1, J = 10.6, 6.1 Hz), 2.4–1.1 (m, 8), 1.32 (dt, 6, J_{HP} = 7.0 Hz, J = 5.5 Hz); ^{13}C NMR δ 208.6 (d, J_{CP} = 4.8 Hz), 62.5 (d, J_{CP} = 5.2 Hz), 62.4 (d, J_{CP} = 5.8 Hz), 53.8 (d, J_{CP} = 126.0 Hz), 42.7, 30.1, 28.1 (d, J_{CP} = 17.1 Hz), 25.7, 25.1 (d, J_{CP} = 5.9 Hz), 16.2 (d, J_{CP} = 6.1 Hz, 2); ^{31}P NMR ($CDCl_3$) 22.7; EIMS m/z (rel intensity) 248 (M^+, 23), 220 (25), 179 (64), 165 (46), 138 (100), 111 (42), 109 (70). Anal. Calcd for $C_{11}H_{21}O_4P·0.5H_2O$: C, 51.36; H, 8.62. Found: C, 51.63; H, 8.47.

General Procedure. The following β-keto phosphonates were prepared on a 2.5 mmol scale according to one of the first two representative procedures given above using the solvent(s) specified in Table I. Purification procedures are described only if different from those above. All purified products were obtained as colorless oils.

2-Methyl-5-(diethoxyphosphinyl)cyclopentanone (6). Purification by column chromatography (silica gel, 2:1 EtOAc/hexane) gave a mixture of phosphonate diastereomers **17** (374 mg, 64%) in a ratio of approximately 3:2 as measured by ^1H NMR: ^1H NMR minor diastereomer, δ 4.25–4.08 (m, 4), 2.89 (ddd, 1, J_{HP} = 28.8 Hz, J = 9.5, 3.2 Hz), 1.15 (d, 3, J = 6.7 Hz); major diastereomer, δ 4.25–4.08 (m, 4), 2.72 (ddd, 1, J_{HP} = 25.9 Hz, J = 10.2, 8.8 Hz), 1.10 (d, 3, J = 6.5 Hz); ^{13}C NMR δ 214.0 (d, J_{CP} = 6.2 Hz), 212.9 (d, J_{CP} = 5.0 Hz), 62.7 (d, J_{CP} = 7.4 Hz), 62.5 (d, J_{CP} = 6.4 Hz), 62.3 (d, J_{CP} = 7.4 Hz), 62.1 (d, J_{CP} = 6.1 Hz), 46.6 (d, J_{CP} = 133.1 Hz), 46.4 (d, J_{CP} = 140.4 Hz), 44.7 (d, J_{CP} = 5.0 Hz), 44.4 (d, J_{CP} = 3.4 Hz), 30.3 (d, J_{CP} = 13.4 Hz), 30.0 (d, J_{CP} = 3.4 Hz), 23.3 (d, J_{CP} = 4.0 Hz), 23.2 (d, J_{CP} = 2.6 Hz), 16.4 (d, J_{CP} = 3.7 Hz, 2), 16.2 (d, J_{CP} = 3.8 Hz, 2), 14.5, 13.4; ^{31}P NMR ($CDCl_3$) 23.1, 23.5 (cis, trans isomers), 26.9 (enol tautomer); ^{31}P NMR (CD_3ONa) 29.6; EIMS m/z (rel intensity) 234 (M^+, 21), 165 (22), 139 (53), 137 (24), 111 (28), 109 (57), 96 (100). Anal. Calcd for $C_{10}H_{19}O_4P$: C, 51.28; H, 8.18. Found: C, 51.63; H, 8.22.

2-Methyl-6-(diethoxyphosphinyl)cyclohexanone (7). Purification by column chromatography (2:1 EtOAc/hexane) gave a mixture of keto phosphonate diastereomers **7** (240 mg, 39%) in an approximately 3:2 ratio as measured by ^1H NMR: ^1H NMR minor diastereomer, δ 4.26–4.05 (m, 4), 3.05 (br dd, 1, J_{HP} = 14.9 Hz, J = 6.4 Hz), 1.05 (d, 3, J = 4.1 Hz); major diastereomer, δ 4.26–4.05 (m, 4), 2.98–2.82 (m, 1), 1.03 (d, 3, J = 4.0 Hz); ^{13}C NMR δ 207.7 (d, J_{CP} = 3.0 Hz), 207.5, 63.4 (d, J_{CP} = 5.7 Hz), 62.3 (d, J_{CP} = 6.8 Hz), 61.9 (d, J_{CP} = 6.8 Hz), 61.7 (d, J_{CP} = 6.2 Hz), 50.4 (d, J_{CP} = 138.8 Hz), 50.1 (d, J_{CP} = 125.6 Hz), 46.1 (d, J_{CP} = 7.5 Hz), 44.3, 36.2, 35.2, 29.7 (d, J_{CP} = 4.2 Hz), 28.0 (d, J_{CP} = 5.8 Hz), 25.2 (d, J_{CP} = 14.9), 21.7 (d, J_{CP} = 2.5 Hz), 16.3, 16.2 (d, J_{CP} = 7.0 Hz), 16.1 (d, J_{CP} = 7.1 Hz), 15.9 (d, J_{CP} = 7.0 Hz), 14.6, 14.2 (d, J_{CP} = 3.0 Hz); ^{31}P NMR ($CDCl_3$) 23.9, 24.8 (cis, trans isomers), 26.9 (enol tautomer); ^{31}P NMR (CD_3ONa) 34.1; EIMS, m/z (rel intensity) 248 (M^+, 24), 220 (15), 178 (17), 165 (29), 139 (43), 111 (34), 110 (100), 109 (38); HRMS calcd for $C_{11}H_{21}O_4P$ 248.1178, found 248.1194.

5-(Diethoxyphosphinyl)-3-methylcyclopent-2-en-1-one (8). Purification by radial chromatography (2:1 EtOAc/hexane, followed by EtOAc) gave 331 mg (57%): ^1H NMR δ 5.96 (d, 1, J = 1.1 Hz), 4.25–4.11 (m, 4), 3.03 (ddd, 1, J_{HP} = 25.2 Hz, J = 6.5, 3.5 Hz), 2.93–2.85 (m, 2), 2.17 (s, 3), 1.33 (dt, 6, J_{HP} = 7.1 Hz, J = 7.1 Hz); ^{31}P NMR ($CDCl_3$) 22.8; ^{13}C NMR 201.7 (J_{CP} = 4.0 Hz), 177.4 (J_{CP} = 6.1 Hz), 130.5, 63.0 (J_{CP} = 6.5 Hz), 62.3 (J_{CP} = 6.7 Hz), 45.5 (J_{CP} = 139.0 Hz), 35.4, 19.2, 16.4 (J_{CP} = 6.1 Hz); EIMS m/z (rel intensity) 232 (M^+, 53), 204 (31), 176 (100), 148 (45), 96 (61), 95 (73), 94 (51), 67 (51); HRMS calcd for $C_{10}H_{17}O_4P$ 232.0865, found 232.0856.

6-(Diethoxyphosphinyl)-3-methylcyclohex-2-en-1-one (9). 3-Methylcyclohex-2-en-1-one (275 mg, 2.5 mmol) gave the expected phosphonate **9** (522 mg, 85%): ^1H NMR, ^{31}P NMR, and EIMS data identical with previous data.[6a]

7-(Diethoxyphosphinyl)cyclohept-2-en-1-one (10). Purification by radial chromatography (1:1 EtOAc/hexane, followed by 2:1 EtOAc/hexane) gave 197 mg (32%): ^1H NMR δ 6.51 (dt, 1, J = 12.2, 5.3 Hz), 6.04 (ddd, 1, J = 12.2, 4.6, 2.7 Hz), 4.23–4.07 (m, 4), 2.6–1.7 (m, 6), 1.32 (dt, 6, J_{HP} = 7.4 Hz, J = 7.1 Hz); ^{31}P NMR 23.5, 28.6 (enol tautomer); EIMS m/z (rel intensity) 246 (M^+, 33), 217 (8), 189 (13), 155 (23), 137 (26), 99 (54), 91 (100), 81 (27). Anal. Calcd for $C_{11}H_{19}O_4P·0.5H_2O$: C, 51.76; H, 7.90. Found: C, 51.72; H, 7.87.

5-(Diethoxyphosphinyl)-2-methylcyclopent-2-en-1-one (11). Purification by radial chromatography (2:1 EtOAc/hexane, followed by EtOAc) gave 291 mg (50%); ^1H NMR δ 7.35 (d, 1, J = 1.2 Hz), 4.28–4.09 (m, 4), 3.02 (ddd, 1, J_{HP} = 18.6 Hz, J = 6.4, 3.1 Hz), 2.95–2.81 (m, 2), 1.80 (s, 3), 1.34 (dt, 6, J_{HP} = 8.0 Hz, J = 7.3 Hz); ^{13}C NMR δ 202.2 (d, J_{CP} = 13.7 Hz), 156.6 (d, J_{CP} = 6.1 Hz), 141.9 (d, J_{CP} = 3.4 Hz), 62.9 (d, J_{CP} = 6.1 Hz), 62.2 (d, J_{CP} = 6.2 Hz), 43.9 (d, J_{CP} = 138.2 Hz), 29.0 (d, J_{CP} = 3.2 Hz), 16.4 (d, J_{CP} = 2.3 Hz), 16.3 (d, J_{CP} = 2.3 Hz), 10.2; ^{31}P NMR ($CDCl_3$) 23.0; EIMS m/z (rel intensity) 232 (M^+, 37), 204 (26), 176 (100), 148 (31), 96 (70), 95 (75), 94 (51), 67 (40). Anal. Calcd for $C_{10}H_{17}O_4P.H_2O$: C, 48.01; H, 7.65. Found: C, 47.97, H, 7.49.

2-(Diethoxyphosphinyl)cyclododecanone (12): yield 525 mg (66%); mp 58–60 °C; ^1H NMR δ 4.17 (m, 4), 3.42 (ddd, 1, J_{HP} = 24.7 Hz, J = 12.2, 2.5 Hz), 2.81 (ddd, 1, J = 15.2, 7.1, 3.1 Hz), 2.59 (ddd, 1, J = 15.2, 11.0, 3.2 Hz), 2.24 (m, 1), 1.90–1.46 (m, 3), 1.46–1.17 (m, 20); selected ^{13}C NMR δ 207.1 (d, J_{CP} = 4.1 Hz), 62.6 (d, J_{CP} = 6.7 Hz), 62.4 (d, J_{CP} = 6.5 Hz), 50.5 (d, J_{CP} = 124.4 Hz), 41.7, 16.3 (d, 2, J_{CP} = 5.7 Hz); ^{31}P NMR ($CDCl_3$) 22.7; EIMS m/z (rel intensity) 318 (M^+, 5), 290 (5), 221 (47), 165 (100), 152 (47), 137 (27), 109 (66), 55 (77). Anal. Calcd for $C_{16}H_{31}O_4P$: C, 60.36; H, 9.81. Found: C, 60.80; H, 9.86.

3-(Diethoxyphosphinyl)camphor (13). Application of the general procedure gave a single diastereomer, assumed to be the endo isomer on the basis of a strong NOESY correlation between the C-3 and C-8 hydrogens: yield 317 mg (44%); ^1H NMR, ^{31}P NMR, and EIMS data identical with previous data.[6a]

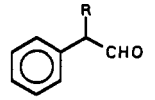
Diethyl (2-phenyl-2-oxoethyl)phosphonate (14): yield 422 mg (66%); ^1H NMR, ^{31}P NMR, and EIMS data identical with previous data.[5]

Diethyl (3,3-methyl-2-oxobutyl)phosphonate (15): yield 401 mg (68%); ^1H NMR, ^{31}P NMR, and EIMS data identical with previous data.[5]

Diethyl (2-oxobutyl)phosphonate (16): yield 374 mg (72%); ^1H NMR, ^{31}P NMR, and EIMS data identical with previous data.[11]

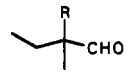
Diethyl (1-Formyl-1-phenylmethyl)phosphonate (18). A solution of phenylacetaldehyde (**17**, 300 mg, 2.5 mmol) in DME (3 mL) was added dropwise to a stirred suspension of potassium hydride[16] (150 mg, 3.75 mmol) in DME (6 mL) at 0 °C. After 45 min, diethyl phosphorochloridite (0.39 mL, 2.75 mmol) was added to the turbid yellow solution at 0 °C, and the mixture was allowed to warm to rt over 20 min. The reaction was quenched by slow addition of acetic acid in ether, the resulting mixture was filtered through a Florisil pad, and the filtrate was concentrated in vacuo. After overnight stirring with exposure to air, the residual oil was purified by column chromatography (1:1 EtOAc/hexane) to give the desired α-phosphono aldehyde **17** (447 mg, 70%): ^1H NMR[17] and ^{31}P NMR[18] data are identical with reported data.

(16) Brown, C. A. *J. Org. Chem.* **1974**, *26*, 3913.
(17) Ioffe, S. T.; Wazuro, K. W.; Petrowskii, P. W.; Kabatschnik, M. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1971**, *4*, 731.



17 R = H

18 R = P(O)(OEt)$_2$



19 R = H

20 R = P(O)(OEt)$_2$

Diethyl (1-Formyl-1-methyl-1-ethylphenyl)phosphonate (20). A solution of 2-methyl butyraldehyde (19, 227 mg, 2.5 mmol) in THF (0.6 mL) was added dropwise to a suspension of potassium hydride (110 mg, 2.75 mmol) at rt. After 20 min, the resulting enolate solution was treated with diethyl phosphorochloridite (0.39 mL, 2.75 mmol) at 0 °C. Standard workup, air oxidation, and final purification by radial chromatography (1:1 EtOAc/hexane) gave the desired product 20 (227 mg, 41%): ^{1}H NMR, ^{31}P NMR, EIMS data are identical with previous data.[19]

Triethyl α-Phosphonoacetate (21). General Procedure for the Prepration of α-Phosphono Esters. A solution of ethyl acetate (0.49 mL, 5 mmol) in ether (1 mL) was added dropwise via syringe to a stirred solution of LDA (1.1 equiv) in ether (12 mL) at −78 °C. After 1 h, diethyl phosphorochloridite (0.77 mL, 5.25 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 N, 6 mL), and the mixture was filtered through a Florisil pad (60–120 mesh). After removal of solvent, the reaction vessel was opened to the air, and magnetically stirred for 2 h. Purification was effected by column chromatography (1:1 EtOAc/hexane, unless otherwise specified) to afford α-phosphono ester 21[20] (1.044 g, 93%): ^{1}H NMR[21] and EIMS[22] data are identical with those previously reported; ^{31}P NMR +19.8.

Triethyl α-phosphonopropionate (22): yield 938 mg (79%); ^{1}H NMR,[21] ^{31}P NMR,[6b] and EIMS[22] data identical with previous data.

Triethyl α-phosphonobutyrate (23): yield 851 mg (68%); ^{1}H NMR, ^{31}P NMR,[6b] and EIMS[22] data identical with previous data.

Triethyl α-phosphono-3-methylbutyrate (24): yield 833 mg (63%); ^{1}H NMR identical with previous data[14]; ^{31}P NMR 22.1.

Triethyl α-phosphono-3,3-dimethylbutyrate (25): yield 639 mg (46%); ^{1}H NMR δ 4.23–4.05 (m, 6), 2.91 (d, 1, J_{HP} = 21.7), 1.37–1.27 (m, 9), 1.19 (s, 9); ^{13}C NMR δ 168.8 (d, J_{CP} = 5.5 Hz), 62.5 (d, J_{CP} = 6.8 Hz), 62.1 (d, J_{CP} = 7.0 Hz), 56.3 (d, J_{CP} = 133.6 Hz), 33.8 (d, J_{CP} = 3.6 Hz), 29.3 (d, J_{CP} = 7.5 Hz, 3), 16.4 (2), 16.3; ^{31}P NMR δ 22.1; EIMS m/z (rel intensity) 265 (M^+ − 15, 7), 224 (100), 197 (74), 179 (53), 152 (54), 123 (43); HRMS calcd for $C_{11}H_{22}O_5P$ 265.1205, found 265.1194.

Acknowledgment. The financial support of the National Institutes of Health is gratefully acknowledged.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds 11, 15, and 25 (6 pages). Ordering information is given on any current masthead page.

(18) Aboujaoude, E. E.; Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, *264*, 9.
(19) Teulade, M.-P.; Savignac, P. *Synth. Commun.* **1987**, *17*, 126.
(20) Arbuzov, A. E.; Dunin, A. A. *Zh. Fiz. Khim.* **1914**, *46*, 295.
(21) Pouchert, C. J. *The Aldrich Library of NMR Spectra*: Aldrich Chemical Co., Milwaukee, WI, 1983.
(22) Nishiwaki, T. *Tetrahedron* **1967**, *23*, 2181.

The Total Synthesis of Alcaligin

R. J. Bergeron,* J. S. McManis, P. T. Perumal, and S. E. Algee

Department of Medicinal Chemistry, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32610

Received January 4, 1991

The first total synthesis of 1,8(*S*),11,18(*S*)-tetrahydroxy-1,6,11,16-tetraazaacycloeicosane-2,5,12,15-tetrone (alcaligin) is presented. The key step involves the coupling of *O*-benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine to 2(*S*)-(benzyloxy)-1,4-bis(tosyloxy)butane (2). The resulting monotosylate 3 was then converted to the primary amine 5, which was subjected to a series of selective acylations and N-deprotections to produce the linear ω-amino acid 11. The ω-amino acid was next cyclized to the 20-membered ring, tetrabenzylalcaligin (12). Finally, deprotection of the hydroxamates and alcohols in the last step afforded the chiral natural product, alcaligin (1).

Microorganisms have adapted to the poor solubility of ferric ion in the biosphere by producing a group of low molecular weight iron chelators, siderophores.[1-5] The iron(III) complexes formed with these ligands provide a readily utilizable source of the metal. Although a substantial number of siderophores have been isolated and characterized, they fall largely into two structural classes: the catecholamides and the hydroxamates.[1] Of the latter group, desferrioxamine B,[5] a linear trihydroxamate ligand, has been the most widely studied. It exhibits a high specificity for iron(III), forming a stable hexacoordinate, octahedral iron(III) complex,[6] $K_f = 1 \times 10^{30}$ M^{-1}.

The same microorganism that produces desferrioxamine, *Streptomyces pilosus*, also synthesizes a number of other linear as well as macrocyclic hydroxamates, e.g., nocardamine.[4] More recently, two related macrocycles have been isolated: bisucaberin,[7] from *Alteromonas haloplanktis* and alcaligin (1), from *Alcaligenes denitrificans*[8] and *A. xylosoxidans*[9] (Figure 1). Both of these compounds are

(1) Bergeron, R. *J. Chem. Rev.* **1984**, *84*, 587–602.
(2) Tait, G. H. *Biochem. J.* **1975**, *146*, 191–204.
(3) Griffiths, G. L.; Sigel, S. P.; Payne, S. M.; Neilands, J. B. *J. Biol. Chem.* **1984**, *259*, 383–385.
(4) Aksoy, M.; Birdwood, G. F. B. *Hypertransfusion and Iron Chelation in Thalassaemia*; Hans Huber Publishers: Berne, 185; p 80.
(5) Bickel, H.; Hall, G. E.; Keller-Schierlein, W.; Prelog, V.; Vischer, E.; Wettstein, A. *Helv. Chim. Acta* **1960**, *43*, 2129–2138.
(6) Modell, B.; Berdoukas, V. *The Clinical Approach to Thalassaemia*; Grune and Stratton: London, 1984; p 217.
(7) Kameyama, T.; Takahashi, A.; Kurasawa, S.; Ishizuka, M.; Okami, Y.; Takeuchi, T.; Umezawa H. *J. Antibiot.* **1987**, *40*, 1664–1670.
(8) Nishio, T.; Tanaka, N.; Hiratake, J.; Katsube, Y.; Ishida, Y.; Oda, J. *J. Am. Chem. Soc.* **1988**, *110*, 8733–8734.
(9) Nishio, T.; Ishida, Y. *Agric. Biol. Chem.* **1990**, *54*, 1837–1839.

0022-3263/91/1956-5560$02.50/0