Syntheses of Ethyl Retinoate with Polymer-Supported Wittig Reagents

Margaret Bernard, Warren T. Ford,* and E. C. Nelson

Department of Chemistry and Biochemistry, Oklahoma State University, Stillwater, Oklahoma 74078

Received February 10, 1983

Insoluble (3-(ethoxycarbonyl)-2-methylallyl)triarylphosphonium bromide (**2**) on 2% cross-linked polystyrene and on 20% cross-linked macroporous polystyrene and insoluble β-cyclogeranyltriarylphosphonium bromide (**3**) on 2% cross-linked polystyrene have been prepared. Generation of the polymer-bound phosphoranes with sodium ethoxide in ethanol in the presence of the appropriate aldehydes gave isomeric mixtures of ethyl retinoate (**1**) in 55–70% yield. The C_5 phosphorane **2** produced seven isomers of **1**. The C_{10} phosphorane **3** produced a 23:77 mixture of 7-*cis*- and *all-trans*-**1**.

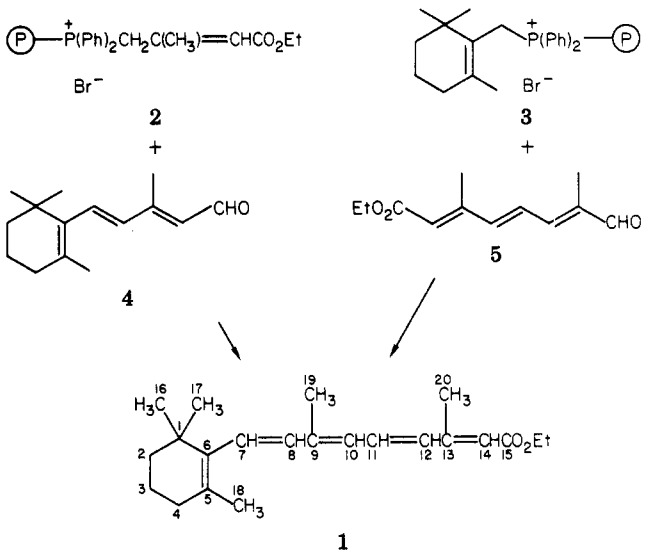
Retinoic acid and its analogues are known to be important in the control of growth, development, and differentiation of epithelial cells.[1] Antitumor activity of retinoids is currently an active area of research.[2] *all-trans*- and 13-*cis*-retinoic acids and their ethyl and methyl esters have carcinostatic activity.[3] We describe here the use of polymer-supported Wittig reagents for the synthesis of ethyl retinoate (**1**).

The Wittig reaction is the most general method for formation of specific carbon–carbon double bonds,[4] and it has been used often for retinoid syntheses.[2b,5] Retinoids are sensitive to light, oxygen, and heat. Polymer-supported Wittig reagents enable isolation of isomeric mixtures of ethyl retinoate without need for chromatography, extraction, or crystallization to remove the usual triphenylphosphine oxide byproduct. The insoluble polystyryldiphenylphosphine oxide can be removed from the retinoids by simple filtration. We reported previously high-yield Wittig reactions of benzyltriaryl- and methyltriarylphosphonium salts bound to 2% cross-linked polystyrene and to 20% cross-linked macroporous polystyrene.[6] In principle any of the four side-chain double bonds could be formed by a Wittig reaction in the final step of a retinoid synthesis, and all have been attempted with soluble Wittig reagents.[5] The most attractive potential polymer-bound Wittig reagents appeared to be **2** and **3** on the basis of their ease of preparation from relatively stable allylic bromides and phosphonium salts and the availability of the aldehydes **4** and **5** with which they must be coupled (Scheme I). We shall refer to the two routes as the C_5 (**2**) + C_{15} (**4**) and C_{10} (**3**) + C_{10} (**5**) routes to ethyl retinoate.

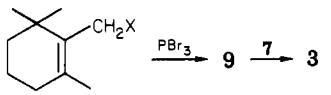
Results

Polymer-bound C_5 phosphonium salt **2** was prepared

Scheme I

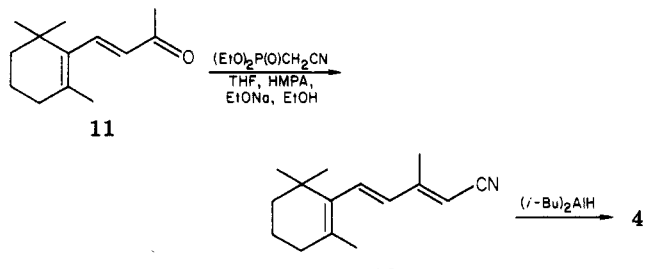


Scheme II



8, X = OH
9, X = Br

Scheme III



form a 41:59 *Z*:*E* isomeric mixture of ethyl 4-bromo-3-methyl-2-butenoate (**6**, eq 1)[7]. No attempt was made to

$$\underset{\mathbf{6}}{BrCH_2C(CH_3)=CHCO_2C_2H_5} + \textcircled{P}\text{—}PPh_2 \rightarrow \mathbf{2} \qquad (1)$$

separate the isomeric esters **6** since it was known[8] that the soluble (*E*)- and (*Z*)-triphenylphosphonium salts corresponding with **2** react with benzaldehyde to produce identical isomeric mixtures of olefins. The mixture **6** was

(1) Boutwell, R. K. "Oncology Overview: Selected Abstracts on Vitamin A in Cancer Biology"; U.S. Department of Health, Education and Welfare, National Cancer Institute: Washington, DC, Sept 1979.

(2) (a) Sporn, M. B.; Newton, D. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2528–2534. (b) Mayer, H.; Bollag, W.; Hanni, R.; Ruegg, R. *Experientia* **1978**, *34*, 1105–1246. (c) Verma, A. K.; Rice, H. M.; Shapos, B. G.; Boutwell, R. K. *Cancer Res.* **1978**, *38*, 793–801. (d) Goodman, D. S. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1980**, *39*, 2716–2722. (e) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.–Chim. Ther.* **1980**, *15*, 9–15. (f) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.; Fung, V. A. *J. Med. Chem.* **1982**, *25*, 583–592. (g) Watjen, F.; Buchardt, O.; Langvad, E. *Ibid.* **1982**, *25*, 956–960.

(3) Newton, D. L.; Henderson, W. R.; Sporn, M. B. "Structure Activity Relationships of Retinoids", revised edition; published by the National Cancer Institute, Feb. 26, 1980.

(4) (a) Maercker, A. *Org. React. (N.Y.)* **1965**, *14*, 270–490. (b) Gosney, I.; Rowley, A. G. "Organophosphorous Reagents in Organic Synthesis"; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 2.

(5) (a) Pommer, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 423–429. (b) Pommer, H. *Angew. Chem.* **1960**, *72*, 811–819, 911–915. (c) British Patent (BASF) 817 884, 1959; *Chem. Abstr.* **1960**, *54*, 11074b. (d) Pommer, H.; Sarnecki, W. U.S. Patent, 3 006 939, **1961**. (e) Pommer, H.; Wittig, G. German Patent 951 212, 1956; *Chem. Abstr.* **1959**, *53*, 437.

(6) Bernard, M.; Ford, W. T. *J. Org. Chem.* **48**, 326–332.

(7) Ahmed, I.; Gedye, R. N.; Nechwatel, A. *J. Chem. Soc. C* **1968**, 185–187.

(8) (a) Howe, R. K., *J. Am. Chem. Soc.* **1971**, *93*, 3457–3462. (b) Gedye, R. N.; Westaway, K. C.; Arora, P.; Bisson, R.; Khalil, A. H. *Can. J. Chem.* **1977**, *55*, 1218–1228.

0022-3263/83/1948-3164$01.50/0

Table I. Formation of (3-(Ethoxycarbonyl)-2-methylallyl)- and β-Cyclogeranylpolystyryldiphenylphosphonium Bromides 2 and 3

copolymer, % cross-linking	phosphine, mequiv P/g[a]	phosphonium salt, mequiv of Br/g[b]	% conversion	% ring substitution
2	2.09	2, 1.22	84	33
2	2.09	2, 1.16	80	31
20	0.70	2, 0.48	78	10
2	2.09	3, 1.11	78.5	31
2	2.09	3, (0.95)[c]	88	26.5

[a] By elemental analysis. [b] By bromide analysis. [c] Prepared from triarylphosphine hydrobromide containing 1.25 mequiv/g of Br.

treated with 2% and 20% cross-linked phosphines 7 to give the corresponding phosphonium salts 2 in 84% and 78% conversion, respectively (Table I). ^{31}P NMR analysis of phosphonium salts 2 showed signals at δ 21.79 and 21.95, indicative of two isomers.

Phosphorus tribromide treatment of β-cyclogeraniol (8) in the presence of catalytic amounts of pyridine led to β-cyclogeranyl bromide (9, 92% crude).[9] Without purification 9 was treated with 2% cross-linked phosphine 7 in DMF to give polystyryldiphenyl-β-cyclogeranylphosphonium bromide (3) (Scheme II) in 78.5% conversion (Table I). ^{31}P NMR analysis showed a signal at δ 18.74, confirming the phosphonium salt formation.

Phosphonium salt 3 also was formed by the reaction of 8 with polystyryldiphenylphosphine hydrobromide (10, eq 2). Phosphine 7 was treated with HBr in benzene for 5

$$8 + \underset{10}{\text{(P)}}\text{—}P^{+}(Ph)_2H,Br^{-} \rightarrow 3 \qquad (2)$$

min at 0 °C, warmed to room temperature, and stirred for 24 h to give 10 in 79% conversion as established by bromide determination. ^{31}P NMR analysis gave a signal at −9.09 ppm. The hydrobromide 10 reacted with 8 to give 3 in 88% conversion.

β-Ionylideneacetaldehyde (4) was obtained in two steps from β-ionone (11) via β-ionylideneacetonitrile[10] (12, Scheme III). GLC and ^1H NMR analyses of 12 indicated the presence of 7(*E*),9(*E*) and 7(*E*),9(*Z*) isomers of 4 in the ratio 80:20. Preparation of 12 in the absence of hexamethylphosphoramide (HMPA) under otherwise the same conditions gave a 60:40 isomeric mixture of nitriles 12. Reduction of 12 with diisobutylaluminum hydride in hexane gave the unstable β-ionylideneacetaldehyde 4 (87%, crude) after the aldimine complex was hydrolyzed with silica gel containing 20% water in a 1:1 (v/v) mixture of ether/hexanes.[11]

The $C_5 + C_{15}$ Wittig reactions were effected by simultaneous addition of 4 and sodium ethoxide in approximately stoichiometric amounts to 2% and to macroporous 20% cross-linked C_5 phosphonium salts in absolute ethanol and stirring of the mixture at room temperature for 20 h. The products were partly purified by filtration through Waters SEP-PAK C_{18} cartridges to give mixtures of isomers 1 that contained no obvious impurities, except for methanol, by ^1H NMR analysis. Yields of 1 were 70% and 65% from the 2% and macroporous 20% cross-linked polymers (Table II). The products were analyzed by HPLC to be mixtures of 7 isomers, which were then separated into five fractions by HPLC and identified by ^1H and ^{13}C NMR analyses. The isomer distributions according to HPLC peak areas are presented in Table III.

Table II. Ethyl Retinoate from 2 and 3

copolymer % cross-linking	P+	mequiv of P+	alde-hyde	mequiv of aldehyde	% yield
2	2	2.16	4	2.00	70[a]
20	2	1.20	4	1.00	65[a]
2	3	1.67	5	1.00	55[b]
2	3[d]	2.80	5	1.90	50[c]

[a] Yield after SEP-PAK purification. [b] Crude yield. [c] Based on yield of recrystallized retinoic acid. [d] Not isolated.

Table III. Isomer Distribution of Ethyl Retinoate from 2 and 4

isomer	copolymer % cross-linking 2	copolymer % cross-linking 20	after I_2 isomerization
all-trans	15.2	21.8	41.3
9-cis	8.0	12.0	12.5
11-cis	14.3	8.4	4.2
9,13-di-cis	9.7	12.0	5.0
13-cis	20.6	27.3	31.2
11,13-di-cis	21.1	11.9	2.5
9,11,13-tri-cis	10.9	5.9	3.2

From the data 46% of the products had an 11-cis double bond when the phosphonium salt 2 was bound to the 2% cross-linked polymer and 26% when 2 was bound to the macroporous 20% cross-linked polymer. The proportion of the most biologically active 13-cis and all-trans isomers of 1 changed from 36% with the 2% cross-linked polymer to 49% with the 20% cross-linked macroporous polymer. There were 30% of 9-cis isomers, 10% more than expected from a 80:20 ratio of *E,E*- and *E,Z*-nitriles 12. The isomeric mixture of bromides 6 produced 13-cis and 13-trans double bonds in 1 in the ratio 62.5:37.5 with the 2% cross-linked polymer and 58:42 with the 20% cross-linked polymer, in close agreement with the 60:40 ratio previously reported[8a] for the reaction of benzaldehyde with the monomeric C_5 phosphonium salt corresponding with 2. Iodine-catalyzed isomerization of 1 (prepared from the macroporous 20% cross-linked polymer) in ether/benzene (1:1) for 3 days at 0 °C reduced the number of major isomers to three, as listed in Table III.

Two $C_{10} + C_{10}$ experiments were tried. In the first, the phosphonium salt 3, formed from 7 and 9, was used for Wittig olefination without isolation. The C_{10} aldehydic ester 5 in THF and NaOEt in ethanol were added simultaneously to 3 in THF (Scheme I). HPLC analysis of the crude product showed two peaks in the ratio 77:23 which were identified by ^1H NMR analysis as the all-trans and 7-cis isomers of ethyl retinoate (1). The esters were hydrolyzed to the acids with ethanolic KOH, and *all-trans*-retinoic acid (38%) was isolated by recrystallization from methanol. In the second experiment the phosphonium salt 3 (from 7 and 9) was separated from the reaction mixture by filtration, washed, and dried at 50 °C. The

(9) Kuhn, V. R.; Hoffer, M. *Chem. Ber.* **1934**, *67*, 357–361.
(10) (a) Stilz, W.; Pommer, H. U.S. Patent 3 157 660, 1964. (b) Pommer, H.; Stilz, W. German Patent 1 116 653, 1961.
(11) Liu, R. S. H.; Matsumoto, H.; Asato, A. H. D,; Dinny, M.; Shichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195–7201.

Table V. ^{13}C NMR Chemical Shifts (ppm) of Ethyl Retinoate Isomers and *all-trans*-Retinoic Acid

isomers	carbon numbers 1	2	3	4	5	6	7	8	9	10	11
all-trans acid	34.22	39.59	19.20	33.09	129.94	137.47	128.83	137.00	140.01	129.20	131.61
all-trans ethyl ester	34.24	39.59	19.21	33.10	129.99	137.69	128.62	137.26	139.54	129.50	130.90
11-cis ester	34.26	39.51	19.21	33.04	129.83	137.68 or 137.63	128.52 or 128.97	137.68 or 137.63	139.83	125.83	131.37 or 128.97 or 128.53
9,13-di-cis ester	34.25	39.50	19.22	33.08	129.91 or 130.00	138.58	128.44	129.91 or 130.00	138.58	129.31 or 128.85	130.95
13-cis ester	34.25	39.59	19.22	33.11	129.97	137.67	128.60	137.46	139.71	130.33	132.12
11,13-di-cis ester	34.25	39.51	19.21	33.02	129.69	137.78 or 137.73	128.41	137.73 or 137.78	139.46	126.38 or 126.65	129.15
9,11,13-tri-cis ester	34.18	39.52	19.22	33.05	130.06 or 130.15	137.91 or 137.88	127.94	130.06 or 129.08	137.88 or 137.91	124.58 or 125.97	130.15 or 130.06

isomers	carbon numbers 12	13	14	16,17	18	19	20	C=O	OCH_2	OCH_2CH_3
all-trans acid	134.70	154.97	117.48	28.92	21.71	12.92	14.06			
all-trans ethyl ester	135.16	152.80	118.58	28.94	21.73	12.89	13.82	167.20	59.64	14.35
11-cis ester	131.40	153.45	119.25	28.95	21.78	12.36	15.28	167.02	59.69	14.34
9,13-di-cis ester	128.85 or 129.31	151.20	116.55	28.97	21.85	20.98 or 20.93	20.98 or 20.93	166.42	59.62	14.35
13-cis ester	129.58	151.04	116.55	28.97	21.74	12.88	20.98	166.42	59.62	14.35
11,13-di-cis ester	126.65 or 126.38	152.42	118.57	28.93	21.74	12.23	25.59	166.09	59.72	14.30
9,11,13-tri-cis	124.58 or 125.97	152.48	118.55	28.97	21.83	21.23	25.65	166.12	59.72	14.29

Wittig reaction **3** and **5** gave a 55% yield of crude **1** consisting of all-trans and 7-cis isomers in the same ratio, 77:23. Iodine-catalyzed isomerization of this mixture in 1:1 ether/benzene gave 13-*cis*- and *all-trans*-**1** with HPLC relative areas 25:75.

^1H NMR chemical shifts at 300 MHz of the ethyl retinoate isomers (Table IV, supplementary material) agreed within 0.02 ppm with previous 100-MHz values of methyl retinoate[12] except as follows. In the spectrum of a mixture of *all-trans*- and 9-*cis*-**1**, H(7) and H(12) of 9-*cis*-**1** appeared at δ 6.28 and 6.21. The latter assignment was confirmed by collapse of the H(12) doublet to a singlet upon irradiation of H(11). The spectrum of 11-*cis*-**1** presented the only case in the entire series of isomers in which two signals were not resolved at 300 MHz. H(10) and H(11) of 11-*cis*-**1** appeared as a multiplet centered at δ 6.57. Irradiation of H(12) at δ 5.92 collapsed the multiplet to a broad singlet.

The ^{13}C NMR spectral data at 75 MHz for six of the isomers of ethyl retinoate are presented in Table V. The spectrum of the mixture of the all-trans and 9-cis isomers did not permit assignments of many signals of 9-*cis*-**1**. The chemical shift values for the all-*trans*- and 13-*cis*-**1** were in good agreement with literature values, within ±0.5 ppm of those of the analogous methyl esters.[13] For the remaining isomers of **1** the closest analogies available for ^{13}C chemical shifts were retinols or retinyl acetates with the same double bond configurations.[13] Not all assignments could be made with certainty from the 75-MHz spectra available, which were achieved by >12 h accumulation times. In principle 2D experiments or single proton decoupling experiments could resolve the ambiguities if larger samples become available.

Discussion

Polymer-supported Wittig reagents **2** and **3** provide isomeric ethyl retinoates **1** in yields as high as those reported from analogous soluble Wittig reagents.[5] The method is potentially adaptable to the synthesis of a wide variety of retinoids. It major advantage is separation of the triarylphosphine oxide byproduct from the retinoid by simple filtration of the insoluble polymer from the solution.

The $C_{10} + C_{10}$ route afforded a mixture of the rare 7-cis isomer[14] and the common *all-trans*-**1** and, after hydrolysis, produced a 38% yield of recrystallized *all-trans*-retinoic acid. The synthetic mixture of **1** could be isomerized by iodine to a new mixture of 13-*cis*- and *all-trans*-**1**. With chromatographic separations of these mixtures (not done in this work) the $C_{10} + C_{10}$ route offers the potential for isolation of pure samples of 7-*cis*-, 13-*cis*-, and *all-trans*-retinoic esters and acids.

The $C_5 + C_{15}$ route produced mixtures of seven isomers of **1**. Separation of pure compounds from these mixtures by chromatography appears difficult to effect on a large scale. The complexity of such mixtures could be reduced by several experimental changes. Use of *all-trans*-β-ionylideneacetaldehyde (**4**), reported to be obtainable by chromatography,[15] should eliminate from the mixture all of the isomers that contain a 9-cis double bond. This could reduce the number of isomers to four. Iodine-catalyzed isomerization converts 11-cis to 11-trans double bonds, as shown in Table III, and can convert the mixture of seven isomers to a mixture of three isomers, 9-cis, 13-cis, and all-trans. Use of the 20% cross-linked polymer support serves to reduce the amounts of isomers with an 11-cis double bond. The 13-*cis*- and *all-trans*-**1** are well resolved by HPLC, while 9-*cis*- and *all-trans*-**1** are not. Although the mixtures produced from the $C_5 + C_{15}$ route are complicated, isolation of pure retinoids from such mixtures on a larger scale than in the present research should be possible.

Experimental Section

Reagents and Solvents. Benzene was distilled from CaH_2. Diethyl ether was distilled from $LiAlH_4$. Tetrahydrofuran was dried over anhydrous $MgSO_4$ and distilled from the sodium ketyl

(12) Halley, B. A.; Nelson, E. C. *J. Chromatogr.* **1979**, *179*, 113–123.
(13) Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367–2390.
(14) Ramamurthy, V.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 201–206.
(15) Dugger, R. W.; Heathcock, C. H. *Synth. Commun.* **1980**, *10*, 509–515.

of benzophenone under nitrogen. Ethyl 3-methyl-2-butenoate, β-cyclocitral, and β-ionone were distilled under vacuum. *N*-Bromosuccinimide was recrystallized. All other chemicals were reagent grade and were used without further purification. Sodium ethoxide was prepared by dissolving a weighed amount of freshly cut sodium in a measured volume of ethanol in a nitrogen atmosphere. 2,6-Dimethyl-7-(ethoxycarbonyl)-2,4,6-heptatrienal was provided by Dr. Michael Rosenberger of Hoffmann-La Roche, Inc. β-Cyclocitral was provided by Dr. V. Rautenstrauch, Firmenich SA, Geneva, Switzerland.

Analyses. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5840A instrument with a 6 ft × 0.125 in. o.d. nickel column of 20% SE-30 on 80/100 mesh chromosorb Q and a thermal conductivity detector. HPLC analyses were accomplished with a Spectra Physics Model 8700 solvent delivery system and a 254-nm UV detector from a Du Pont Model 830 chromatograph. A Partisil M9 10/50 ODS-2 column was used with a solution of 90% by volume methanol and 10% 0.01 M acetic acid in water as the solvent at a flow rate of 2 mL/min. Mass spectral analyses were done with a CEC Model 21-110B high-resolution double focusing mass spectrometer with a Data General DS-50S data system at 70 eV. ^1H, ^{13}C, and ^{31}P NMR spectra were obtained in $CDCl_3$ solvent on Varian Model XL-100(15) and XL-300 instruments with $(CH_3)_4Si$ as internal standard for ^1H and ^{13}C and 85% H_3PO_4 as external standard for ^{31}P. ^1H NMR spectra were recorded at 100 MHz and at 300 MHz, ^{13}C NMR at 25.2 MHz and at 75.5 MHz, and ^{31}P NMR at 40.5 MHz and at 121.5 MHz. IR spectra were recorded on a Perkin-Elmer Model 681 instrument. Elemental analyses were carried out by Galbraith Laboratories (Knoxville, TN).

General Procedures with Polymeric Reagents. General procedures for preparation, handling, and analysis of Wittig reagents have been reported.[6] Reactions involving retinoids were protected from light in a curtained area of a windowless laboratory.

(*E*)- and (*Z*)-(3-(Ethoxycarbonyl)-2-methylallyl)polystyryldiphenylphosphonium Bromide (2). A. 2% Cross-linked. By the general procedure 4.92 g (10.30 mequiv) of 2% cross-linked phosphine **7**[6] with 3.30 g (15.0 mequiv) of **6**[7] in 50 mL of benzene provided 6.83 g of the phosphonium salt **2**. ^{31}P NMR (121.5 MHz) 21.79 and 20.95 ppm. Anal. Found: Br^-, 1.22 mequiv/g (84%) by ion exchange analysis.

B. 20% Cross-Linked. By the general procedure 10.0 g of the phosphonium salt **2** was obtained from 8.70 g (6.08 mequiv) of 20% cross-linked phosphine **7**[6] and 3 mL (14.0 mequiv) of **6** in 60 mL of DMF. Anal. Found: Br^-, 0.48 mequiv/g (78%) by ion exchange analysis.

β-Cyclogeranylpolystyryldiphenylphosphonium Bromide (3). To 3.50 g (7.30 mequiv) of phosphine **7** in 30 mL of DMF was added 2.04 g (9.0 mmol) of β-cyclogeranyl bromide (**9**). The mixture was stirred at room temperature for 20 h, at 50 °C for 6 h, and at room temperature for 16 h. The polymer was filtered, washed, and dried as in the general procedure to give 4.79 g of **3**; ^{31}P NMR (121.5 MHz) 18.74 ppm. Anal. Found: Br^-, 1.11 mequiv/g (78.5%) by ion exchange analysis.

Polystyryldiphenylphosphonium Bromide (10). Into 2.0 g (3.6 mequiv) of phosphine **7** (partially oxidized to the phosphine oxide by impure THF washing) in 15 mL of benzene was passed hydrogen bromide gas for 5 min. The reaction mixture was stirred at room temperature for 24 h, filtered, and washed 8 times with 5-mL portions of benzene and with 10 mL of diethyl ether. The polymer was dried under vacuum at 40 °C to give 2.45 g of **10**; ^{31}P NMR (121.5 MHz) −9.09 ppm. Anal. Found: Br^-, 1.25 mequiv/g (79%) by ion exchange analysis.

Preparation of 3 from 10. To 2.01 g (2.50 mequiv) of **10** in 7 mL of DMF was added 0.648 g (4.60 mmol) of β-cyclogeraniol (**8**). The mixture was stirred at 50 °C for 16 h and at room temperature overnight. The polymer was filtered, washed, and dried as in the general procedure to give 2.30 g of **3**; ^{31}P NMR (121.5 MHz) 18.74 ppm. Anal. Found: Br^-, 0.95 mequiv/g (88%) by ion exchange analysis.

β-Ionylideneacetonitrile (12).[10] To a mixture of 10.5 mmol of β-ionone (**11**), 9.0 mL (55.6 mmol) of diethyl cyanomethylphosphonate, 17 mL of HMPA, and 30 mL of THF at −10 °C was added dropwise 54 mL (56 mequiv) of NaOEt in HOEt. The mixture was warmed to room temperature and stirred overnight. It was neutralized with 1:10 (v/v) (ca. 2 N) HOAc to pH 7, and after addition of 50 mL of 50% CH_3OH, the solvents were evaporated. The residue was extracted with ether. The ether layer was washed with saturated NaCl and H_2O and dried over $MgSO_4$, and the solvents were evaporated. The residue was vacuum distilled to afford 9.96 g (90.5%) of **12**, bp 100–103 °C (0.25 mm), GLC analysis of **12** showed two isomers, 7(*E*),9(*Z*) and 7(*E*),9(*E*), in the ratio 20:80. ^1H NMR data agreed with literature values.[16]

β-Ionylideneacetaldehyde (4) was prepared by reduction of **12** with diisobutylaluminum hydride followed by hydrolysis wth wet silica gel. The crude **4** was used immediately for the Wittig reaction without further purification.

Ethyl Retinoate (1) from 2% Cross-Linked 2 and 4. To 1.87 g (2.16 mequiv) of **2** in absolute ethanol (20 mL) at −10 °C were added dropwise and simultaneously 1.25 mL (2.20 mequiv) of NaOEt and 2.70 mL (ca. 2.0 mequiv) of an ethanolic solution of **4**. The mixture was stirred overnight in the dark, filtered under nitrogen pressure, and washed 9 times sequentially with 10 mL portions of deoxygenated ethanol, CH_2Cl_2, and diethyl ether. Solvents were evaporated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 and filtered, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in HPLC grade methanol and filtered through a Waters Associates SEP-PAK C_{18} cartridge with methanol washes. The solvent was evaporated with a stream of nitrogen to give 0.46 g (70%) of **1** by ^1H NMR integration. HPLC analysis showed seven isomers of **1** (Table III). Samples for NMR analysis were isolated as follows: The isomeric mixture of **1** (0.1 g) was dissolved in 2 mL of the HPLC eluant. Sample volumes of 0.4 mL were chromatographed at 2.0 mL/min at 24 °C. Elution order and volumes were 9,11,13-tri-cis at 157 mL, 11,13-di-cis at 170 mL, 13-cis at 191 mL, 9,13-di-cis at 199 mL, 11-cis at 217 mL, 9-cis at 236 mL, and all-trans at 244 mL. The seven isomers were collected 4 times in five fractions: (1) 9,11,13-tri-*cis*-**1**; (2) 11,13-di-*cis*-**1**; (3) 13-*cis*- and 9,13-di-*cis*-**1**; (4) 11-*cis*-**1**; (5) 9-*cis* and *all-trans*-**1**. Each sample was isolated by evaporation of solvents with a stream of nitrogen in a warm water bath followed by addition of HPLC grade methanol and evaporation 5 times. NMR analyses were performed in 100% $CDCl_3$ in 5-mm tubes.

Ethyl Retinoate (1) from 20% Cross-Linked 2. The procedure in the previous experiment was repeated with 3.48 g (1.66 mequiv) of 20% cross-linked **2**, 1.10 mL (1.70 mequiv) of NaOEt, and an ethanolic solution of **4** (2.0 mL, ca. 1.50 mmol). After SEP-PAK purification the yield was 0.345 g (65% by ^1H NMR integration). HPLC analysis revealed the isomer distribution in Table III.

Iodine-Catalyzed Isomerization of 1. The esters **1** (0.0452 g) from 20% cross-linked **2** in ether/benzene (2.0 mL, 1:1) were treated with 0.2 mL of 0.5% iodine in benzene[17] at 0 °C for 3 days. The solvents were evaporated with a stream of nitrogen and a warm water bath. HPLC grade methanol (2.0 mL) was added and evaporated 5 times to remove the iodine. HPLC analysis of the sample showed three major peaks corresponding to all-trans, 9-cis, and 13-cis isomers (Table III).

Ethyl Retinoate (1) from C_{10}-Phosphonium Bromide 3 and C_{10}-Aldehyde 5. A. Without Isolation of 3. To 2.26 g (4.75 mequiv) of phosphine **7** in THF (20.0 mL) was added 0.825 g (3.6 mmol) of β-cyclogeranyl bromide (**9**). The mixture was stirred at room temperature for 36 h and at 50 °C for 2 h. At −10 °C 0.414 g (1.90 mmol) of **5** and 1.8 mL (3.0 mmol) of NaOEt in HOEt were added dropwise simultaneously. After stirring at room temperature for 24 h, the mixture was filtered and washed as in the previous experiment. The filtrate was concentrated on a rotary evaporator and the residue was extracted with ether. The ether layer was washed with saturated NaCl, dried, and evaporated to give 0.58 g of **1**, which contained some unreacted **5**. HPLC analysis indicated two isomers in the ratio 77:23, which were characterized by ^1H NMR analaysis to be the all-trans and 7-cis isomers of **1**.

(16) (a) Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 193–199. (b) Samokvolov, G. I.; Zakharkin, L. I.; Davydova, L. P.; Khorlina, I. M. *Dokl. Akad. Nauk SSSR* **1959**, *126*, 1013–1026; *Dokl. Chem. (Engl. Trans.)* 447–450.

(17) Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984–1997.

The characteristic ^1H NMR signals used to identify 7-*cis*-1 in the mixture were H(7) at δ 5.96, H(11) at δ 6.95, CH_3(19) at δ 1.90, and CH_3(18) at δ 1.56.

The product esters 1 (0.58 g) in ethanol (2.0 mL) were hydrolyzed by boiling for 2 h with 0.208 g (3.5 mmol) of KOH in 2 mL of ethanol and 0.5 mL of water. The mixture was cooled, diluted with water (10 mL), neutralized with ca. 8 N acetic acid, and extracted with CH_2Cl_2. The organic layer was washed several times with water, dried, and evaporated to give 0.47 g of the acid. Recrystallization from methanol provided 0.20 g (38% overall yield) of *all-trans*-retinoic acid, mp 179–180 °C (lit.[5d] mp 179–181 °C). From the recrystallization yield, the total yield of two isomers of 1 was ≥50%.

B. With Isolation of 3. Wittig olefination conditions were similar to the previous experiment. From 1.52 g (1.67 mequiv) of 3 in THF (15.0 mL), 0.22 g (1.00 mmol) of 5, and 1 mL (1.67 mequiv) of NaOEt was obtained 0.18 g (55%) of crude 1. Mass spectral analysis showed M^+ at *m/e* 328, and the fragmentation pattern agreed with that of the corresponding methyl ester.[18] HPLC analysis showed two peaks in agreement with 7-cis and all-trans isomers of 1 which were further confirmed by the ^1H NMR spectrum. The esters 1 (0.10 g) in ether/benzene (4 mL, 1:1) were treated with 0.4 mL of 0.5% iodine in benzene at 0 °C for 3 days. After removal of iodine and solvents as before, HPLC analysis showed two peaks corresponding to 13-*cis*- and *all-trans*-1 in the ratio 25:75.

(18) Reid, R.; Nelson, E. C.; Mitchell, E. D.; McGregor, M. L.; Waller, G. R.; John, K. V. *Lipids* **1973**, *8*, 558–565.

Acknowledgment. We gratefully acknowledge the U.S. Army Research Office for Grants DAAG-29-79-C-0195 and DAAG-29-82-K-0133 (WTF), the National Institutes of Health for Grant AM 09191 (ECN), the partial support of the National Science Foundation by Grant CHE81-06157 to purchase the XL-300 NMR spectrometer, Dr. Michael Rosenberger of Hoffman-LaRoche, Inc., for a generous sample of aldehyde 5, and Dr. V. Rautenstrauch of Firmenich SA for a generous sample of β-cyclocitral.

Registry No. *all-trans*-1, 3899-20-5; 9-*cis*-1, 86708-67-0; 11-*cis*-1, 51249-34-4; 9,13-di-*cis*-1, 86708-68-1; 13-*cis*-1, 59699-82-0; 11,13-di-*cis*-1, 86708-69-2; 9,11,13-tri-*cis*-1, 86708-70-5; 7(*E*),9(*Z*)-4, 54226-17-4; 7(*E*),9(*E*)-4, 3917-41-7; 5, 63826-41-5; 8, 472-20-8; 11, 79-77-6; 7(*E*),9(*Z*)-12, 5299-99-0; 7(*E*),9(*E*)-12, 5299-98-9; $(EtO)_2P(O)CH_2CN$, 2537-48-6.

Supplementary Material Available: ^1H chemical shifts and coupling constants of ethyl retinoate isomers and *all-trans*-retinoic acid (Table IV) (1 page). Ordering information is given on any current masthead page.

Crown Ethers of Low Symmetry. Spiro Crown Ethers and 16-Crown-5 Derivatives

Mikio Ouchi, Yoshihisa Inoue,* Hidefumi Sakamoto, Atsushi Yamahira, Masanobu Yoshinaga, and Tadao Hakushi*

Department of Applied Chemistry, Himeji Institute of Technology, 2167 Shosha, Himeji, Hyogo 671-22, Japan

Received May 25, 1982

Spiro crown ethers **3a–c**, spiro bis(crown ethers) **5a–e**, and the related 16-crown-5 derivatives **6a–d** were synthesized and their cation binding abilities were evaluated by study of the extraction of aqueous alkali picrates. Crown ethers carrying 13-crown-4 and 16-crown-5 skeletons showed significant changes in cation selectivity as compared with the corresponding 12-crown-4 and 15-crown-5. Spiro-13-crown-4 **3a** and spiro-bis[4.4] **5a** showed extremely low extractabilities for all cations examined, while the 16-crown-5 derivatives, including spiro-bis[4.5] **5b** and spiro-bis[5.5] **5c**, showed anomalously high Na^+ selectivity. In a quantitative study of extraction equilibrium constants (K_{ex}), 16-crown-5 was again found to have much higher selectivity for Na^+ than 15-crown-5. This result is attributed to the less symmetrical spatial arrangement of donor oxygen atoms in 16-crown-5; the symmetry–extractability relationship is discussed on the basis of the size–fit concept.

Control of the cation binding ability of crown ethers has been the subject of several recent investigations. A wide variety of highly functionalized crown ethers have been synthesized to control the complexation phenomena, as exemplified by chiral crown ethers,[1] photoresponsive crown ethers,[2] poly- and bis(crown ethers) containing more than one adjacent crown ether unit,[3] polymer-supported crown ethers,[4] and lariat ethers carrying a flexible side chain with a donor group.[5] It has also been shown that even a slight conformational change in dicyclohexano-18-crown-6 alters the complex stability drastically.[6] However, little has been reported on the effects of the decrease in molecular symmetry caused, for example, by extending the methylene chain between two oxygen atoms of a 3*m*-crown-*m* into a (3*m* + 1)-crown-*m*.

Spiro bis(crown ethers) are of interest because they have an extra methylene group and a bulky spiro substituent, both of which may affect their complexing ability. The first spiro bis(crowh ethers) were synthesized by Weber,[7] but subsequent studies of them have been devoted exclusively to the preparation of 1:2 dicationic complexes where

(1) For a recent review see: Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43.

(2) Shinkai, S.; Shigematsu, K.; Sato, M.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2735; Shinkai, S.; Kouno, T.; Kusano, Y.; Manabe, O. *Ibid.* **1982**, 2741 and earlier references.

(3) Kopolow, S.; Hogen Esch, T. E.; Smid, J. *Macromolecules* **1973**, *6*, 133; Kimura, K.; Maeda, T.; Shono, T. *Talanta* **1979**, *26*, 945; Maeda, T.; Kimura, K.; Shono, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3506 and earlier references.

(4) See, for example, Smid, J. *Ind. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 364 and the references cited therein.

(5) Schults, R. A.; Dishong, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625; Nakatsuji, Y.; Nakamura, T.; Okahara, M. *Chem. Lett.* **1982**, 1207 and earlier references.

(6) Coxon, A. C.; Laidler, D. A.; Pettman, R. B.; Stoddart, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 8260.

(7) (a) Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 219. (b) *J. Org. Chem.* **1982**, *47*, 3478.

0022-3263/83/1948-3168$01.50/0