PGE_1 (8a and 8b). The 1:1 mixture of epimeric ester alcohols **7a** and **7b** (1.15 g, 0.003 26 mol) was dissolved in 15 mL of methanol. An aqueous sodium hydroxide solution [NaOH (150 mg, 0.00375 mol) and 6 mL of H_2O] was added to the above solution and the resulting mixture was stirred at room temperature for 20 h.

The reaction mixture was poured into 50 mL of H_2O and extracted with two 50-mL portions of ether. The aqueous layer was acidified with concentrated HCl at 0 °C and extracted with three 200-mL portions to CH_2Cl_2. The dried methylene chloride extracts were concentrated to give 1.0 g (90%) of an oil, crude **8**, which solidified on standing at −5 °C. The solid was chromatographed using silica gel G and elution with hexane–ether and ether–CH_2Cl_2 solutions yielded 800 mg (72%) of a pure 1:1 epimeric mixture of 15α- and 15-*epi*-11-deoxy-8-aza PGE_1: mp 82.5–85 °C; NMR ($CDCl_3$) δ 0.87 (t, distorted, 3 H), 1.10–1.90 (br hump), 2.0–2.60 (m) and 2.8–3.70 (m) (24H), 4.28–3.86 (m, 1 H), 5.48–5.75 (m, 2 H) and 6.37 (s, 2 H). After addition of D_2O the resonance peak at δ 6.37 disappeared: IR (KBr) 3400 (shoulder), 3200, 2910, 2600 (shoulder), 1715 and 1650 cm^{-1}; mass spectrum *m/e* 339 (M), 322 (M − OH), 321 (M − H_2O), 268 (M − C_5H_{11}), 264 [M − H_2O and $(CH_2)_3CH_3$], 250 (M − C_5H_{11} and H_2O), 238 (M − $C_5H_{11}CHOH$), 225 [M − CH_2=$CH(CH_2)_4CO_2H$], 224 [M − $(CH_2)_5CO_2H$], 212 (M − CH=$CHCHOHC_5H_{11}$), 210 [M − $(CH_2)_6CO_2H$)].

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.08; H, 9.91; N, 4.08.

Acknowledgment. We would like to thank the A. H. Robins Co. for a grant in support of this work, Mr. John Forehand for mass spectra data, Mr. Malcolm Stone for microanalysis, and Mr. Ashby F. Johnson, Jr., for coordinating the data obtained from the Robins Co.

Registry No.—**1**, 149-87-1; **2**, 62842-02-8; **2** methiodide, 62861-45-4; **3** isomer 1, 62861-46-5; **3** isomer 2, 62842-03-9; **4** isomer 1, 62861-47-6; **4** isomer 2, 62861-48-7; **5**, 57740-57-5; **6**, 57740-58-6; **7a**, 57740-59-7; **7b**, 57740-60-0; **8a**, 57740-61-1; **8b**, 57740-62-2; 2-amino-2-methylpropanol, 124-68-5; methyl 7-bromoheptanoate, 54049-24-0; dimethyl (2-oxoheptyl)phosphonate, 36969-89-8.

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Use of Insoluble Polymer Supports in Organic Synthesis. 9. Synthesis of Unsymmetrical Carotenoids on Solid Phases[1]

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Carotenoids have been synthesized by many routes.[2] One of the most attractive routes to *symmetrical* carotenoids, such as β-carotene, is the $C_{15} + C_{10} + C_{15}$ approach,[3] whereby 2 mol of a suitable C_{15} Wittig reagent reacts with the *symmetrical* C_{10} dialdehyde, 2,7-dimethyl-2,4,6-octatrien-1,8-dial (**1**).[4] This approach has also been used in the synthesis of *unsymmetrical* carotenoids such as γ-carotene, whereby the symmetrical dialdehyde **1** first reacts with one C_{15} Wittig reagent to yield the product from reaction at just one end of the aldehyde, namely an apocarotenal.[3,5,6] All these cases give apocarotenals or their analogues <60% yield and in some cases under 5% yield.[6] Subsequent reaction of the apocarotenal with a second C_{15} Wittig reagent yields the unsymmetrical carotenoid. Alternatively, the symmetrical dialdehyde **1** can react with a 1:1 mixture of two different C_{15} Wittig reagents to give unsymmetrical carotenoids contaminated with large quantities of symmetrical carotenoids.[6] The unsymmetrical carotenoids are formed in moderate to poor yields by solution methods due to the formation of substantial amounts of symmetrical products and recovery of unreacted reagents. The pure products are then obtained only after careful chromatography.

Table I. Yields of Apocarotenals and Analogues Prepared on Solid Phases

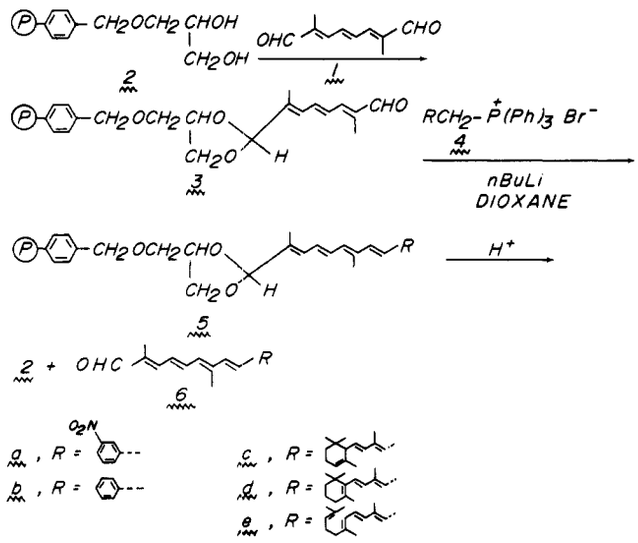
Apocarotenal or analogue	Registry no.	Quantity of 1 bound to 3, mmol/g	Quantity of apocarotenal or analogue, mmol/g	Yield, %
6a	62930-48-7	0.26	0.182	70
6b	62930-49-8	0.26	0.22	86
6c	62948-59-8	0.195	0.195	100[a]
6d	1638-05-7	0.195	0.056	29
6e	1071-52-9	0.195	0.140	72[a]

[a] The literature yields[3] by solution methods were 45 and 52% for **6c** and **6e**, respectively.

In our laboratory, we have shown that insoluble polymer supports[7] can be used as monoblocking groups for symmetrical diols and have applied this advantage to the synthesis of insect sex attractants.[8] Similarly, polymer-bound 1,2- and 1,3-diols have been used as monoblocking agents of symmetrical aromatic dialdehydes,[9,10] although attempted monoprotection of symmetrical aliphatic dialdehydes failed.[10] In any event, the completely conjugated symmetrical dialdehyde **1** reacted with the previously prepared 2% cross-linked divinylbenzene–styrene copolymer **2**,[9] containing vicinal diol groups, in anhydrous dioxane containing *m*-benzenedisulfonic acid as catalyst. This product gave the monoblocked polymer-bound aldehyde **3**, which exhibited an absorption in its IR spectrum at 1680 cm^{-1}. Cleavage of the aldehyde from the polymer in 0.5 N HCl in wet tetrahydrofuran (THF) led to recovered **1** and **2**, the latter exhibiting no absorption in the carbonyl region of its IR spectrum. Based on recovered **1**, the capacity of **3** was 0.2–0.3 mmol of 1/g. Condensation of **3** with the Wittig reagent prepared from *m*-nitrobenzyltriphenylphosphonium bromide (**4a**) and base[11] yielded the polymer-bound Wittig product **5a**, exhibiting IR absorption bands at 1530 and 1350 cm^{-1} typical of the nitro group. Indeed, as IR spectroscopy remains one of the few tools by which reactions can be followed on polymer supports, the nitro-Wittig reagent was carefully selected in the first instance in order to follow the progress of this synthetic route. Thus, in this reaction a polymer-bound product **5a** containing a diagnostic IR absorption band was obtained. Acid hydrolysis of **5a** gave the mono Wittig adduct, 2,7-dimethyl-9-(*m*-nitrophenyl)-2,4,6,8-nonatetraen-1-al (**6a**) in good yield (Table I). Similarly, the Wittig reagent, prepared from benzyltriphenylphosphonium bromide (**4b**)[11] gave the polymer-bound product **5b**, which on acid cleavage yielded 2,7-dimethyl-9-phenyl-2,4,6,8-nonatetraen-1-al (**6b**) in high yield (Table I).

The Wittig reagents, prepared from α[3], β[12], and ψ-ionylideneethyltriphenylphosphonium bromides[3] and *n*-butyllithium, respectively, reacted with polymer-bound aldehyde **3** in anhydrous dioxane to give the polymer-bound apocarotenals **5c**, **5d**, and **5e**, respectively. Cleavage of **5c–e** under acidic conditions led to α-apo-12′-carotenal (**6c**),[3] β-apo-12′-carotenal (**6d**),[13] and apo-12′-lycopenal (**6e**)[3] in good yields (Table I). The formation of **6d** was accompanied by the recovery of 64% of unreacted dialdehyde **1**, but no dialdehyde

Scheme I



1 was recovered in the synthesis of **6a, 6b, 6c,** and **6e.** As apocarotenals have been previously converted to unsymmetrical carotenoids,[3] the above procedure represents an improved procedure for the total synthesis of unsymmetrical carotenoids. The almost quantitative formation of the Wittig product in one instance, the generally high yields of the Wittig products (except for **6d**), and the general lack of recovery of starting dialdehyde 1 upon isolation of the Wittig products precludes the possibility that symmetrical dialdehyde 1 was initially bound to the polymer at both ends; thus, we feel that 1 was almost exclusively monoblocked by polymer **2.**

In conclusion, the synthesis of apocarotenoids can be readily achieved from the symmetrical dialdehyde 1 in high yield by using insoluble polymer supports without concomitant formation of symmetrical by-products and the recovery of starting material. This procedure represents a useful addition to the repertoire of synthetic procedures for the preparation of unsymmetrical carotenoids.

Experimental Section

All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Unicam SP1000 IR spectrophotometer using KBr disks unless otherwise stated. Ultraviolet spectra were measured using a Unicam SP800A UV spectrometer. The NMR spectra were measured on a Varian A60 spectrometer using tetramethylsilane as an internal standard (δ 0) and deuteriochloroform as solvent. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer. The number in brackets after the indicated ion shows the percent of the base peak represented by that ion. Silica gel was used for thin- and thick-layer chromatography. Microanalyses were performed by G. Gygli of Toronto. Filtering procedures were done under vacuum using a sinterglass funnel. All the stirring described below was performed using a Fisher magnetic stirrer.

Preparation of Polymer-Bound Aldehyde 3. Excess symmetrical dialdehyde 1 (4.0 g, 0.024 mol) and polymer **2** (8.5 g) in 120 mL of dioxane, containing anhydrous sodium sulfate (2.0 g) and *m*-benzenedisulfonic acid (0.5 g), were stirred under argon for 48 h in a 250-mL round-bottom flask fitted with a septum cap. The light yellow product **3** was isolated by a procedure previously described.[9] The infrared spectrum of **3** exhibited an absorption at 1680 cm^{-1} (m) typical of a conjugated aldehyde.

Determination of the Quantity of Dialdehyde 1 Bound to Polymer Aldehyde 3. Polymer-bound aldehyde **3** (0.5 g) was suspended in a solution of 0.5 N anhydrous HCl and wet THF and stirred for 48 h under argon. The polymer was filtered and washed six times with 10-mL portions of water, six times with acetone (10 mL), three times with ethanol (10 mL), and three times with ether (10 mL). The filtrate was extracted with ether–tetrahydrofuran, washed with water, dried ($MgSO_4$), and evaporated to give crude 1. This product on preparative TLC (ether–benzene 3:7) yielded pure recovered dialdehyde 1 (21 mg, 0.13 mmol), which represents a loading capacity of 0.26 mmol of 1/g of polymer **3.** Recovered polymer **2** did not exhibit a residual absorption at 1680 cm^{-1}, indicative of uncleaved polymer-bound aldehyde **3.**

General Procedure for the Preparation of Apocarotenoids from Polymer-Bound Aldehyde 3. In a typical procedure, an excess of the Wittig precursor α-ionylideneethyltriphenylphosphonium bromide (**4c**) (1.75 g, 3.2 mmol) was added to 20 mL of anhydrous dioxane in a 50-mL round-bottom flask, fitted with a Claisen adapter. Polymer-bound aldehyde **3** (2.0 g, containing 0.39 mmol of 1) was added to the side arm of the adapter. The flask was tilted so that the polymer did not fall into the flask. The two outlets of the Claisen adapter were fitted with septum caps. The stirred solution was purged with argon and 2 mL of 1.6 M *n*-butyllithium in hexane was added dropwise through the septum with a syringe. The solution was stirred for an additional 5 min, polymer **3** was washed into the reaction flask with 20 mL of anhydrous dioxane, and the suspension stirred under argon for 24 h. The polymer was filtered and washed three times with 20-mL portions each of dioxane–water (1:1), water, methanol, and ether. The orange-brown polymer-bound Wittig product (**5c**) did not exhibit an absorption band at 1680 cm^{-1} in its IR spectrum, indicative of unreacted **3.** In the preparation of **5e,** however, some residual absorption at 1680 cm^{-1}, due to unreacted **3,** was observed.

Isolation of the apocarotenals was achieved by acid cleavage of the polymer-bound Wittig products as described for the determination of 1 in **3.** Purification of the filtrate by preparative TLC (ether–benzene 1:7) gave the known apocarotenals **6c–e** in yields outlined in Table I.

2,7-Dimethyl-9-(*m*-nitrophenyl)-2,4,6,8-nonatetraen-1-al (6a) and 2,7-Dimethyl-9-phenyl-2,4,6,8-nonatetraen-1-al (6b). Polymer **3** (2.0 g), containing 0.52 mmol of 1, was treated with **4a** (4.8 g, 10 mmol) in a Wittig reaction as described above. The polymer-bound Wittig product **5a** was cleaved under acidic conditions similar to that for the cleavage of **3.** Purification by preparative TLC (ether–benzene 1:10) gave 103 mg (yield, Table I) of pure **6a** as deep red crystals: mp 60–63 °C; UV (THF) λ_{max} 378 and 398 nm (ϵ 24 650 and 21 750); IR 1657 (aldehyde, C=O) 1530 (NO_2), 1350 (NO_2), and 961 (trans CH=CH) cm^{-1}; NMR δ 9.50 (s, 1, aldehyde proton), 8.35–7.2 (m, 4, aromatic protons), 7.1–6.1 (m, 6, olefinic protons), 2.05 (s, 3, 2-methyl protons), and 1.88 (s, 3, 7-methyl protons); mass spectrum *m/e* 283 (100) (M^+), 254 (15), 145 (33).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.31; N, 4.78.

Similarly, treatment of **3** (1.0 g, containing 0.26 mmol of 1) with **4b** (2.2 g, 5 mmol) yielded **5b,** which on acid cleavage and purification yielded 53 mg (yield, Table I) of pure **6b** as orange crystals: mp 62–64 °C; UV (cyclohexane) λ_{max} 364, 383, and 402 nm (ϵ 14 360, 19 880, and 16 500); IR 1668 (aldehyde, C=O) and 960 (trans CH=CH) cm^{-1}; NMR δ 9.45 (s, 1, aldehyde proton), 7.4–7.3 (m, 5, aromatic protons), 7.1–6.1 (m, 6, olefinic protons), 2.05 (s, 3, 2-methyl protons), and 1.88 (s, 3, 7-methyl protons); mass spectrum *m/e* 238 (100) (M^+), 209 (15), 147 (27).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.23; H, 7.96.

Acknowledgment. The authors wish to thank the National Research Council of Canada for a grant in aid of this research.

Registry No.—**1,** 5056-17-7; **4a,** 1530-41-2; **4b,** 1449-46-3; **4c,** 62930-50-1; **4d,** 62285-98-7; **4e,** 59060-56-9.

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Analysis of the Stereochemical Integrity at C_α in Sequences Employing Ketone Tosylhydrazones

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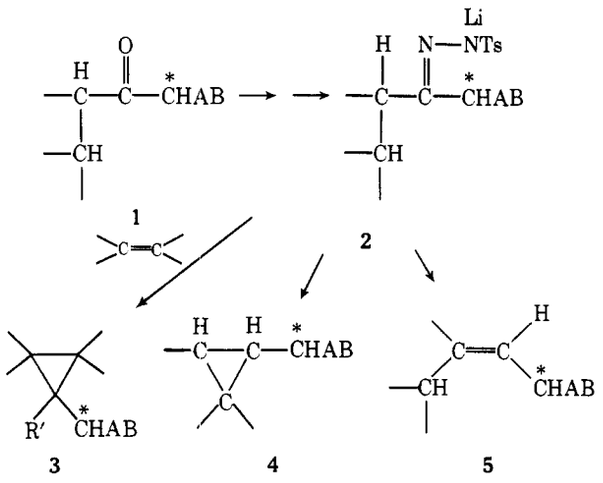
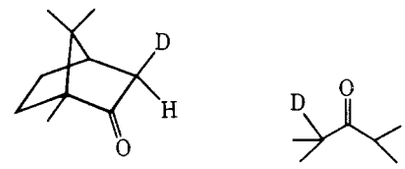
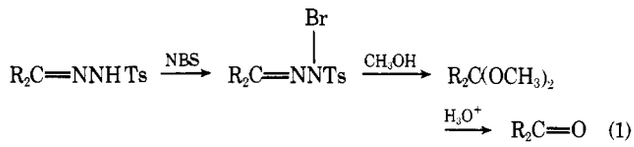
February 28, 1977

The tosylhydrazones of ketones and their alkali metal salts are most useful synthetic intermediates. Ketones generally may be readily converted in high yields to alkali metal salts of tosylhydrazones (**2**). Pyrolysis or photolysis may be used to create either an alkene (**5**) or cyclopropane (**4**) species in an intramolecular process or a cyclopropane adduct (**3**) as a consequence of an intermolecular reaction with an olefin.[1] In mechanistic studies of carbene intermediates ketone tosylhydrazones and their alkali metal salts usually represent the most readily available precursors for the generation of dialkyl carbenes. In either a synthetic or mechanistic application the preservation of stereochemical integrity at the α position may be of paramount importance. Conversion of a ketone to tosylhydrazone (H_2NNHTs, H^+) and then to lithium salt (CH_3Li) might very well alter the stereochemical environment at C_α through enolization. One convenient method to check on this might involve the reconversion of ketone tosylhydrazone salt **2** to ketone **1**, using a procedure which is mild enough not to cause additional enolization.



We chose to consider *exo*-3-deuteriocamphor[2] (**6**) and 4-deuterio-2,4-dimethyl-3-pentanone (**7**) as representative ketone substrates and cleavage using pyruvic acid catalysis[3] or the method of Rosini (*N*-bromosuccinimide)[4] (eq 1). Since





the *exo*-3-deuterium should be lost in preference to *endo*-3-hydrogen in the case of *exo*-3-deuteriocamphor,[2,5] deuterium loss from either **6** or **7** should be a sensitive measure of enolate formation.

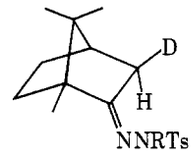
The deuterium content of ketones **6** and **7** was determined and both were converted to tosylhydrazone (**8a** and **9**). Analysis of cleavage back to ketone from tosylhydrazone (**8a**, **9**) or lithium salt of tosylhydrazone (**8b**) (Table I) clearly demonstrates that the *N*-bromosuccinimide method is an eminently suitable method to check the stereochemical integrity at C_α in tosylhydrazone intermediates.

Experimental Section

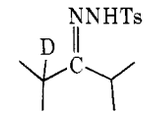
Melting points were obtained using either a Buchi melting point apparatus or a Mel-Temp device and are uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 or at 60 MHz with a Varian Anaspect EM-360. Infrared spectra were obtained with either a Beckman IR-8 or a Perkin-Elmer Model 621. Vapor-phase chromatographic analyses were carried out using a Varian Aerograph A-90-P, an 18 ft × ¼ in. 5% OV-17 on 60/80 chromosorb G column; yields were determined using *p*-cymene as an internal standard.

Deuterium analyses were accomplished by a low-voltage, mass-spectral technique using a Varium MAT CH-7 spectrometer, inter-

Table I. Reconversion of Ketone Tosylhydrazones to Parent Ketone



8a, R = H
b, R = Li



9

Cleavage method		Pyruvic acid	NBS	NBS
% yield		75	70	93
D content of initial ketone	D_0	7.0 ± 0.4[a]	7.0 ± 0.4	27.4 ± 0.6
	D_1	79.3 ± 0.4	79.3 ± 0.4	49.1 ± 0.6
	D_2	13.7 ± 0.3	13.7 ± 0.3	23.5 ± 0.5
D content of final ketone from reconversion of **8a** or **9**	D_0	63.1 ± 1.0	7.1 ± 0.4	27.7 ± 1.1
	D_1	32.8 ± 1.0	79.2 ± 0.4	49.8 ± 1.1
	D_2	4.1 ± 0.5	13.7 ± 0.2	22.5 ± 0.9
D content of ketone from reconversion of **8b**	D_0		7.4 ± 0.4	
	D_1		78.8 ± 0.6	
	D_2		13.8 ± 0.8	

[a] Standard deviation.