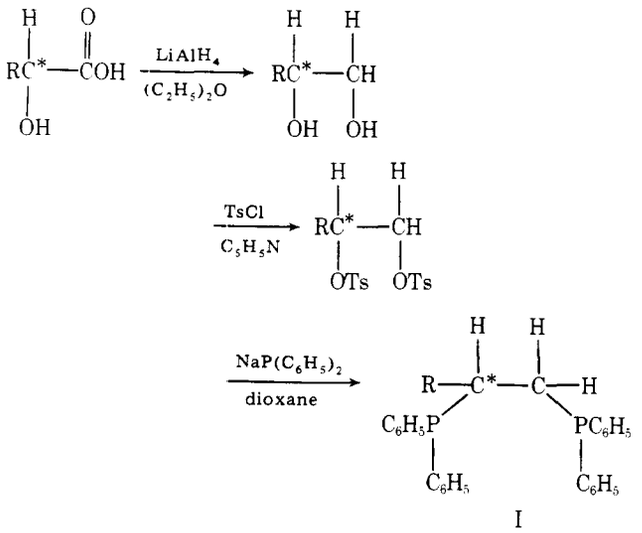

Figure 1. General scheme for converting chiral α-hydroxycarboxylic acids to chiral ditertiary phosphines (Ts = *p*-toluenesulfonyl).

Method B (In Situ Method). In these experiments the catalyst was generated in situ from $[(nor\text{-}C_7H_8)RhCl]_2$ and the ditertiary phosphine $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ using a phosphorus/rhodium mole ratio of 2.2:1 and a substrate/catalyst ratio of 100:1. The hydrogenations were conducted at 70 bars of hydrogen pressure in 20-mL stainless steel autoclaves at room temperature overnight. A catalyst for a typical in situ experiment was prepared from 5.75 mg of $[(nor\text{-}C_7H_8)RhCl]_2$ and 13.04 mg of $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ under argon in a mixture of 4.5 mL of benzene and 4.5 mL of methanol

Results and Discussion

The procedure for converting mandelic acid to the ditertiary phosphine $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ (Figure 1, R = C_6H_5) corresponds entirely to the procedure previously used by Fryzuk and Bosnich[6] for the conversion of (*S*)-(+)-lactic acid to (*R*)-(+)-$(C_6H_5)_2PCH(CH_3)CH_2P(C_6H_5)_2$ (Figure 1, R = CH_3) and apparently represents a general procedure for the conversion of α-hydroxycarboxylic acids to chelating ditertiary phosphines containing $PCHRCH_2P$ structural units and an asymmetric carbon atom. The ready commercial availability of both enantiomers of mandelic acid makes readily available both enantiomers of the chiral ditertiary phosphine $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ (I, R = C_6H_5) in contrast to the synthesis of $(C_6H_5)_2PCH(CH_3)CH_2P(C_6H_5)_2$ (I, R = CH_3) from lactic acid,[6] where only one of the enantiomers is readily available.

The ligand $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ (I, R = C_6H_5) is more readily isolated in the pure state than its methyl analogue I (R = CH_3), apparently because of its higher melting point. The analyses and NMR spectra (proton, carbon-13, and phosphorus-31) of $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ agree with the proposed structure I (R = C_6H_5). The phosphorus-31[9] and carbon-13[10] NMR assignments indicated in the Experimental Section are made by analogy with the NMR spectra of related compounds described in the cited references.

The catalytic activities of rhodium(I) complexes of both enantiomers of $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$(I, R = C_6H_5) were evaluated for the asymmetric hydrogenation of α-amidocinnamic acid precursors of phenylalanine. The results for the (*S*)-(+) enantiomer of I (R = C_6H_5) are given in Table I; in all cases the *R* configuration of the product was found. Two general types of reaction conditions were used: (1) use of the preformed cationic complex of the type [(diene)Rh(diphos)]$^+$, which was isolated as the perchlorate salt;[11] (2) use of a catalyst prepared in situ from the diene complex $[(nor\text{-}C_7H_8)RhCl]_2$ and the free ditertiary phosphine in a P/Rh mole ratio of 2.2:1.[12] The in situ catalysts were appreciably less reactive and required elevated hydrogen pressures for complete hydrogenation within a reasonable period of time. The optical yields from hydrogenation of a given substrate under both types of reaction conditions, however, were very similar (Table I) and also were similar or slightly lower (~80% vs. ~90%) than corresponding optical yields found by Fryzuk and Bosnich[6] for the related chiral ditertiary phosphine $(C_6H_5)_2PCH(CH_3)CH_2P(C_6H_5)_2$ (I, R = CH_3). As expected, rhodium(I) complexes of the (*R*)-(−) enantiomer of $(C_6H_5)_2PCH(C_6H_5)CH_2P(C_6H_5)_2$ (I, R = C_6H_5) gave the same optical yields of the *S* configuration of the product within experimental error as those reported in Table I for the (*S*)-(+) enantiomer of I (R = C_6H_5).

Several less successful attempts were made to use the chiral phosphine I (R = C_6H_5) in rhodium(I) catalysts for the asymmetric hydrogenations of the other substrates. Thus the in situ (method B) hydrogenation of citraconic acid dimethyl ester at 50 °C (70 bars) gave chemical yields of the hydrogenation product in the range 77–90%, but the optical yields were only 2–3%.

Acknowledgment. This work is part of a U.S.–Hungarian cooperative science program funded jointly by the U. S. National Science Foundation (Grant INT-76-20080) and the Hungarian Institute for Cultural Relations. We acknowledge the assistance of Mr. C. Pape at the University of Georgia and Mr. S. Iglewski at the Veszprém University of Chemical Engineering with the NMR spectra.

Registry No.—(*S*)-(+)-phenyl-1,2-ethanediylbis(diphenylphosphino)norbornadienerhodium perchlorate, 69401-65-6; (*S*)-(+)-phenyl-1,2-ethanediylbis(diphenylphosphine), 69381-90-4; (*R*)-(−)-phenyl-1,2-ethanediylbis(diphenylphosphine), 69381-91-5; (*S*)-(+)-1-phenyl-1,2-ethanediol bis(*p*-toluenesulfonate), 69381-92-6; (*R*)-(−)-1-phenyl-1,2-ethanediol bis(*p*-toluenesulfonate), 69381-93-7; (*R*)-(−)-phenyl-1,2-ethanediol, 16355-00-3; (*S*)-(+)-phenyl-1,2-ethanediol, 25779-13-9; D-(−)-mandelic acid, 611-71-2; L-(+)-mandelic acid, 17199-29-0; chlorodiphenylphosphine, 1079-66-9; bis[(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene]di-μ-chlorodirhodium, 12257-42-0.

References and Notes

(1) L. Markó and B. Heil, *Catal. Rev.*, **8**, 269 (1973).
(2) J. D. Morrison, W. F. Masler, and S. Hathaway in "Catalysis in Organic Syntheses, 1976", P. N. Rylander and H. Greenfield, Eds., Academic Press, New York, 1976.
(3) J. D. Morrison, W. F. Masler, and M. K. Neuberg, *Adv. Catal.*, **25**, 81 (1976).
(4) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2567 (1975); B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachmann, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **99**, 5946 (1977).
(5) M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977).
(6) M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **100**, 5491 (1978).
(7) F. R. Jensen and R. C. Kiskis, *J. Am. Chem. Soc.*, **97**, 5825 (1975).
(8) E. W. Abel, M. A. Bennett, and G. Wilkinson, *J. Chem. Soc.*, 3178 (1959).
(9) R. B. King and P. N. Kapoor, *J. Am. Chem. Soc.*, **93**, 4158 (1971).
(10) R. B. King and J. C. Cloyd, Jr., *J. Chem. Soc., Perkin Trans. 2*, 938 (1975).
(11) R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, **98**, 2134 (1976).
(12) J. A. Osborn, F. J. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc.*, 1711 (1966).

Reaction of Enol Silyl Ethers with Silver Acetate–Iodine. Synthesis of α-Iodo Carbonyl Compounds

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The reaction of enol acetates with thallium(I) acetate–iodine[1] and the oxidation of alkenes with silver chromate–

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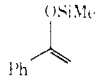
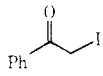
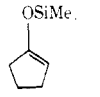
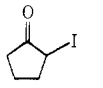
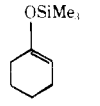
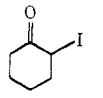
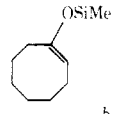
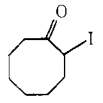
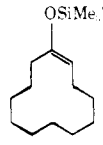
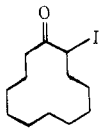
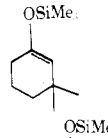
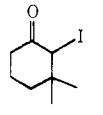
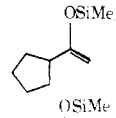
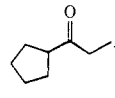
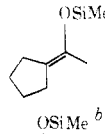
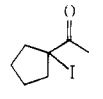
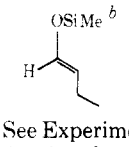
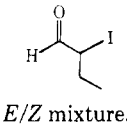
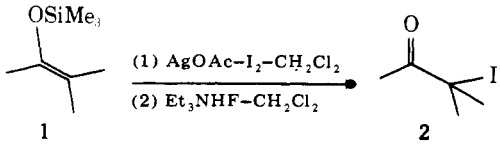
Table I. Preparation of α-Iodo Carbonyl Compounds 2 from Treatment of Enol Silyl Ethers 1 with Silver Acetate–Iodine (eq 1)

entry	enol silyl ether 1[a]	registry no.	α-iodo carbonyl compd 2[c]	% isolated 2	registry no.
1		13735-81-4		70	4636-16-2
2		19980-43-9		78	69381-32-4
3		6651-36-1		84	35365-19-6
4		50338-42-6		77	63641-49-6
5				69	69381-33-5
6		61175-92-6		94	69381-34-6
7		69381-31-3		83	69381-35-7
8		64661-75-2		69	69381-36-8
9				64	20175-17-1

[a] See Experimental Section. [b] *E/Z* mixture. [c] See Experimental Section for physical data.

iodine[2] have recently been reported as improved methods for the preparation of α-iodo carbonyl compounds.[3] Although both approaches represent a significant advance,[4] the former suffers from the necessity to employ toxic thallium(I) acetate and from the problems associated with general methods available for regiospecific enol acetate formation. The latter is limited in that only 1-iodo-2-alkanones can be prepared from terminal alkenes. Also, regioselectivity with cyclic alkenes does not seem possible, although this point was not tested.

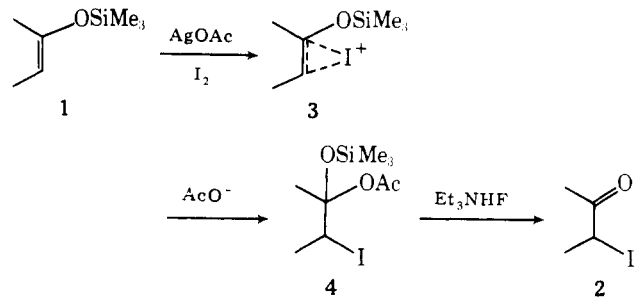
We would like to report that sequential treatment of enol silyl ethers 1 with silver acetate–iodine followed by triethylammonium fluoride affords high yields of the corresponding α-iodo carbonyl compounds 2 (eq 1).[5,6] The ready accessibil-

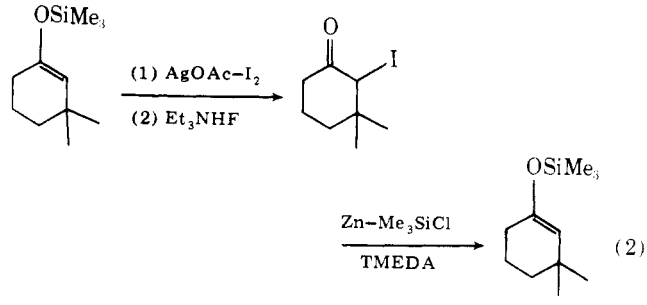


1 2 (1)

ity[7,8] and regiostability[8,9] of 1 coupled with the mild reaction conditions needed for transformation of 1 into 2 recommend the current method. Typical results are summarized in Table I. Aside from the general applicability of the procedure, several additional features emerge from the data presented. Sole production of 2-iodo-3,3-dimethylcyclohexanone (entry 6), (iodoacetyl)cyclopentane (entry 7) and 1-acetyl-1-iodocyclopentane (entry 8) from the corresponding enol silyl ethers indicates the regiospecific nature of the method. Conversion of 2-iodo-3,3-dimethylcyclohexanone back to 1-(trimethylsiloxy)-3,3-dimethylcyclohexene by treatment with zinc–Me_3SiCl–TMEDA[7a] gave no detectable formation of regioisomers (eq 2) (see Experimental Section). Entries 6 and 8 are also indicative of the fact that sterically encumbered enol silyl ethers are converted smoothly into 2. The production of 2-iodobutanal (entry 9) is an example of the utility of the current method for transformation of 1 into a regioisomer unaccessible via the silver chromate–iodine–alkene sequence.[2]

Scheme I





(2)

It is of interest that 1, due to enhanced nucleophilicity, reacts readily with silver acetate–iodine, whereas enol acetates give much less favorable results with this reagent system.[1] Further, reaction of 1 with molecular iodine gave no useful results.[11]

The mechanism of the reaction of 1 with silver acetate–iodine can be envisioned as occurring with initial formation of the iodonium ion 3, followed by acetate attack to afford 4 (Scheme I).[10] No attempt was made to isolate 4, but this seems a likely intermediate in light of other reactions of 1 with electrophilic species.[8] Use of fluoride ion in the workup procedure finds analogy in previous work dealing with intermediates such as 4.[12]

Production of 2 thus makes α-iodo, α-chloro,[13] and α-bromo[14] carbonyl compounds all readily available from 1 by regiospecific processes. Work continues in our laboratories to develop new and useful synthetic methodology based on the chemistry of 1.

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (NMR) spectra were recorded at 60 MHz on a Varian Anaspect EM 360 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained on a Perkin-Elmer 621 grating infrared spectrometer using neat samples. Low-resolution mass spectra (MS) were obtained with a Perkin-Elmer RMU 6E instrument at 15 eV and are recorded as *m/e* values with relative abundances in parentheses. Elemental microanalyses were determined with a Perkin-Elmer 240 elemental analyzer. For column chromatography, Woelm silica gel, 0.032–0.063

mm (ICN Pharmaceuticals GmbH & Co.), was used. Triethylammonium fluoride was prepared according to the procedure of Hunig.[15] Anhydrous magnesium sulfate served as drying agent.

Preparation of Enol Silyl Ethers 1. In general, compounds 1 were prepared according to procedure "A" outlined by House, Czuba, Gall, and Olmstead.[16]

1-Phenyl-1-(trimethylsiloxy)ethylene: 73%; bp 92–93 °C (12 mm); n^{22}_D 1.5010 (lit.[16] bp 89–91 °C (12 mm), n^{26}_D 1.4988).

1-(Trimethylsiloxy)cyclopentene: 76%; bp 150–153 °C (700 mm); n^{23}_D 1.4362 (lit.[16] bp 158–159 °C (760 mm), n^{25}_D 1.4377).

1-(Trimethylsiloxy)cyclohexene: 74%; bp 70.5–71 °C (20 mm); n^{23}_D 1.4458 (lit.[16] bp 74–75 °C (20 mm), n^{24}_D 1.4451).

1-(Trimethylsiloxy)-1-butene (*E*/*Z* Mixture): 59%; bp 53–58 °C (75 mm); n^{23}_D 1.4012 (lit.[16] bp 56–62 °C (75 mm), n^{25}_D 1.4042–1.4097).

1-(Trimethylsiloxy)cyclooctene: 81%; bp 59.5–61 °C (2 mm); n^{21}_D 1.4612; IR (neat) 1660 cm^{-1}; NMR (CCl_4) δ 0.18 (s, 9 H), 1.2–2.7 (m, 12 H), 4.60 (t, 1 H, J = 8 Hz); MS *m/e* 199 (12), 198 (M^+, 63), 183 (22), 170 (52), 169 (35), 155 (22), 143 (100), 130 (36). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.59; H, 11.18. Found: C, 66.48; H, 11.16.

1-(Trimethylsiloxy)cyclododecene (*E*/*Z* Mixture): 72%; bp 99–100 °C (1.25 mm); $n^{19.5}_D$ 1.4710; IR (neat) 1660 cm^{-1}; NMR (CCl_4) δ 4.42 (t, 1 H, J = 7 Hz; *Z*), 4.48 (t, 1 H, J = 7 Hz; *E*); GLC (¼ in. × 6 ft, 5% SE-52, 175 °C) indicated an *E*/*Z* ratio of 2.8:1; MS *m/e* 255 (22), 254 (M^+, 100), 239 (9), 211 (10), 199 (10), 197 (11), 183 (21), 170 (12), 144 (10), 143 (53), 131 (10), 130 (70). Anal. Calcd for $C_{15}H_{30}OSi$: C, 70.79; H, 11.88. Found: C, 70.74; H, 12.04.

1-Cyclopentyl-1-(trimethylsiloxy)ethylene: 53%; bp 94–96 °C (53 mm); n^{19}_D 1.4412; IR (neat) 1650 cm^{-1}; NMR (CCl_4) δ 0.20 (s, 9 H), 1.33–1.88 (m, 8 H), 1.88–2.67 (m, 1 H), 3.92 (s, 1 H), 4.02 (s, 1 H); MS *m/e* 185 (10), 184 (M^+, 49), 169 (28), 139 (15), 138 (100), 117 (27), 75 (16), 73 (15). Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.03; H, 11.11.

[1-(Trimethylsiloxy)ethylidene]cyclopentane was prepared by the method cited in ref 7a: 63%; bp 101–102 °C (50 mm); n^{21}_D 1.4482; IR (neat) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.11 (s, 9 H), 1.22–1.88 (m, 4 H), 1.77 (s, 3 H), 1.88–2.38 (m, 4 H); MS *m/e* 185 (17), 184 (M^+, 100), 169 (49), 156 (13), 143 (10), 75 (11); metastable 155, 132, 111. Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.32; H, 10.80.

3,3-Dimethyl-1-(trimethylsiloxy)cyclohexene. The title compound was prepared by the general method presented by Stotter and Hill.[17] A stirred mixture of 9.55 g (50 mmol) of copper(I) iodide in 80 mL of dry ether ($LiAlH_4$) under an atmosphere of nitrogen was cooled with an ice–methanol bath and treated with 62.5 mL of a 1.6 M solution of methyllithium in ether (100 mmol). After 10 min, 4.4 g (40 mmol) of 3-methylcyclohex-2-en-1-one in 25 mL of dry ether was slowly added (~10 min) with stirring. After 15 min, a solution containing 13.7 g (12.6 mmol) of chlorotrimethylsilane, 4 mL of HMPA, and 16 mL of triethylamine was added and the resulting mixture was stirred for 8 h at 25 °C. The crude mixture was then filtered and the ether removed in vacuo. The residue was dissolved in 50 mL of pentane and filtered once again. The filtrate was then sequentially washed with 1 × 25 mL of cold saturated aqueous sodium bicarbonate solution and 1 × 25 mL of saturated aqueous sodium chloride solution. Drying, filtration, and solvent removal in vacuo afforded a pale yellow oil that was vacuum distilled to give 6.7 g (85%) of pure 3,3-dimethyl-1-(trimethylsiloxy)cyclohexene: bp 73–74 °C (10 mm); n^{21}_D 1.4408; IR (neat) 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H), 1.00 (s, 6 H), 1.12–2.10 (m, 6 H), 4.69–4.75 (m, 1 H); MS *m/e* 198 (M^+, 15), 184 (17), 183 (100); metastable 169, 29. Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.59; H, 11.18. Found: C, 66.66; H, 10.98.

Preparation of α-Iodo Carbonyl Compounds 2. General Procedure. A mixture of 0.508 g (2 mmol) of iodine and 0.334 g (2 mmol) of silver acetate in 15 mL of dry methylene chloride was stirred for 15 min at 25 °C under 1 atm of N_2. At this point a solution of 2 mmol of 1 in 1 mL of methylene chloride was added rapidly (~10 s), and the resulting slurry was stirred for 15 min at 25 °C. The mixture was then filtered and the filter cake washed with ~15 mL of methylene chloride. The filtrate was then treated with 4 mmol of triethylammonium fluoride, and the solution was stirred for 0.5 h at 25 °C under 1 atm of N_2. The solution was then placed in a separatory funnel and washed successively with 1 × 25 mL of 5% aqueous sodium thiosulfate, 2 × 25 mL of water, and 1 × 25 mL of saturated sodium chloride solution. Drying, filtration, and solvent removal (in vacuo) gave crude **2**, which was purified by either column chromatography, molecular distillation, or crystallization.

Phenacyl Iodide: 70%; mp 35.5–36 °C (methanol–water) (lit.[2] mp 34–34.5 °C).

2-Iodocyclopentanone: 78%; bp 50 °C (1 mm); molecular distillation; n^{24}_D 1.5681; IR (neat) 1735 cm^{-1}; NMR (CCl_4) δ 1.70–2.63 (m, 6 H), 4.46 (m, 1 H); MS *m/e* 210 (M^+, 100), 154 (11), 83 (47), 55 (64). Anal. Calcd for C_5H_7IO: C, 28.60; H, 3.36. Found: C, 28.87; H, 3.42.

2-Iodocyclohexanone: 84%; bp 45 °C (1 mm) [lit.[2] bp 54 °C (1 mm)]; molecular distillation; n^{27}_D 1.5600.

2-Iodocyclooctanone: 77%; bp 45 °C (1.75 mm) [lit.[2] bp 58 °C (1.5 mm)]; molecular distillation; n^{23}_D 1.5494.

2-Iodocyclododecanone: 69%; mp 52–52.5 °C (methanol); IR (KBr) 1695 cm^{-1}; NMR (CCl_4) δ 1.00–3.30 (m, 21 H), 4.72 (m, 1 H); MS *m/e* 308 (M^+, 10), 182 (18), 181 (100), 163 (28), 121 (13), 112 (10), 111 (13), 98 (41), 97 (16), 95 (26), 89 (10), 88 (19), 86 (35), 69 (16), 67 (13), 55 (15); metastable 147, 106.5. Anal. Calcd for $C_{12}H_{21}IO$: C, 46.76; H, 6.87. Found: C, 46.66; H, 6.92.

2-Iodo-3,3-dimethylcyclohexanone: 94%; purified by column chromatography; n^{21}_D 1.5468; IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 1.35 (s, 3 H), 1.38 (s, 3 H), 1.47–2.40 (m, 4 H), 2.40–2.63 (m, 1 H), 3.10–3.73 (m, 1 H), 4.45 (m, 1 H); MS *m/e* 253 (6), 252 (M^+, 62), 126 (12), 125 (100), 97 (39), 83 (29), 69 (20), 55 (65); metastable 75, 62. Anal. Calcd for $C_8H_{13}IO$: C, 38.11; H, 5.20. Found: C, 38.33; H, 5.37.

(Iodoacetyl)cyclopentane: 83%; bp 45 °C (2 mm); molecular distillation; n^{18}_D 1.5370; IR (neat) 1698 cm^{-1}; NMR (CCl_4) δ 1.25–2.10 (m, 8 H), 2.95–3.60 (m, 1 H), 3.83 (s, 2 H); MS *m/e* 238 (M^+, 21), 111 (23), 97 (100), 69 (85); metastable 52, 49. Anal. Calcd for $C_7H_{11}IO$: C, 35.31; H, 4.66. Found: C, 35.56; H, 4.80.

1-Acetyl-1-iodocyclopentane: 69%; bp 51 °C (1 mm); molecular distillation; n^{19}_D 1.5388; IR (neat) 1703 cm^{-1}; NMR (CCl_4) δ 1.50–2.40 (m, 8 H), 2.46 (s, 3 H); MS *m/e* 238 (M^+, 9), 112 (11), 111 (100), 67 (22), 43 (92); metastable 52, 40.5, 16.5. Anal. Calcd for $C_7H_{11}IO$: C, 35.31; H, 4.66. Found: C, 35.57; H, 4.90.

2-Iodobutanal: 64%; bp 46 °C (13.5 mm); molecular distillation; n^{23}_D 1.5174 (lit.[6c] bp 53 °C (14 mm), n^{20}_D 1.5050).

Preparation of 3,3-Dimethyl-1-(trimethylsiloxy)cyclohexene from 2-Iodo-3,3-dimethylcyclohexanone. The transformation was carried out using the general procedure noted in ref 7a. A mixture of 0.2 g (3 mg-atom) of zinc dust and 0.23 g (2 mmol) of TMEDA in 3 mL of ether was stirred under 1 atm of nitrogen with external cooling (ice bath). A solution containing 0.50 g (2 mmol) of 2-iodo-3,3-dimethylcyclohexanone and 0.6 g (5.5 mmol) of chlorotrimethylsilane in 5 mL of dry ether ($LiAlH_4$) was added, and the resulting mixture was stirred at 25 °C for 8 h. Filtration, removal of ether in vacuo, dissolution of the residue in pentane, filtration, and removal of pentane in vacuo afforded essentially pure 3,3-dimethyl-1-(trimethylsiloxy)cyclohexene. This material exhibited IR and NMR properties identical with those of authentic material and had a GLC retention time (¼ in. × 3 m, 5% SE-30, 80 °C) identical with that of authentic material. Spectral analysis (NMR) also indicated that no regioisomer was present.

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Registry No.—(*E*)-1-(Trimethylsiloxy)-1-butene, 19980-23-5; (*Z*)-1-(trimethylsiloxy)-1-butene, 19980-22-4; (*E*)-1-(trimethylsiloxy)cyclododecene, 55314-44-8; (*Z*)-1-(trimethylsiloxy)cyclododecene, 55314-46-0; 3-methylcyclohex-2-en-1-one, 1193-18-6; chlorotrimethylsilane, 75-77-4; iodine, 7553-56-2; silver acetate, 563-63-3.

References and Notes

(1) R. C. Cambie, R. C. Hayward, J. L. Jurlina, P. S. Rutledge, and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 126 (1978).
(2) G. Cardillo and M. Shimizu, *J. Org. Chem.*, **42**, 4268 (1977).
(3) For methods reported previously, see (a) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, **80**, 250 (1958); (b) C. Djerassi, J. Grossman, and G. H. Thomas, *ibid.*, **77**, 3826 (1955); (c) C. Djerassi and C. T. Lenk, *ibid.*, **76**, 1722 (1954); (d) *ibid.*, **75**, 3493 (1953); (e) P. L. Julian and W. J. Karpel, *ibid.*, **72**, 362 (1950).
(4) See ref 1 for a brief discussion of the pitfalls associated with earlier methods.
(5) A preliminary account of this work was presented at the 33rd Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 14–16, 1978, Abstract 180.
(6) For interesting recent studies employing **2**, see (a) H. M. R. Hoffmann and R. Chidgey, *Tetrahedron Lett.*, 85 (1978); (b) D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, **40**, 1990 (1975); (c) J. J. Riehl, A. Fougerousse, and Fr. Lamy, *Tetrahedron Lett.*, 4415 (1968).
(7) For two recent examples, see (a) G. M. Rubottom, R. C. Mott, and D. S. Krueger, *Synth. Commun.*, **7**, 327 (1977); (b) E. Nakamura, K. Hashimoto, and I. Kuwajima, *Tetrahedron Lett.*, 2079 (1978).
(8) For a review concerning the preparation and reactions of **1**, see J. K. Rasmussen, *Synthesis*, 91 (1977).
(9) See also E. W. Colvin, *Chem. Soc. Rev.*, **7**, 15 (1978).
(10) For a complete study of the analogous reaction of 3-*tert*-butylcyclohexene

with silver acetate–iodine, see R. C. Cambie, D. M. Gash, P. S. Rutledge, and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 1157 (1977). Note also the references cited in this article.
(11) G. M. Rubottom, unpublished results.
(12) For analogous use of fluoride ion, see G. M. Rubottom, J. M. Gruber, and G. M. Mong, *J. Org. Chem.*, **41**, 1673 (1976).
(13) R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).
(14) (a) L. Blanco, P. Amice, and J. M. Conia, *Synthesis*, 194 (1976); (b) ref 13; (c) J. Strating, S. Reitters, and H. Wynberg, *Synthesis*, 211 (1971).
(15) S. Hunig and G. Wehner, *Synthesis*, 180 (1975).
(16) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(17) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973).

Synthesis of an 11-Deoxy-8-azaprostaglandin E_1 Intermediate

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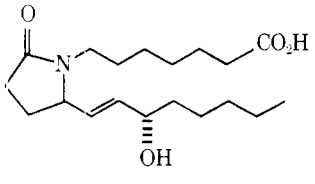
In recent years considerable chemical and medicinal interest has been focused on prostaglandin analogues in which carbon atoms are replaced by heteroatoms.[1] Among the azaprostaglandin analogues, which contain one or more nitrogens at almost every position of the cyclopentane nucleus, the 11-deoxy-8-azaprostaglandin E_1 (**1**) is of special interest because of the attractive biological activities.



1

The synthesis of **1** from pyroglutamic acid via synthon **14** has recently been reported.[2,3] In connection with our recent studies in the field,[4] we report herein two alternative approaches to **14** employing the ω-carbinol lactam **4** and the isoxazole acid **9** respectively as starting materials.

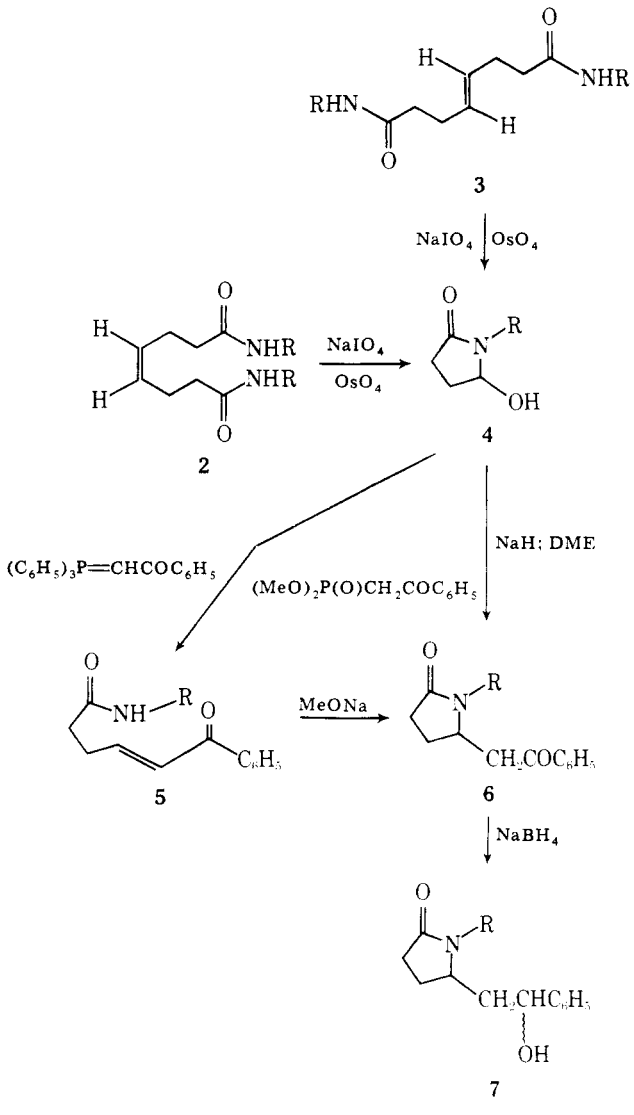
A synthetic approach to **7**, a precursor to the desired aldehyde **14**, could be realized by utilizing the 5-hydroxy-2-pyrrolidinone **4**, as outlined in Scheme I. Reaction of **2** or **3** with OsO_4 in the presence of $NaIO_4$[5] gave the hydroxy lactam **4** in 91% yield. Treatment of **4** with the sodium salt of dimethylphenacylphosphonate, by applying the recently developed elegant condensation of ω-carbinol lactams with Horner–Wittig reagents,[6] afforded a 68% yield of the keto lactam **6**. Alternatively, **6** could be obtained in 80% yield by reacting enone **5**, prepared by condensation of **4** with triphenylphenacylidenephosphorane, with NaOMe via an intramolecular Michael addition.

Reduction of **6** with sodium borohydride in methanol at 0 °C gave **7** in 80% yield as an epimeric mixture of alcohols which was converted to **14** without purification as shown in Scheme II.

The second approach to aldehyde **14** deals with a reaction sequence previously used in the synthesis of 14-hydroxy-8-azaprostanoids.[4] The isoxazole ester **8**,[7] prepared in 70% yield by cycloaddition of the nitrile oxide, derived from methyl 4-nitrobutyrate in the presence of phosphorus oxychloride[8] instead of phenyl isocyanate and phenylacetylene, was quantitatively saponified to give the acid **9**.

The vinylogous amide **10**, readily formed by hydrogenolysis

Scheme I



2 **3** **4** **5** **6** **7**

of **9**, underwent ring closure to the known[7] keto lactam **11** by treatment with ethyl chlorocarbonate in tetrahydrofuran at −10 °C. Exclusive N-alkylation of **11** with methyl 7-iodoheptanoate occurred smoothly to give **12** in 87% yield. Transformation of **12** into the alcohol **7** by catalytic hydrogenation at atmospheric pressure is quite critical and profoundly affected by the solvent and the catalyst used.

When the reduction was carried out in dioxane or methanol in the presence of PtO_2, **12** was recovered unchanged. However, the use of 10% Pd/C in dioxane afforded **7** in 79% along with minor quantites of over-reduced product. The latter, probably a 2-phenylethyl derivative, is the major product if methanol is substituted for dioxane as the solvent.

Dehydration of the alcohol **7** to the *trans*-styryl-derivative **13** proceeded without difficulty by heating **7** in toluene containing a trace amount *p*-toluensulfonic acid. When **13** was treated with Lemieux–Johnson reagent[5] in aqueous dioxane, double-bond cleavage occurred smoothly to give the known[2,3] aldehydo ester **14** in better than 70% yield, after chromatography. Since **14** has been transformed to 11-deoxy-8-azaprostaglandin E_1,[2,3] these sequences provide a convenient and new entry to **1** and related compounds.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R24A instrument using Me_4Si as an internal

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