(d, J = 9 Hz, 1 H), 7.40–7.60 (m, 4 H), 7.75–8.00 (m, 2 H).

Anal. Calcd for $C_{14}H_{13}BrO_3S$: C, 49.28; H, 3.84; S, 9.40. Found: C, 49.24; H, 3.87; S, 9.40.

Acknowledgment. I thank Dr. Ray Grabiak, Professor Peter Beak, and Professor W. Urry for their helpful discussions.

Registry No. 1, 59414-23-2; 2, 32501-93-2; 4, 76741-80-5; 5, 76756-18-8; 6, 76741-81-6; 7, 7402-69-9; 8, 76756-19-9; 9, 76741-82-7; 10, 76741-83-8; 11, 76741-84-9.

Practical Synthesis of 6a-Carbaprostaglandin I_2[1]

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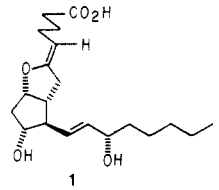
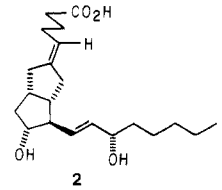
Prostacyclin (PGI_2, 1),[2] a recently discovered metabolite of arachidonic acid, appears to have an important role in preventing stroke, thrombosis, and heart attack.[3] However, because of the labile enol ether linkage, prostacyclin is a very unstable compound, and a chemically stable analogue would be potentially a much more useful therapeutic agent. Currently the intense search for such a stable mimic has focused upon 6a-carbaprostaglandin I_2 (**2**)[4] which has recently been shown to have a very similar biological profile to PGI_2.[5]



1



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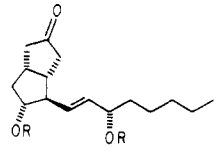
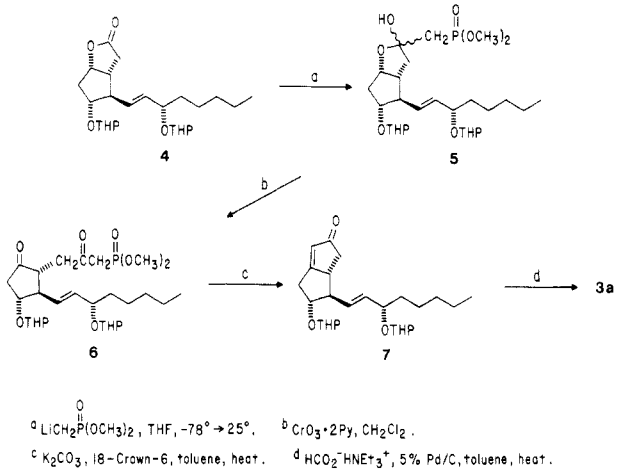


3a R = THP
3b R = H

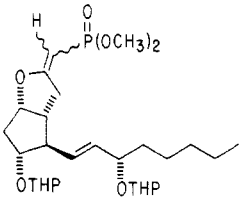
The synthesis of 6a-carba-PGI_2 was first reported in 1978 independently by Morton, Gandolfi, Nicolaou, and Kojima.[6] Since then several additional syntheses have appeared.[7] However, most of these syntheses require many steps and produce racemic material. An efficient synthesis suitable for the large-scale preparation of this important compound is still needed. A key intermediate in all except one of the aforementioned syntheses is the bicyclo[3.3.0]octanone compound **3**. This compound is then transformed to 6a-carba-PGI_2 by a Wittig reaction with (4-carboxybutyl)triphenylphosphorane. Herein is reported an efficient synthesis of optically active **3** utilizing a novel Wadsworth–Emmons reaction (see Scheme I).

Scheme I

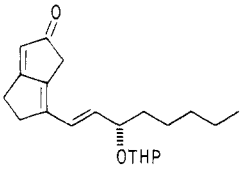


[a] $LiCH_2P(OCH_3)_2$, THF, −78° → 25°. [b] $CrO_3 \cdot 2Py$, CH_2Cl_2. [c] K_2CO_3, 18-Crown-6, toluene, heat. [d] $HCO_2^-HNEt_3^+$, 5% Pd/C, toluene, heat.

The readily available and optically pure lactone bis(tetrahydropyranyl ether) **4**, a general synthetic intermediate for the natural prostaglandins,[8] was utilized as starting material for the synthesis of 6a-carbaprostaglandin I_2. Treatment of lactone **4** with lithium dimethyl methylphosphonate[9] in tetrahydrofuran at −78 °C furnished the crystalline hemiketal **5** in 79% yield (99% yield based on recovered starting lactone). A modified Collins oxidation[10] of **5** afforded the desired diketone **6** in 64% yield along with 32% of the enol ether byproduct **8** formed from the β elimination of water from **5**. Carefully controlled Jones oxidation of **5** at −15 to −10 °C yielded 50% of **6** (63% based on recovered hemiacetal) and only 3% of byproduct **8**. Most other oxidation methods gave enol ether **8** as the major product.



8



9

Cyclization of ketone **6** to the strained bicyclo[3.3.0]octenone **7** could not be accomplished by using standard methods.[11,25] A variety of procedures were investigated for this intramolecular Wadsworth–Emmons reaction including sodium hydride in glyme or toluene, potassium carbonate in *tert*-butyl alcohol, and *n*-butyllithium in

(1) This work was described in part at the 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 1980; Abstract No. ORGN 236.

(2) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915. (c) Vane, J. R.; Bergström, S. "Prostacyclin"; Raven Press: New York, 1979.

(3) Moncada, S.; Vane, J. R. *J. Med. Chem.* **1980**, *23*, 591.

(4) This compound has also been called 9(*O*)-methanoprostacyclin, carboprostacyclin, and carbacyclin.

(5) (a) Whittle, B. J. R.; Moncada, S.; Whiting, F.; Vane, J. R. *Prostaglandins* **1980**, *19*, 605. (b) Aiken, J. W.; Shebuski, R. J. *Ibid.* **1980**, *19*, 629.

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(7) (a) Shibasaki, M.; Ueda, J.; Ikegami, S. *Tetrahedron Lett.* **1979** 433. (b) Katsube, J.; Shimomura, H.; Sugie, A.; Yamamoto, H. *Ibid.* **1979**, 2607. (c) Shibasaki, M.; Iseki, K.; Ikegami, S. *Chem. Lett.* **1979**, 1299. (d) Konishi, Y.; Kawamura, M.; Arai, Y.; Hayashi, M. *Ibid.* **1979**, 1437.

(8) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.

(9) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.

(10) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(11) (a) Henrick, C. A.; Böhme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926. (b) Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synth. Commun.* **1975**, *5*, 1. (c) Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979**, 3279. (d) Altenbach, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 940. See also: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011 and references therein.

0022-3263/81/1946-1954$01.25/0

tetrahydrofuran. However, in all cases either starting material was recovered or, if more vigorous reaction conditions were employed, the major products of the reaction were PGA type compounds arising from the β elimination of the THP ether in the cyclopentane ring.

Thus it appeared that proton transfer was taking place before intramolecular attack of the β-ketophosphonate anion and elimination of the phosphate occurred. Therefore, in an attempt to increase the nucleophilicity of the β-ketophosphonate anion and also possibly to increase the rate of phosphate elimination, crown ether was employed. The initial results were encouraging. Treatment of diketone **6** with potassium hydride and 18-crown-6 in THF at 0 °C afforded 29% of enone **7** along with 28% starting material and 15% of trienone **9**. The trienone byproduct is probably formed by the elimination of the THP ether of the enone **7** followed by double bond migration around the ring, a vinylogous base-catalyzed PGE to PGA to PGB type transformation.

Apparently the "naked" β-ketophosphonate anion was now nucleophilic enough to undergo the desired cyclization, but the reaction conditions were also basic enough to enolize the product. Therefore the reaction was attempted with potassium carbonate, a much milder base and certainly a much safer and more easily handled reagent than potassium hydride. Now when the diketone was treated with 1 equiv of potassium carbonate and 2 equiv of 18-crown-6 in warm toluene, a 65% yield (77% based on recovered **6**) of enone **7** was obtained along with 13% of trienone **9**. Use of less than 2 equiv of crown ether necessitated longer reaction times, leading to increasing amounts of the trienone byproduct. Use of potassium carbonate or potassium hydride without crown ether failed to effect the cyclization.

This is the first example of the use of crown ether in a Wadsworth–Emmons reaction, and these reaction conditions should be applicable to the formation of other systems including other bicyclo[3.3.0]octenones. The usual method for the formation of these strained systems is via an intramolecular aldol-type condensation of the corresponding 1,4-diketone.[12] However, the aldol conditions can lead to double bond migration around the cyclopentenone ring and are unsuitable if either the starting material or product contains a β leaving group.[13] The procedure employing potassium carbonate and crown ether represents a mild method for forming this very strained and base-sensitive product.[14] A number of natural products such as hirsutic acid[15] and isocomene[16] and the antitumor compounds coriolin,[17] pentalenolactone,[18] and quadrone[19] contain bicyclo[3.3.0]octane ring systems, and this reaction could potentially be used in their synthesis.[24]

Reduction of **7** to **3a** was initially accomplished in 40–50% yield by employing lithium in ammonia. However, this procedure proved to be cumbersome on a large scale since a very dilute solution of enone was required to prevent side reactions. An excellent procedure for this reduction utilized the method of Heck, who reported the reduction of conjugated double bonds in the presence of isolated double bonds.[20] Thus when octenone **7** was treated with 1 equiv of triethylammonium formate in warm toluene containing some palladium catalyst, a quantitative yield of the desired bicyclo[3.3.0]octanone **3a** was achieved (40–50% overall from lactone **4**).

The structure of octanone **3a** was proven by hydrolysis to the keto diol **3b** and comparison with authentic material.[21] Compound **3a** was converted to 6a-carbaprostaglandin I_2 by a Wittig reaction with (4-carboxybutyl)triphenylphosphorane followed by THP hydrolysis in about an overall 50% yield.[7a,b] Compound **2** prepared by this route was identical with authentic 6a-carba-PGI_2.[21]

Thus in six steps the readily available lactone **4** was converted to optically active 6a-carbaprostaglandin I_2. This practical synthesis (20% overall yield) has proven feasible on a large scale and should make this important compound more readily available for additional biological studies.

Experimental Section[22]

(3′*S*)-3-[(Dimethylphosphono)methyl]-2-oxa-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo[3.3.0]octan-3-ol (5). A solution of 19 mL (170 mmol) of dimethyl methylphosphonate in 600 mL of THF at −78 °C was treated over a 10-min period with 110 mL (172 mmol) of 1.56 M *n*-butyllithium in hexane. The resulting suspension was stirred for 30 min at −78 °C and then treated with

(12) (a) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1971**, 1829. (b) Sakan, F.; Hashimoto, H.; Ichihara, A.; Shirahama, H.; Matsumoto, T. *Ibid.* **1971**, 3703.

(13) The synthesis of **7** was attempted via an intramolecular aldol-type approach using a variety of acid- and base-catalyzed procedures. However, either starting material was recovered unchanged or else the major reaction was β elimination of the tetrahydropyranyl ether of the cyclopentanone ring of the starting 1,4-diketone to give PGA-type products.

(14) For the use of potassium carbonate and a catalytic amount of 18-crown-6 in a Wittig reaction with benzaldehyde, see: Boden, R. M. *Synthesis* **1975**, 784.

(15) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4761. For syntheses of hirsutic acid see: Trost, B. M.; Shuey, C. D.; DiNinno, F. *J. Am. Chem. Soc.* **1979**, *101*, 1284; Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 3745; Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1978**, 1991; Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Ibid.* **1972**, 2053.

(16) Bohlmann, F.; LeVan, N.; Pickardt, J. *Chem. Ber.* **1977**, *110*, 3777. Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. For syntheses of isocomene see: Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130.

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(18) Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970**, 4901. Takeuchi, S.; Ogawa, Y.; Yonehera H. *Ibid.* **1969**, 2737. For syntheses of pentalenolactone see: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536; Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *Ibid.* **1980**, *102*, 889.

(19) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38. For a synthesis of quadrone see: Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262.

(20) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3985.

(21) Authentic **3b** and 6a-carbaprostaglandin I_2 (**2**) were kindly provided by D. R. Morton, The Upjohn Co. (see ref 6a).

(22) All melting points and boiling points are uncorrected. All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The ^1H NMR spectra were obtained on a Varian A-60D spectrometer operating at 60 MHz or on a Varian HFT-80 spectrometer operating at 80 MHz of chloroform-*d* solutions. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) glass plates precoated with silica gel GF (250 μm). The solvent system A-IX[23] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11) and then by spraying with 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck, 70–230 mesh). Acid-washed silica gel was Mallinckrodt CC-4. Brine refers to a saturated aqueous solution of NaCl. $NaHCO_3$ refers to a saturated aqueous solution of sodium bicarbonate. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available. All reactions were done under an inert atmosphere.

a solution of 25.4 g (58.2 mmol) of lactone 4[8] in 100 mL of THF. The solution was allowed to warm to room temperature and stirred for an additional 3 h at room temperature before being cooled to 0 °C and treated with 10 mL of glacial acetic acid. The reaction mixture was partitioned between brine and diethyl ether, and the organic extracts were washed with $NaHCO_3$ and brine and dried (Na_2SO_4). After removal of solvents under reduced pressure, the crude product was crystallized from 3:1 hexane–diethyl ether to give 22.1 g (68%) of **5**, mp 89.0–92.4 °C. Chromatography of the mother liquors on silica gel (gradient elution from 100% ethyl acetate to 1:1 acetone–acetate) gave 5.0 g (20%) of starting lactone 4 (R_f 0.60 in ethyl acetate) and an additional 3.6 g (11%) of **5** as a white solid: R_f 0.20 (in ethyl acetate); NMR δ 0.88 (t, J = 5 Hz, 3 H), 1.0–3.0 (m, 28 H), 3.10–4.34 (m including two 3 H doublets, each J = 11 Hz, at 3.72 and 3.83, 12 H), 4.68 (br s, 3 H), 5.00 (br s, 1 H), 5.27–5.76 (m, 2 H); IR (mull) 3340, 1250, 1185, 1130, 1075, 1030 cm^{-1}; mass spectrum, m/e 458, 356. Anal. Calcd for $C_{28}H_{49}O_9P$: C, 59.98; H, 8.81. Found: C, 60.04, H, 8.61.

(3′*S*)-2α-[2-Oxo-3-(dimethylphosphono)propyl]-4α-[(tetrahydropyran-2-yl)oxy]-3β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]cyclopentanone (6). (a) Collins Procedure.[10] A suspension of 20.3 g of chromium trioxide and 34.6 mL of pyridine in 475 mL of methylene chloride at room temperature was treated all at once with 18.8 g (33.5 mmol) of hemiketal **5** in 40 mL of methylene chloride, and the resulting suspension was stirred for 45 min and then filtered through 225 g of silica gel eluted with 1500 mL of 2:1 ethyl acetate–acetone. The solvents were removed under reduced pressure to give 19 g of crude product which was chromatographed on silica gel eluted with 20% acetone in methylene chloride to give 3.1 g (32%) of byproduct **8** as a colorless oil (R_f 0.30 in 20% acetone in methylene chloride) and 6.3 g (64%) of **6** as a colorless oil (R_f 0.22 in 20% acetone in methylene chloride). For **8**: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–2.7 (m, 24 H), 2.84–3.19 (m, 2 H), 3.19–4.25 (m including 6 H d, J = 11 Hz, at 3.65, 12 H), 4.47–5.0 (m, 4 H), 5.33–5.7 (m, 2 H); IR (film) 1640, 1260, 1245, 1200, 1180, 1135, 1075, 1020, 975, 810 cm^{-1}; mass spectrum, m/e 542, 458, 374. Anal. Calcd for $C_{28}H_{47}O_8P$: C, 61.98; H, 8.73. Found: C, 61.39; H, 9.06. For **6**: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.1–2.98 (m, 26 H), 3.14 (d, J = 23 Hz, 2 H), 3.3–4.4 (m including 6 H d, J = 11 Hz, at 3.80, 12 H), 4.7 (br s, 2 H), 5.4–5.8 (m, 2 H); IR (film) 1745, 1715, 1260, 1200, 1185, 1130, 1030, 970, 870, 815 cm^{-1}; mass spectrum, m/e 390, 372, 354. Anal. Calcd for $C_{28}H_{47}O_9P$: C, 60.20; H, 8.48. Found: C, 60.21; H, 8.78.

(b) Jones Procedure. A solution maintained at −10 to −15 °C of 10.0 g (17.8 mmol) of hemiketal **5** in 75 mL of acetone was treated dropwise over 30 min with 9.0 mL of Jones reagent. The resulting suspension was stirred for an additional 30 min at −15 to −10 °C before being quenched with 4 mL of 2-propanol. The solution was decanted and most of the solvent removed at reduced pressure. The residue was partitioned between $NaHCO_3$ and diethyl ether, and the organic extracts were washed with $NaHCO_3$ and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to afford 8.9 g of crude product which was chromatographed on silica gel eluted with 20% acetone in methylene chloride to give 0.27 g (3%) of **8**, 4.95 g (50%) of **6**, and 2.13 g (21%) of starting hemiketal **5**.

(3′*S*)-7α-[(Tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo[3.3.0]oct-1-en-3-one (7). A suspension of 5.37 g (9.61 mmol) of compound **6**, 1.33 g (9.62 mmol) of anhydrous potassium carbonate, and 5.37 g (20.3 mmol) of 18-crown-6 in 200 mL of toluene was heated at 75 °C for 6 h, cooled to 0 °C, washed with brine, and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the crude product was filtered through 50 g of silica gel by elution with ethyl acetate. The first 250 mL of solution eluted contained 3.9 g of impure product and the next 600 mL contained 0.87 g (16%) of starting diketone **6**. The 3.9 g of impure product was chromatographed on silica gel eluted with 40% ethyl acetate in hexane to give 0.40 g (13%) of trienone **9** as a pale yellow oil (R_f 0.32 in 40% ethyl acetate in hexane) and 2.70 g (65%) of enone **7** as a colorless oil (R_f 0.22 in 40% ethyl acetate in hexane). For **9**: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–2.02 (m, 14 H), 2.90 (br s, 6 H), 3.23–4.43 (m, 3 H), 4.62 (br s, 1 H), 5.50–6.70 (m, 3 H); IR (film) 1695, 1650, 1615, 1580, 1200, 1125, 1110, 1075, 1035, 1020, 980, 820 cm^{-1}; mass spectrum, m/e 330, 229, 246, 85. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.09; H, 9.11. For **7**: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–3.26 (m, 26 H), 3.26–4.56 (m, 6 H), 4.73 (br s, 2 H), 5.18–5.86 (m, 2 H), 5.94 (br s, 1 H); IR (film) 1710, 1632, 1200, 1130, 1115, 1080, 1035, 1020, 970, 915, 870, 815 cm^{-1}; mass spectrum, m/e 361, 330, 246, 85. Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.31; H, 9.23.

(3′*S*)-7α-[(Tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyan-2-yl)oxy]-*trans*-1′-octenyl]bicyclo[3.3.0]octan-3-one (3a). A modification of the procedure of Heck was employed.[20] A suspension of 0.10 g (0.23 mmol) of enone **7**, 10 μL (0.27 mmol) of 97% formic acid, 0.05 mL (0.36 mmol) of triethylamine, and 0.01 g of 5% palladium on carbon in 2 mL of toluene was warmed to 85 °C (vigorous effervensence took place at about 70–75 °C), heated for 30 min at 85 °C, cooled, diluted with ethyl acetate, and filtered through Celite. The filtrate was washed with $NaHCO_3$ and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the crude product was chromatographed on silica gel eluted with 25% ethyl acetate in hexane to give 0.10 g (100%) of pure **3a** as a colorless oil: R_f 0.19 (in 25% ethyl acetate in hexane); NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–3.0 (m, 29 H), 3.25–4.33 (m, 6 H), 4.71 (br s, 2 H), 5.33–5.78 (m, 2 H); IR (film) 1740, 1200, 1160, 1130, 1075, 1035, 1020, 975 cm^{-1}; mass spectrum, m/e 248, 177, 85. Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.83; H, 9.74. Found: C, 72.01; H, 9.56.

(3′*S*)-7α-Hydroxy-6β-(3′-hydroxy-*trans*-1′-octenyl)bicyclo[3.3.0]octan-3-one (3b). A solution of 0.25 g (0.58 mmol) of ketone **3a** in 14 mL of 4:2:1 glacial acetic acid–water–THF was heated at 45 °C for 3 h, cooled, and partitioned between brine and ethyl acetate. The organic extracts were washed with $NaHCO_3$ and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the crude product was chromatographed on silica gel eluted with ethyl acetate to give 0.15 g (98%) of pure **3b** as a colorless oil: R_f 0.23 (in ethyl acetate): NMR δ 0.88 (t, J = 5 Hz 3 H), 1.0–2.9 (m, 17 H), 3.67 (m, 2 H), 3.6–4.23 (m, 2 H), 5.4–5.65 (m, 2 H); IR (film) 3400, 1735, 1160, 1130, 1095, 1070, 1020, 970 cm^{-1}; mass spectrum, calcd for $C_{22}H_{42}Si_2O_3$ [M^+ of bis(trimethylsilyl) derivative] m/e 410.2672, found m/e 410.2651. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.69; H, 9.69.

Compound **3b** was also found to be identical with authentic material[6a,21] by GC/MS [of the bis(trimethylsilyl) derivative] and TLC.

(5*E*)-6a-Carbaprostaglandin I_2 (2).[6a,7a,b] A solution of 30.2 mmol of sodium methylsulfinylmethide (prepared from 1.27 g of a 57% sodium hydride dispersion and 80 mL of Me_2SO) was cooled to 17 °C and treated with 6.70 g (15.1 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting red solution was stirred at 17 °C for 30 min, treated with 1.95 g (4.49 mmol) of ketone **3a** in 20 mL of Me_2SO, and stirred for 46 h at about 40 °C. The solution was cooled, quenched with water, neutralized with 1 N HCl, and extracted with ether. The ether extracts were washed several times with water and then with brine and were dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was chromatographed on acid-washed silica gel eluted with 15% ethyl acetate in hexane to give 0.54 g (23%) of the (5*Z*)-6a-carba-PGI_2 bis(tetrahydropyranyl) ether (R_f 0.31 in 65:34:1 hexane–ethyl acetate–glacial acetic acid) and 1.48 g (64%) of the desired (5*E*)-6a-carba-PGI_2 bis(tetrahydropyranyl) ether (R_f 0.25 in 65:34:1 hexane–ethyl acetate–acetic acid).

Without further purification, 0.69 g (1.33 mmol) of the above (5*E*)-6a-carba-PGI_2 bis(tetrahydropyranyl) ether (more polar isomer) was heated at 45 °C in a solution of 10 mL of THF, 14 mL of water, and 30 mL of glacial acetic acid. After 3 h the solution was cooled and partitioned between brine and ethyl acetate. The organic portion was dried (Na_2SO_4) and the solvent removed under reduced pressure (using a toluene azeotrope to remove any remaining acetic acid). The crude product was chromatographed on acid-washed silica gel eluted with 50% ethyl acetate in hexane to give 0.45 g (97%) of **2** as a white solid.

Recrystallization from hexane and ether furnished 0.35 g (75%) of 6a-carbaprostaglandin I_2 (**2**)[6a] as a white solid: mp 61–62.5 °C; R_f 0.31 (in A-IX[23]); NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.0–2.62 (m,

(23) Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1966**, *241*, 275.

23 H), 3.52–4.27 (m, 2 H), 5.03–5.68 (m, 3 H), 6.0 (s, 3 H); IR (mull) 3480, 3340, 3140, 2720, 2640, 2560, 1725, 1675, 1265, 1250, 1090, 1075, 970 cm^{-1}; mass spectrum, calcd for $C_{29}H_{55}Si_3O_4$ [$M^+ - CH_3$ for the tris(trimethylsilyl) derivative] m/e 551.3408, found m/e 551.3387 (other ions at m/e 566, 495, 476, 405, 386, 73); $[\alpha]_D$ +91° (c 0.964, CH_3OH). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.80; H, 9.68.

Compound **2** was also identical by TLC with authentic material (mixture melting point 60–61.5 °C).[6a,21]

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Registry No. 2, 69552-46-1; **2** bis(tetrahydropyranyl) ether, 71845-98-2; **2** tris(trimethylsilyl) derivative, 70398-64-0; **3a**, 70870-92-7; **3b**, 69552-54-1; **3b** bis(trimethylsilyl) derivative, 70398-74-2; **4**, 37517-42-3; **5**, 76794-00-8; **6**, 76794-01-9; **7**, 76794-02-0; **8**, 76794-03-1; **9**, 76794-04-2; dimethyl methylphosphonate, 756-79-6; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6; (5*Z*)-6a-carba-PGI_2 bis(tetrahydropyranyl) ether, 76822-29-2.

(24) Since the completion of this work the synthesis of 5-methyl-6-oxobicyclo[3.3.0]oct-1-en-3-one has been reported utilizing an intramolecular Wittig reaction of a stabilized phosphorane with potassium carbonate at 40 °C: Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. Since a stabilized phosphorane is generally less nucleophilic than the corresponding β-ketophosphonate anion, this route would probably not be effective for the formation of bicyclo[3.3.0]octenone **7**.

(25) For a very recent review of the intramolecular Wittig reaction see: Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.

Cation–Anion Combination Reactions. 19.[1] Some Reactions of Ortho-Substituted Triarylmethyl Cations in Water

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As a part of our general studies of electrophile–nucleophile reactions,[1] we have studied the reactions of two tri-ortho-substituted triarylmethyl cations with several nucleophiles in aqueous solution. The results are reported in the present paper.

Experimental Section

Synthesis of Tris(2,4-dimethoxyphenyl)methyl Alcohol. To a solution of 0.094 mol of phenyllithium in ca. 50 mL of absolute ether was added 0.092 mol of 2,4-dimethoxybromobenzene (Aldrich) in ca. 30 mL of ether. The resulting solution was stirred at room temperature for 4 h, and then a solution of 0.025 mol of dimethyl carbonate in ca. 10 mL of ether was added dropwise. The reaction mixture was heated to reflux for ca. 20 min and then cooled to ice bath temperature. Excess lithium reagent and salts were decomposed by the addition of ca. 75 mL of 6 M acetic acid followed by 25 mL of concentrated ammonium hydroxide. The aqueous layer was separated and washed with several portions of ether, and the combined ether solutions were then washed with dilute sodium carbonate and dried over potassium carbonate. The ether was removed on a rotary evaporator and the remaining oil was dissolved in the minimum amount of hot ethanol. On cooling, the ethanol solution yielded crystals which were recrystallized once from ethanol and then once from acetone to give ca. 3.5 g of purified product, mp 153.0–153.5 °C (lit.[2] mp 149 °C). The ^1H NMR spectrum of the material in $CDCl_3$ solution showed the methoxy singlets at 3.42 and 3.73 ppm, the OH singlet at 5.2 ppm, and the aromatic multiplets at 6.3–7.1 ppm, with the expected relative intensities. A solution of the compound in 0.1 M HCl showed absorbance peaks at 552 nm (ϵ 3.1 × 10^4 M^{-1} cm^{-1}), 415 (1.4 × 10^4), and 277 (1.9 × 10^4), and a strong shoulder at ca. 515 nm (3.0 × 10^4).

Synthesis of Tris(2-methyl-4-methoxyphenyl)methyl Alcohol. The Sandmeyer reaction of 2-methyl-4-methoxyaniline[3] was used for the preparation of 2-methyl-4-methoxybromobenzene.

To ca. 30 g of the aryl bromide in 60 mL of anhydrous ether under argon was slowly added a 10% excess of *n*-butyllithium in hexane at 0 °C. The solution was allowed to stand at ice-bath temperature for ca. 1 h, and then a solution of 6 g diethyl carbonate in ether was added dropwise over the period of 0.5 h. The reaction mixture was stirred at 0 °C for ca. 1.25 h. Water was then added, the layers were separated, and the ether layer was washed with water and then dried over potassium carbonate. The carbinol crystallized from the remaining hexane when most of the ether had been removed by evaporation, giving ca. 3.0 g of a slightly red solid. The product was repeatedly recrystallized from hexane, mp 172–173 °C. Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.35; H, 7.20. The ^1H NMR spectrum of the compound in $CDCl_3$ solution showed the methyl singlet at 2.17 ppm, the methoxy singlet at 3.77 ppm, the OH singlet at 2.71 ppm, and the aromatic multiplet at 6.4–6.8 ppm, with the expected relative intensities. A solution of the carbinol in 0.1 M HCl showed absorbance peaks at 512 nm (ϵ 6.1 × 10^4 M^{-1} cm^{-1}) and 265 (1.6 × 10^4).

Rate and Equilibrium Studies. All measurements were carried out at room temperature of 23 ± 1 °C.

The pK_R measurements for both cations utilized cation concentrations of 1–2 × 10^{-6} M and 10-cm pathlength spectrophotometer cells. Absorbances of the solutions at the wavelength of maximum absorbance were measured with a Cary Model 14 spectrophotometer. For the tris(2,4-dimethoxyphenyl)methyl cation, both chloroacetic acid and succinic acid buffers were used with ionic strengths ranging from 0.01 to 0.1 M. There was no detectable effect of buffer or ionic strength change on the equilibrium. All of the measurements showed a precision of ca. ±0.04 pK units. For the tris(2-methyl-4-methoxyphenyl)methyl cation, both chloroacetic acid and citric acid buffers were utilized. Again there was no detectable effect of buffer change or ionic strength change (0.01–0.1 M) on the equilibrium, and the precision was ca. ±0.04 pK units.

With the exceptions of the reactions of water and hydroxide ion with tris(2-methyl-4-methoxyphenyl)methyl cation, reaction kinetics were studied by stop-flow spectrophotometry, using techniques analogous to those reported in earlier papers.[1] The extreme insolubility of the tris(2-methyl-4-methoxyphenyl)methyl alcohol caused problems at the concentrations necessary for accurate stop-flow measurements (ca. 10^{-5} M). The reactions of the corresponding cation with water and hydroxide ion were, therefore, studied in 10.0-cm cells, using the Cary Model 14 spectrophotometer. It was possible to begin observation within ca. 15 s of mixing the cation solution, and, even in the fastest reactions studied, this was no more than one half-life of the reaction.

The reactions of both cations were followed by observations of the visible absorbance peaks of the cations and, in separate experiments, the ultraviolet absorbance peaks. The spectra of the reaction solutions immediately after reaction showed no evidence for formation of quinoid structures.

The rate and equilibrium constants obtained are reported in Table I.

Results

Previous work[1] and literature reports[4] concerning reactions of ortho-substituted triarylmethyl cations had led us to expect some difficulties from reactions of nucleophiles

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(2) H. Kaufmann and F. Kieser, *Chem. Ber.*, **45**, 2333 (1912); G. Wittig and U. Pockels, *ibid.*, **72B**, 89 (1939).

(3) R. A. B. Bannard and L. C. Leitch, *Can. J. Chem.*, **34**, 1464 (1956).

(4) R. Breslow, L. Kaplan, and D. LaFollette, *J. Am. Chem. Soc.*, **90**, 4056 (1968).

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