There appears to be a subtle and unexpected balance between the rates of cyclopropyl anion ring opening and loss of chloride ion that depends sensitively on the structure of the pyridine.

The first pyridinium-1-ylcarbons, **1** and **2**, show a chemistry that invites further study. They have the potential of opening up a whole new field of organic chemistry in which their high concentration of charge may provide exciting properties.

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Total Synthesis of C_{22}-Prostanoids in the E and F Series Based on Docosahexaenoic Acid

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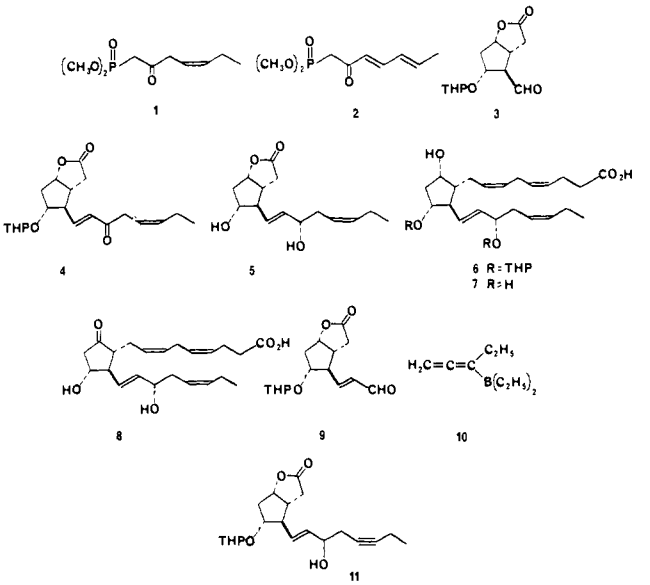
Docosa-4,7,10,13,16,19-(*Z*)-hexaenoic acid (docosahexaenoic acid, DCHA) is a major polyunsaturated fatty acid in marine lipid, along with eicosa-5,8,11,14,17-(*Z*)-pentaenoic acid (EPA). The obvious question as to whether DCHA might be the progenitor of a family of C_{22}-prostanoids, analogous to those derived from arachidonic acid or EPA, was made more intriguing by the reported isolation of a C_{22}-prostanoid of the F_α type from fish.[1] Although this claim has recently been retracted,[2] the key issue regarding the occurrence of C_{22}-prostanoids in marine organisms remains unresolved. It has been proposed that C_{22}-prostanoids can be synthesized in mammalian tissue from 7,10,13,16-(*Z*)-docosatetraenoic (adrenic) acid.[3] On the other hand, studies in these laboratories have shown that DCHA is not a substrate for mammalian PG synthetase from ram seminal vesicles or human platelets and is in fact a potent competitive inhibitor of the conversion of arachidonate to PGs (ca. 10^4 times that of aspirin on a molar basis).[4] In order to demonstrate whether C_{22}-prostanoids occur naturally and to evaluate their biological effects, it is clearly desirable to synthesize the compounds in question. We describe herein two processes for the synthesis of the E- and F_α-type prostaglandins which would be derived from DCHA. These syntheses employ standard PG precursors[5] and illustrate two new methods for generating the required ω-appendage which are applicable to the synthesis of PG_3s such as $PGF_{3\alpha}$ and PGE_3. Although the PG_3s have been synthesized previously,[6] their preparation until now has been much more difficult than those for the PG_1 or PG_2 series.

The first process for the synthesis of ω-3 PGs utilized as a key reagent dimethyl (*Z*)-(2-oxohept-4-enyl)phosphonate (**1**). This new substance was synthesized in two steps as follows. Reaction of methyl sorbate with the lithio derivative of dimethyl methylphosphonate[7] in tetrahydrofuran (THF) at −78 °C for 8 h afforded after extractive isolation and column chromatography on silica gel (sg) 52% of dimethyl (*E*,*E*)-(2-oxohepta-3,5-dienyl)-phosphonate (**2**) as a colorless liquid. Hydrogenation of freshly distilled **2** with 10 mol % of (methyl benzoate)chromium tricarbonyl[8] (750 psi H_2, methylene chloride, 140–150 °C, 1.5 h)



1 2 3 4 5 6 R=THP 7 R=H 8 9 10 11

proceeded by stereospecific 1,4-addition to give, after sg chromatography and distillation, **1**, bp 90 °C (0.01 mm), in 77% yield. Horner–Emmons coupling of **1** with optically active aldehyde **3**,[6] unsuccessful under a wide variety of conditions, proceeded as desired by using a solution of sodium methoxide (methanol free) in dry THF at −78 °C for 1 min to convert **1** to its anion, promptly adding **3**, raising the temperature to 0 °C rapidly, and allowing the reaction to proceed at 0 °C for 3 h. Quenching with acetic acid, extractive isolation, and chromatography on sg provided keto lactone **4** in 50% yield.[9] Cleavage of the tetrahydropyranyl group of **4** (pyridinium tosylate in methanol at 50 °C for 1.5 h) and carbonyl reduction using diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide[10] at −78 °C in toluene afforded with 91:9 selectivity (85% yield) the required 15-*S*-diol **5** which readily separated from the less polar 15-*R* isomer by sg chromatography using 1:1 benzene–ethyl acetate for elution.[11] The minor 15-*R* isomer upon treatment with Attenburrow manganese dioxide in methylene chloride was converted to the corresponding 15-ketone and recycled.

Transformation of **5** into the bis(tetrahydropyranyl) ether of C_{22}-$PGF_{4\alpha}$ (**6**) was accomplished in 65% overall yield by the following sequence: (1) tetrahydropyranylation of **5** using 3 equiv of dihydropyran in methylene chloride with camphor-10-sulfonic acid catalyst at 0 °C for 20 min (99% yield); (2) lactone to lactol reduction using 1.6 equiv of diisobutylaluminum hydride in toluene at −78 °C for 30 min (99% yield); (3) Wittig reaction with the ylide from (*Z*)-7-(triphenylphosphonio)hept-4-enoate (generated using sodium bis(trimethylsilyl)amide in THF–toluene) at −40 °C then at 0 °C for 3.5 h; (4) esterification (CH_2N_2), sg chromatography and saponification.

The methyl ester of **6** was transformed into C_{22}-$PGF_{4\alpha}$ (**7**) by THP cleavage (pyridinium tosylate in methanol at 55 °C for 1 h) followed by saponificiation with 0.5 N sodium hydroxide in 50% aqueous methanol at 55 °C for 2.5 h (90% overall yield). Conversion of **6** to C_{22}-PGE_4 (**8**) was accomplished by Jones oxidation at 0 °C for 30 min followed by THP cleavage (6:3:1 acetic acid–water–THF, 35 °C for 8 h).

A second route to **5** was developed which also started from lactone aldehyde **3** via the enal **9**, which was produced from **3** by the sequence: (1) RCHO → $RCH{=}CHCOOC_2H_5$ chain extension using the sodium derivative of triethylphosphonoacetate

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(9) This yield has not been optimized with respect to reaction temperature and probably can be increased.
(10) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc.* **1981**, *54*, 3033.
(11) Thin-layer chromatographic (TLC) R_f values (sg, 1:1 benzene–ethyl acetate) were 0.19 and 0.26 for **5** and the 15-*R* diastereomer, respectively.

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(from NaH) and **3** in THF at 23 °C for 1 h (84% yield); (2) reduction of lactone–ester to lactol–alcohol using 3.3 equiv of diisobutylaluminum hydride in toluene at −78 °C for 40 min (99%); (3) oxidation to **9** using Collins reagent $[CrO_3(py)_2]$ in methylene chloride at 0 °C for 20 min (85% yield). The enal **9** was treated with allenylborane **10**, generated by reaction (−95 °C, THF) of the lithio derivative of propargyl chloride with triethylborane,[12] and after a reaction time of 1.5 h at −78 °C, the product was isolated by extraction, freed of boranes by treatment with hydrogen peroxide in methanol (23 °C, 2 h), and purified by sg chromatography to afford 85% yield of acetylenic lactones **11** (15-*S* and 15-*R* mixture). After THP cleavage the two acetylenic alcohols were separated chromatographically on sg and reduced (H_2, 1 atm, Lindlar catalyst) to **5** and the 15-*R* diastereomer, with the latter being recycled as described above.

The biological profiles of the C_{22}-PGs **7** and **8** are under active study. Preliminary results obtained in the laboratory of Prof. Peter W. Ramwell suggest that they are much less active on smooth muscle (guinea pig, rat) than $PGF_{2\alpha}$ and PGE_2. The methodology described herein allows the facile synthesis of PG_3s and should stimulate more detailed biological evaluation of this relatively neglected family of PGs. We have also utilized this approach for the synthesis of the C_{22}-PG_3s 19, 20-dihydro **7** and **8**.[13]

Supplementary Material Available: Spectroscopic data on compounds **1–9** and **11** (2 pages). Ordering information is given on any current masthead page.

(12) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561.

(13) This research was assisted financially by a grant from the National Science Foundation. The first preparation of **1** was performed in these laboratories by Dr. Haruhisa Shirahama (1970).

Stereoselective Generation of Acyclic Tetrasubstituted Enolates and Diastereoselective Aldol-Type Condensation

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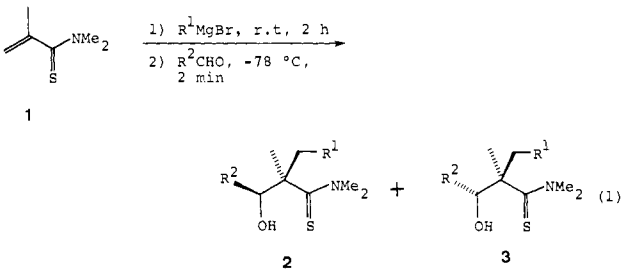
In recent years, the correlation between the structures of enolates and the stereochemical outcome in the aldol condensation has been well established.[1] Many elegant total syntheses of natural products owe their success to this methodology.[2] Interestingly, however, most of these are confined to reactions with the disubstituted (e.g., aldimine)[3] and trisubstituted (e.g., ester,[4] ketone,[5] etc.) enolates. As for the tetrasubstituted enolates, only a few examples have been reported with cyclic systems (α-substituted β-lactams,[6] γ-butylrolactones),[7] and only one example is known of an acyclic case (O-protected lactic acid ester).[8] The main reason for the scarcity of the tetrasubstituted enolate chemistry is due to the difficulty in preparing the stereochemically homogeneous enolates.

We wish to report the highly stereoselective aldol-type condensation with acyclic tetrasubstituted enolates, generated by the Michael addition of Grignard reagents to *N,N*-dimethyl-α-methacrylothioamide (**1**):[9] A THF solution of **1** (1 mmol in 10 mL of THF) was treated with 2 equiv of Grignard reagent at room temperature. After the solution was allowed to stir at this temperature for 2 h, the reaction mixture was cooled to −78 °C and an aldehyde (2 mmol) was added in one portion. After an appropriate time (see Table I), the reaction was quenched by the addition of 2 N HCl (eq 1). Results are summarized in Table I.



The yield and selectivity largely depend both on the kinds of Grignard reagents and aldehydes and may be classified into the following three groups. The first is the reaction of alkyl Grignards and alkyl aldehydes, which exclusively provides the erythro product **2** in good yield (entries 1–4). A thorough examination of the reaction mixture revealed that no detectable amount of threo isomer **3** was present (HPLC and ^1H and ^{13}C NMR). The threo isomer **3** (R^1 = Et, R^2 = *i*-Pr) was obtained in 10% yield, together with *N,N*-dimethyl-2-methylvalerothioamide (55%), at the complete expense of erythro **2** (R^1 = Et, R^2 = *i*-Pr), after allowing the reaction mixture of entry 2 to warm and stir at 0 °C for 3 h. The similar accumulation of **3** was also observed when similar conditions were used for R^1 = *i*-Pr, R^2 = Me (entry 3).[10] The second is the reaction of **1** with PhMgBr and alkyl or unsaturated aldehydes (entries 5–7). In these cases, the stereoselectivities are similarly high (>99%), but the yields are low. The residues of these reaction mixtures mainly consist of *N,N*-dimethyl-3-phenylisobutyrothioamide, and hence the low yields may be ascribed to diminished nucleophilicity of the enolate **7** (R^1 = Ph) toward the aldehyde carbonyl (cf. entry 11, eq 3).[11] The third is the reaction of the enolate **7** (irrespective of the kind of R^1) with benzaldehyde, which results in the nonstereoselective formation of **2** and **3** (entries 8, 10, and 11). The low selectivities in these runs may be due to a very facile retro-aldol, which seems to occur even at −78 °C, because the reaction of entry 10, when quenched at 2 s after addition of the aldehyde, showed a substantially increased erythro selectivity (**2**:**3** (R^1 = *i*-Pr, R^2 = Ph) = 50:50). The result in entry 9 (thermodynamic control) supports this explanation.

Although the experiments run under the conditions of thermodynamic control suggest that the product **3** is a sterically less hindered threo isomer, no conclusive evidences for the structure of **2** and **3** could be obtained from the attempted chemical

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(10) HPLC (μ-Porasil, hexane–ethyl acetate 85:15 or 90:10) showed base-line separations for these **2** and **3**. The reaction with organolithium reagents showed somewhat diminished selectivity: the reaction of **1** with *n*-BuLi (−78 °C for 2 h then 0 °C for 2 h in THF) and acetaldehyde (−78 °C for 2 min) provided a mixture of **2** and **3** (R^1 = *n*-Bu, R^2 = Me) in a 90:10 ratio in 90% isolated yield, while the reaction of **1** with *n*-BuMgCl (room temperature for 1 day in THF) and acetaldehyde gave **2** (R^1 = *n*-Bu, R^2 = Me) exclusively in 91% isolated yield. All compounds reported showed satisfactory spectral and analytical data.

(11) The lower nucleophilicity of **7** (R^1 = Ph), compared with **7** (R^1 = alkyl), may be due to an intramolecular π-coordination of arenes to the counterion of enolate: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

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