of methanesulfonic acid, was placed in a flask attached to a short distilling column and heated to distil the ethyl formate and ethanol formed in the reaction. When the distillation of the ester and alcohol ceased, the residue was distilled *in vacuo* to give a 95% yield of *n*-heptanoic acid nitrile, bp 70–72° (10 mm).

Typical Procedure for Conversion of Oxime Diethyl Ortho Esters. A. In Chloroform.[9] A solution of *n*-butyraldehyde oxime diethyl orthoacetate (20.3 g, 100 mmol) in chloroform (100 ml) was placed in a flask attached to a short distilling column and 0.2 g of methanesulfonic acid added. The solution was stirred at room temperature and the extent of the reaction was followed by neutralizing small aliquots which were then analyzed by glpc. After 30 min the reaction was complete and distillation afforded 5.48 g (94% yield) of *n*-butyronitrile.

B. In Sulfur Dioxide. A 100-ml heavy glass ampoule containing benzaldehyde oxime diethyl orthoformate (19.5 g, 100 mmol) was charged with approximately 50 ml of liquid sulfur dioxide at −70°, sealed, and kept at room temperature[10] for 48 hr. The ampoule was cooled in Dry Ice, opened, and the content transferred into a distilling flask containing 100 ml of cold chloroform. The flask was attached to a short column and excess of solvents removed *in vacuo*. The residue was distilled to give 9.3 g (90%) of benzonitrile, bp 68–70° (10 mm).

Typical Procedure for Preparation of Oxime Diethyl Ortho Esters. A solution of *n*-butyraldehyde oxime (a mixture of *Z* and *E* isomers in approximate ratio of 3:2) (8.7 g, 100 mmol) and triethyl orthoacetate (16.2 g, 100 mmol) was placed in a distilling flask attached to a short distilling column and heated at 120–150° until 4.6 g of ethanol distilled. Vacuum distillation of the residue gave a 95% yield of *n*-butyraldehyde oxime diethyl orthoacetate: bp 47–49° (0.6 mm); nmr ($CDCl_3$) δ 7.38 (t) and 6.68 (t) [1 H (total)], 3.54 (q, 4 H), 2.21 (m, 2 H), 1.5 (m + s, 5 H), 1.21 (t, 9 H).

Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.92. Found: C, 59.30; H, 10.50; N, 6.81.

Beckmann Fragmentation of Benzil Monooxime. A 50-ml heavy glass ampoule containing benzil monooxime (2.25 g, 10 mmol) and triethyl orthoformate (1.52 g, 11 mmol) was charged with approximately 25 ml of liquid sulfur dioxide at −70°, sealed, and heated at 72° for 70 hr. The ampoule was placed in Dry Ice, opened, and the contents were diluted with chloroform. Glpc analysis indicated a 95 and 98% yield of benzonitrile and ethyl benzoate, respectively.

Beckmann Fragmentation of 2-Oximinocyclohexanone Dimethyl Ketal. A 50-ml three-neck flask equipped with a magnetic stirrer, a Dry Ice condenser, and a nitrogen bubbler was charged with approximately 20 ml of sulfur dioxide at −70°, and 2-oximinocyclohexanone dimethyl ketal (1.73 g, 10 mmol), trimethyl orthoformate (1.2 g, 11 mmol), and a drop of methanesulfonic acid were then added. The solution was maintained under reflux (~−10°) for 30 min, and then 10 ml of chloroform and an internal standard were added. Glpc analysis indicated a 97% yield of 5-cyanopentanoic acid methyl ester.

Registry No.—Benzil monooxime, 14090-77-8; 2-oximinocyclohexanone dimethyl ketal, 52540-36-0.

References and Notes

(1) Mukaiyama, *et al.*, have reported[2] the synthesis of several oxime dialkyl ortho esters by the addition of an oxime to a ketene acetal.
(2) T. Mukaiyama, K. Tonooka, and K. Inoue, *J. Org. Chem.*, **26**, 2202 (1961).
(3) This observation is in accord with the known tendency of isomeric oximes to undergo various acylation reactions without isomerization.[4]
(4) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N.Y., 1966, p 46.
(5) We have also shown that oximes react with various ketone acetals to give the corresponding oxime alkyl ketone acetals. These, in turn, also undergo similar transformations as the oxime dialkyl ortho esters.
(6) The extent of the reaction was followed either by nmr or glpc analysis or both.
(7) This slow transformation is very likely a consequence of the syn arrangement of the carbon–hydrogen and nitrogen–oxygen bonds in the benzaldehyde oxime ortho ester, which eventually undergoes rate-determining isomerization to the more reactive anti isomer under the reaction conditions.
(8) Nmr analysis indicated that these oxime ortho esters were undergoing a series of reversible disproportionation reactions which will be discussed elsewhere.
(9) The experimental procedure in other solvents, *e.g.*, toluene, ether, tetrahydrofuran, or nitromethane, was essentially the same.
(10) When the reaction was unusually slow, as in the case of *p*-methoxybenzaldehyde derivatives, the ampoule was heated at 70°, cooled in Dry Ice, opened, and worked up in the same way.

Synthesis and Resolution of 2-Hydroxyheptanoic Acid

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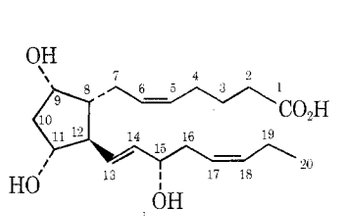
In an elegant synthesis of PGE_3 (**1**) reported by Corey and coworkers[1] the (*S*)-15-hydroxy-13,17-octadienyl side chain at C-12 was introduced stereospecifically by the condensation of the optically active aldehyde (**2**) with the ylide derived from the phosphonium salt (**3c**). The salt (**3c**) was prepared from (*S*)-(−)-malic acid by the multistep process (*S*)-(−)-malic acid → **3a** → **3b** → **3c**. It is apparent that the (*S*)-15-hydroxy-13-octenyl side chain at C-12 of prostaglandins and prostaglandin analogs could be introduced by the condensation of the ylide derived from the phosphonium salt (**5c**) with the appropriate aldehyde. The salt (**5c**) could be prepared from (+)-2-hydroxyheptanoic acid [(+)-**4**] by the sequence (+)-**4** → **5a** → **5b** → **5c**. In the present paper, we present an efficient and economical synthesis and resolution of (±)-2-hydroxyheptanoic acid [(±)-**4**].



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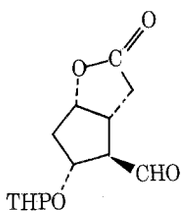

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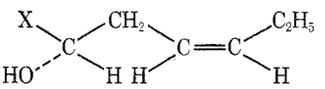
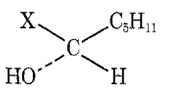


3a, X = CH_2OH
b, X = CH_2I
c, X = $CH_2\overset{+}{P}(C_6H_5)_3$



4, X = CO_2H
5a, X = CH_2OH
b, X = CH_2I
c, X = $CH_2\overset{+}{P}(C_6H_5)_3$

The preparation of (±)-**4** was accomplished in excellent yield from the cyanohydrin of hexanal. Numerous salts of (±)-2-hydroxyheptanoic acid with optically active amines were prepared, but only two, quinine and dehydroabeitylamine, were sufficiently crystalline to warrant further investigation. Recrystallization of both salts and liberation of the acid gave optically active material with opposite rotations. A large scale resolution employing quinine was performed and, in the very early recrystallizations of the quinine salt, two types of crystals were apparent. The progress of the resolution was followed by obtaining the rotation of the liberated and recrystallized acid. When a value of $[\alpha]^{25}D$ +5.55° was obtained, further recrystallization of the quinine salt did not increase the rotation of the acid.

The initial filtrate from the resolution of the plus (+) isomer was acidified, and the enriched minus (−) isomer was converted to its dehydroabeitylamine salt. The progress of the resolution of this isomer was followed as before with the final acid rotation being $[\alpha]^{26}D$ −5.52°.

In a study which established the absolute configuration of the C-15 hydroxyl group of prostaglandins, Nugteren and coworkers[2] degraded certain prostaglandins by ozonolysis and obtained 2-hydroxyheptanoic acid which possessed an optical rotation of $[\alpha]^{25}D$ +6.9, *c* 5.8, $CHCl_3$. Since the magnitude of our final rotations is different from

the value obtained by Nugteren and coworkers,[2] it was necessary to establish the optical purity of the individual optical isomers. The method of Westly and Halpern,[3] which involves the glc analysis of the *l*-menthol carbonate ester derivative of the methyl ester of (±)-4 proved to be a facile check on the completeness of the resolution. When we applied this method to (±)-4, we found that the glc of (±)-4 showed two peaks (one for each diastereoisomer) for the *l*-menthol ester derivative, while the glc of the individually resolved and derivatized acids shows only one peak indicating that each acid was >98% optically pure.

Experimental Section[4]

(±)-2-Hydroxyheptanoic Acid. Sodium metabisulfite (54 g, 0.28 mol) in water (60 ml) was added dropwise to a magnetically stirred mixture of ether (100 ml), hexanal (50 g, 0.5 mol), potassium cyanide (34.5 g, 0.53 mol), ice (50 g), and water (10 ml) at 0 to 10°. After completion of the addition, the reaction mixture was stirred for 15 min at 0° and 15 min at room temperature. The reaction was extracted with ether (4 × 100 ml), and the ether extracts were dried ($MgSO_4$) and evaporated at reduced pressure to give an oil: ir (film) 3400 (OH) and 2140 cm^{-1} (C≡N).

The crude cyanohydrin in ethanol (200 ml) was saturated at 0° with hydrogen chloride, and allowed to stand overnight. Excess ethanolic hydrogen chloride was removed at reduced pressure, and the resulting oil was stirred with ice water (50 ml), then rapidly extracted with ether (2 × 100 ml) and chloroform (2 × 100 ml). The combined extracts were dried ($MgSO_4$), then evaporated at reduced pressure to give a yellow oil. Distillation of the crude product gave 68.2 g (93%) of pure ester: bp 105–107° (17 mm); ir (film) 3480 (OH) and 1735 cm^{-1} (CO_2Et).

The pure ester (50 g, 0.287 mol) in water (70 ml) and dioxane (70 ml) was magnetically stirred while slowly adding sodium hydroxide (12.6 g, 0.315 mol). After stirring overnight, the solution was acidified with hydrochloric acid and extracted with ether (3 × 100 ml). The ether extracts were dried ($MgSO_4$), then evaporated at reduced pressure to give a solid. Recrystallization of the crude acid from benzene–hexane (1:2) gave 39.8 g (95%) of pure 2-hydroxyheptanoic acid: mp 64–65° (lit.[2] mp 64–65°); ir ($CHCl_3$) 3400 (OH) and 1710 cm^{-1} (CO_2H).

D-(−)-2-Hydroxyheptanoic Acid. Four separate but identical resolutions were performed simultaneously. Anhydrous quinine (55.75 g, 0.172 mol) and 2-hydroxyheptanoic acid (25.0 g, 0.171 mol) were combined in methanol (400 ml) and heated to boiling. Hot (70°) water (1 l.) was added with stirring, and the solution became cloudy. Enough hot methanol was added to clarify the solution. After cooling, the salt which had crystallized from solution was collected, washed (2:5 methanol–water), and dried. The collected salt weighed 38 g (47%). This and the remaining recrystallizations are shown in Table I.

Table I

Crystallization	Methanol, ml	Water, ml	Weight, g	% yield
1	400	1000	38	47
2	150	700	35	44.5
3	175	700	36	43.7
4	200	600	26	33.2

The final rotation of the salt was $[\alpha]^{27}D$ +122.53 ± 0.15 (*c* 4.0, MeOH), and the liberated acid had an average rotation of $[\alpha]^{27}D$ −5.55 ± 0.05° (*c* 5.8, $CHCl_3$), after extraction into base, washing with ether, reacidification, extraction, and recrystallization of the collected acids from hexane.

L-(+)-2-Hydroxyheptanoic Acid. The filtrates from the first crystallization were treated with acid and extracted into ether, dried, and evaporated to give 49.26 g of L-(+)-2-hydroxyheptanoic acid.

Dehydroabeitylamine (50.38 g, 0.175 mol) and the partially resolved L-(+)-2-hydroxyheptanoic acid (23.45 g, 0.159 mol) were dissolved in hot methanol (250 ml), and hot water (100 ml) was added. The solution became cloudy and a small additional amount of methanol was added to clarify the solution. This and the remaining crystallization are shown in Table II.

Table II

Crystallization	Methanol, ml	Water, ml	Weight, g	% yield
1	250	100	63.4	91.6
2	450	200	62.3	89.9

The final rotation of the dehydroabeitylamine salt was $[\alpha]^{26}D$ +14.47 ± 0.06 (*c* 4.0, MeOH) while the liberated acid had a rotation of $[\alpha]^{26}D$ +5.53 ± 0.05° (*c* 5.8, $CHCl_3$).

Optical Purity Analysis. The methyl esters of individual acid samples were prepared by reaction with diazomethane in ether. One drop of the neat ester in five drops of pyridine was treated with four drops of L-menthol chlorocarbonate solution[3] (an excess). Glc analysis was performed at 180° on a 6-ft 1% QF, 1% OV-17 column with a 30-cm^3/min flow rate. Flame ionization was used for detection. The retention times for the derivatized methyl esters follow: (+), 6.57 min; (−), 7.20 min. The major components of the glc trace were identified by glc–mass spectrometry and by comparison of the individual components with authentic samples.

Acknowledgment. This work was supported under Contract NIH-NICHD-72-2712 with the Contraceptive Development Branch of the National Institutes of Child Health and Human Development.

Registry No.—(±)-4, 52358-05-1; (−)-4, 52437-20-4; (+)-4, 52437-21-5; hexanal, 66-25-1; (±)-hexanal cyanohydrin, 52358-06-2; ethyl (±)-2-hydroxyheptanoate, 52438-78-5.

References and Notes

(1) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **93**, 1490 (1971).
(2) D. H. Nugteren, D. A. van Dorp, S. Bergstrom, M. Hamburg, and B. Samuelesson, *Nature (London)*, **212**, 38 (1966).
(3) J. Westly and B. Halpern, *J. Org. Chem.*, **33**, 3978 (1968).
(4) Melting points were taken on a Kofler hot stage microscope and are uncorrected. Nmr spectra were determined on a Varian Associates Model HA-100 spectrophotometer in chloroform with tetramethylsilane as an internal standard. Glc–mass spectra were determined on a Varian MAT CH-7 mass spectrometer. Infrared spectra were obtained with a Perkin-Elmer Model 267 double beam spectrophotometer. Rotations were taken on a Perkin-Elmer Model 141 polarimeter.

Synthesis of 3,5-Dialkyl-1,2-dioxolanes[1]

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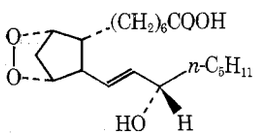
The prostaglandin endoperoxide, **1**, has been proposed as an intermediate in the biosynthesis of other prostaglandins.[2,3] Such structures have been detected in *in vitro* biosyntheses.[3] In view of the biological importance of the prostaglandins, it is pertinent to develop synthetic schemes for the chemical preparation of **1**.



1

Saturated 1,2-dioxanorborananes have not been described in the literature. The synthesis of simple model structures may furnish necessary background for synthesis of compounds such as **1**. For this reason, we undertook to synthesize and investigate the decomposition of the 3,5-dialkyl-1,2-dioxolanes, **2**, cyclic alkyl peroxides with secondary carbon atoms adjacent to the oxygen atoms.