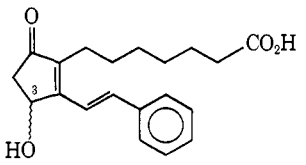
Prostaglandins. VI.[1] Correlation of the Absolute Configuration of Pyrethrolone with That of the Prostaglandins

Masateru Miyano* and Clifford R. Dorn

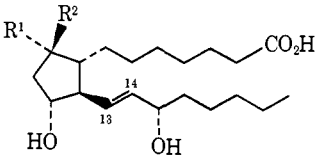
Contribution from Searle Laboratories, Division of G. D. Searle and Company, Chicago, Illinois 60680. *Received October 13, 1972*

Abstract: Racemic 7-(2-*trans*-styryl-3-hydroxy-5-oxocyclopentenyl)-*n*-heptanoic acid (**1**), the key intermediate in our total synthesis of racemic prostaglandins, was resolved into 3(*R*) acid **5a** and 3(*S*) acid **6a**. The former (**5a**) was converted into (8*S*,12*S*)-dihydroprostaglandin E_1 (**16**) and (8*S*,12*S*,15*R*)-dihydroprostaglandin E_1 (**17**) by an unequivocal procedure (Chart I). Based upon an ORD–CD study, it was demonstrated that **16** and **17** are (8*S*,-12*S*)-prostanoic acids. Consequently, compounds **5a**, **12**, **13**, **14**, and **15** must be 11(*R*)-$\Delta^{8(12)}$-prostanoic acids. The enantiomer **6a** was hydrogenated to **8a**, which was shown by ORD–CD measurements to have the same absolute configuration as natural pyrethrolone (**9a**). Thus the absolute configuration of rethrolones, previously proposed by other investigators based upon somewhat uncertain evidence, was confirmed by correlation with the well-established absolute configuration of prostaglandins.

Racemic 7-(2-*trans*-styryl-3-hydroxy-5-oxocyclopentenyl)-*n*-heptanoic acid (**1**) is the readily available key intermediate for our total syntheses[1,2] of racemic prostaglandin $F_{1\alpha}$[2a,b] (**2**), prostaglandin E_1[2a] (**3**, PGE_1), dihydroprostaglandin E_1[1,2a] (**4**), and their

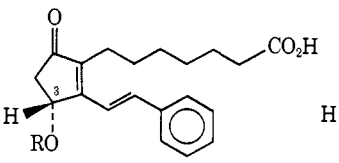


1, racemic

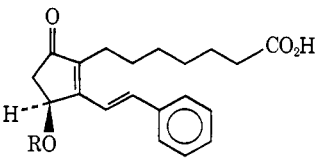


2, R^1 = OH, R^2 = H
3, R^1 and R^2 = O
4, 13,14-dihydro-3

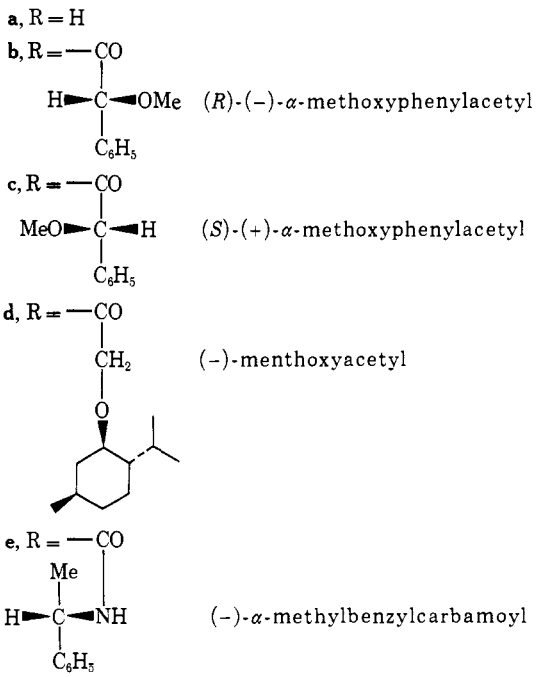
stereoisomers. To prepare the naturally occurring enantiomers[3] of **2**, **3**, and **4**, the optical resolution of **1** was undertaken. Routine resolutions with commercially available alkaloids, amines, and basic amino acids were futile, presumably because the chiral carbinol carbon C-3 and the carboxyl group in **1** are too far apart to produce any significant difference between the two diastereomeric salts. Accordingly, a logical approach to this problem entailed the preparation of diastereomers in which the second chiral element is as close to C-3 as possible.[4,5] The (*R*)-(−)-α-methoxyphenylacetic acid ester of **1** seemed particularly attractive inasmuch as the two chiral carbons are removed by only two atoms. Thus, **1** was treated with (*R*)-(−)-α-methoxyphenylacetyl chloride[6] in pyridine to afford a mixture containing two crystalline compounds **5b** and **6b**, which were readily separated by adsorption chromatography. In a similar manner,



5, 3-(*R*)



6, 3-(*S*)



5c and **6c** were obtained by treatment of **1** with (*S*)-(+)-α-methoxyphenylacetyl chloride.

The diastereotopic benzylic protons in **5b** and **6b** exhibited singlet nmr signals having different chemical shifts[7] (see Table I) since the chiral benzyl carbon is close enough to the other chiral center to interact through space. Therefore, the optical purity of **5b** or **6b** could be determined by nmr spectroscopy[8] without resorting to optical data.

It was anticipated that the α-methoxyphenylacetic esters of **1** would be hydrolyzed readily owing to the

(1) Part V: M. Miyano and C. R. Dorn, *J. Org. Chem.*, 37, 1818 (1972).

(2) (a) M. Miyano, R. A. Mueller, and C. R. Dorn, *Intra-Sci. Chem. Rep.*, 6 (1), 43 (1972); (b) M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, 37, 1810 (1972).

(3) For a review article on prostaglandins, see P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. R. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, 9, 231 (1968).

(4) Apparently glycosides of **1** best met this condition; however, we felt these substances could not be prepared easily and efficiently.

(5) The (−)-menthoxy acetate of **1** was a crystalline complex of **5d** and **6d** and could not be resolved by chromatography or by repeated crystallization. Even when the chiral centers were separated by only three carbon atoms, as in the (−)-α-methylbenzylcarbamoyl esters **5e** and **6e**, no resolution could be achieved.

(6) J. Jabobus, M. Rabin, and K. Mislow, *J. Org. Chem.*, 33, 1142 (1968).

(7) This region is clear of any overlapping signals.

(8) There are some precedents of this sort: (a) M. Raban and K. Mislow, *Top. Stereochem.*, 2, 199 (1967); (b) P. H. Boyle, *Quart. Rev., Chem. Soc.*, 25, 323 (1971); (c) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

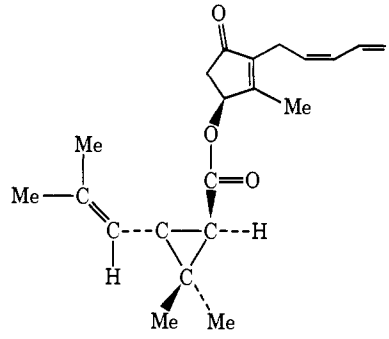
Table I. Properties of **5a**, **6a**, **5b**, **6b**, **5c**, and **6c**

	$[\alpha]^{25}D$ (c 1.00, MeOH)	Mp, °C	Nmr (60 MHz, $CDCl_3$) of benzylic H, δ (ppm from TMS)	Elementary analyses % C	% H
5a	−16.5	114–115		72.97	7.23[b]
6a	+16.0[a]	113–114		72.84	7.11[b]
6b	−22	122–124	4.80	73.00	6.95[c]
5b	−84	96–98	4.77	73.20	6.83[c]
6c	+84	97–98	4.77	73.16	6.82[c]
5c	+20.2	122–124	4.80	73.00	6.77[c]

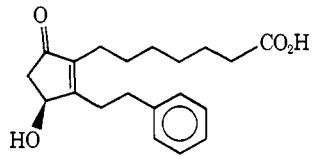
[a] $[\alpha]^{25}D$ in chloroform (c 1.088) was −16.1; the sign was reversed. [b] Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. [c] Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77.

inductive effect of the α-methoxy group. However, ordinary base-catalyzed hydrolysis (for instance, aqueous potassium carbonate or hydroxide at room temperature) of **5b** and **6b**, although very rapid, yielded mainly uncharacterized material, whereas the desired alcohols (**5a** or **6a**) were isolated in poor yield after chromatography. Eventually, it was found that cold lithium hydroxide in the presence of lithium chloride in aqueous tetrahydrofuran afforded the desired product in 65% yield by direct crystallization.[9]

In order to determine the absolute configuration of **5a** and **6a**, we elected to correlate the dihydro compounds **8a** and **11a** with the known absolute configura-



7, pyrethrin I



8a, X = O
b, X = $NNHCONH_2$

tion[10] of rethrolones, the alcohol components of the pyrethrins, a group of naturally occurring insecticides (see structure **7** for pyrethrin I) in certain chrysanthemum flowers. The absolute configuration of pyrethrolone (**9a**) was proposed by Japanese workers,[10b-d] but it was apparent that the optical data of **6a** and **9a** could not be compared directly because they possess different chromophores adjacent to the chiral carbinol carbon. Thus **6a** was hydrogenated to **8a** which was converted into the semicarbazone **8b**. Comparison[11] of the optical rotations (Table II) of **8a**, **8b** and **9a**, **9c**

Table II. Optical Rotation of **8a**, **8b**, **9a**, **9c**, and **11a**

	[α]D, deg	Temp, °C	Solvent	Concn, %
Pyrethrolone hydrate (**9a**)	+13.7[a]	20	Ether	12.7
	+12.5[a]	19	Ethanol	13.1
	+13.6[b]		Neat	
8a	+33.2	25	Methanol	1.00
Pyrethrolone semicarbazone (**9c**)	−186[a]	20	Pyridine	0.60
	−155[c]	25	Acetic acid	2.0
8b	−86.8	26	Pyridine	1.21
11a	−30.1	25	Methanol	1.01

[a] See ref 12. [b] T. F. West, *J. Chem. Soc.*, 463 (1946). [c] See ref 10b.

strongly suggested that they belong to the same enantiomeric series. (+)-Pyrethrolone[12] (**9a**) and **8a** exhibited almost identical ORD–CD curves, each showing negative ($\pi \rightarrow \pi^*$) and positive ($n \rightarrow \pi^*$) Cotton effects (see Table III). Therefore, it was evident that **8a** has the same absolute configuration as natural pyrethrolone, and consequently the stereochemistry of **5a** and **6a** was temporarily assigned as depicted.

Table III. ORD and CD of **8a**, Pyrethrolone (**9a**), and **11a** in Methanol[a]

	8a	**9a**	**11a**
ORD $n \rightarrow \pi^*$			
Peak	340 nm	338 nm	290 nm
	+5590	+4650	+10,900
Trough	294 nm[b]	290 nm[b]	333 nm
	−12,000	−12,000	−7,830
ORD $\pi \rightarrow \pi^*$			
Peak	224 nm	*c*	250 nm
	+35,000		+29,800
Trough	252 nm	247 nm	221 nm
	−26,900	−29,400	−47,000
CD			
$n \rightarrow \pi^*$		312 nm	314 nm
		+12,900	−15,300
$\pi \rightarrow \pi^*$		227 nm[b]	238 nm
		−63,100	+47,100

[a] The figures are molecular rotation and molecular ellipticity. [b] Only an approximate value was obtained. [c] Could not be measured because of a strong uv absorption.

(9) Later, selective microbial cleavage of the *dl*-acetate of **1** was found to be more practical (Dr. W. J. Marsheck, Department of Microbiology) than chemical resolution. This finding will be published elsewhere.

(10) (a) L. Crombie and M. Elliot, *Fortschr. Chem. Org. Naturst.*, **19**, 121 (1961); (b) Y. Katsuda, T. Chikamoto, and Y. Inouye, *Bull. Agr. Chem. Soc. Jap.*, **23**, 174 (1959); (c) *ibid.*, **22**, 427 (1958); (d) *ibid.*, **23**, 171 (1959); (e) G. Büchi, D. Minster, and J. C. F. Young, *J. Amer. Chem. Soc.*, **93**, 4319 (1971); (f) P. J. Godin, R. J. Sleeman, M. Snarey, and E. M. Thain, *J. Chem. Soc. C*, 332 (1966).

(11) Freudenberg's rule of shift: E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 110.

(12) The specimen was kindly provided by Dr. M. Elliot: M. Elliot, *J. Chem. Soc.*, 5225 (1964).

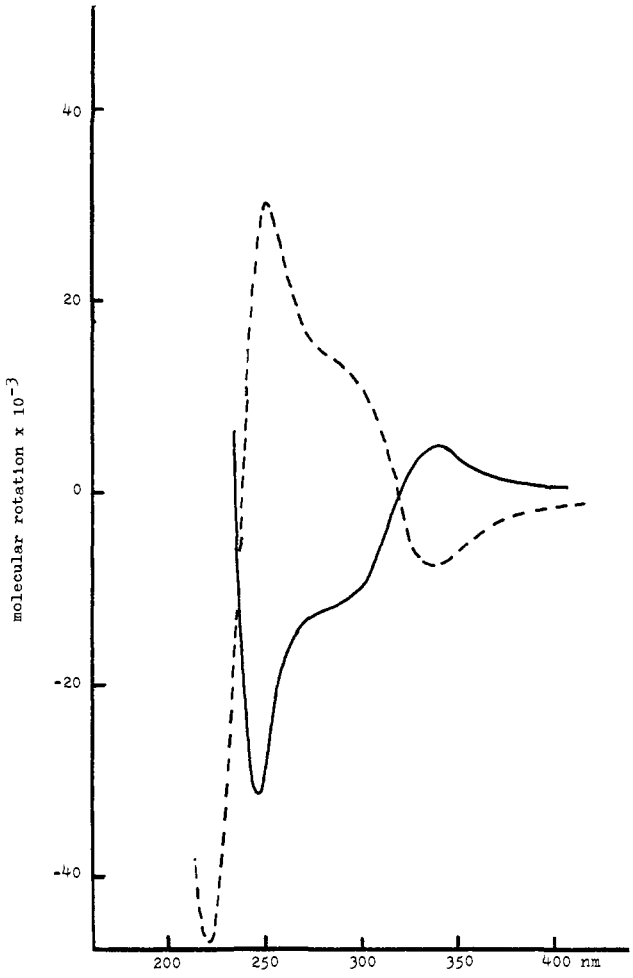


Figure 1. ORD curves of **9a** (——) and **11a** (---) in methanol.

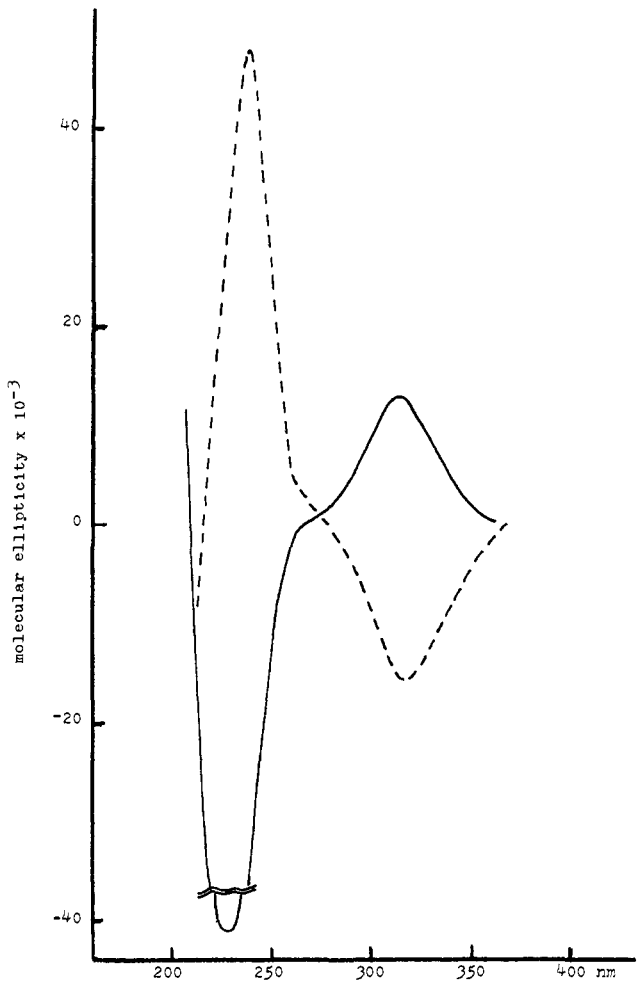
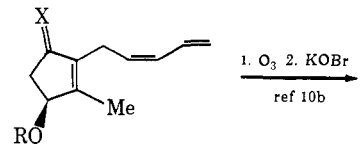


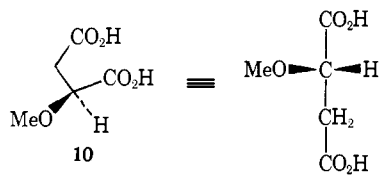
Figure 2. CD curves of **9a** (——) and **11a** (---) in methanol.

Catalytic hydrogenation of **5a** furnished the corresponding 3-*R* enantiomer (**11a**) whose ORD–CD curves in methanol were mirror images of those of **9a**, as shown in Figures 1 and 2.

We were intrigued to have found that the absolute configuration of **8a** was opposite to that predicted by Brewster's rule.[13] This prompted us to carefully examine the original proposal by Katsuda, *et al.*[10b-d] They prepared[10b] pyrethrolone methyl ether (**9b**) from



9a, X = O; R = H
b, X = O; R = Me
c, X = NNHCONH$_2$; R = H
d, X = NNHCONH$_2$; R = Me



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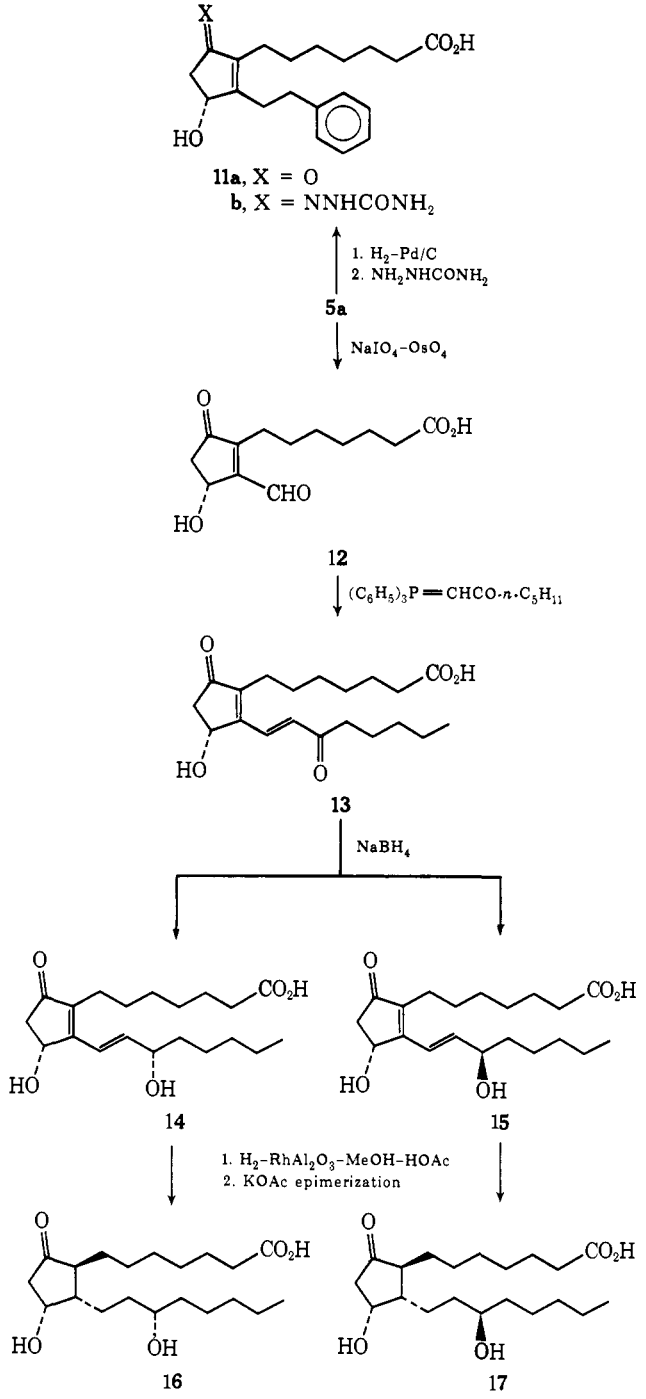
pyrethrolone semicarbazone (**9c**) by refluxing in 6% methanolic sulfuric acid for 2.5 hr. The methyl ether was ozonized and then oxidized to afford (−)-α-methoxysuccinic acid (**10**) of known configuration. The Japanese workers stated that this reaction sequence involved no process likely to disturb the asymmetric center and therefore the conversion of pyrethrolone into (−)-α-methoxysuccinic acid determined the absolute configuration of natural pyrethrolone (**9a**). However, it appears quite likely that step **9c** → **9b** involves cleavage of the carbon–oxygen linkage of **9c** inasmuch as **9c** is an allylic alcohol. It is then probable that this step is accompanied by rearrangement, or racemization, and even predominant inversion cannot be ruled out. In addition, the optical rotation of $[\alpha]^{25}D$ +10.5° (5.8% in ethanol) of **9b** given by Katsuda, *et al.*,[10b] was significantly different[14] from the same compound prepared by methylation of **9a** with dimethyl sulfate, this reaction involving no carbon–oxygen cleavage. Furthermore, the crystalline semicarbazone (**9d**) prepared from **9b** by Katsuda, *et al.*,[10b] had the empirical formula $C_{12}H_{18}ON_2$ rather than $C_{13}H_{19}O_2N_3$. In spite of these uncertainties, the absolute configuration of rethrolones proposed by Katsuda, *et al.*, seems to have never been challenged and apparently has been accepted by many investigators without additional evidence.[10a,e,f] Some confusion is

(13) J. H. Brewster, *J. Amer. Chem. Soc.*, 81, 5475, 5483, 5493 (1959).

(14) (a) Private communication by M. Elliot; (b) $[\alpha]^{20}D$ +99° (2.08% in methanol): M. Elliot, *J. Chem. Soc.*, 888 (1964); (c) $[\alpha]D$ +97.3° (16.6% in ethanol): T. F. West, *J. Chem. Soc.*, 240 (1944).

Chart I



seen, however, as the opposite configuration is cited in at least one well-known text.[15]

We submit independent evidence for the absolute configuration of **5a** and **6a**, and, consequently, for that of rethrolones.

Periodate–osmium tetraoxide cleavage[1,16] of (−)-7-[2-*trans*-styryl-3(*R*)-hydroxy-5-oxocyclopentenyl]-*n*-heptanoic acid (**5a**) afforded the unsaturated aldehyde (**12**), which was condensed with the Wittig reagent[1,17] to give rise to the 11(*R*)-(−)-dienedione (**13**).[18] Boro-

(15) P. G. Stecher, Ed., "Merck Index," 8th ed, Merck & Co., Rahway, N. J., 1968: p 264 for cinerins, p 889 for pyrethrins.

(16) For a general procedure, see R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(17) P. F. Beal, III, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, 88, 3131 (1966).

(18) In prostaglandin nomenclature 11α and 11β rather than 11-*R* and 11-*S* are commonly used; see ref 3.

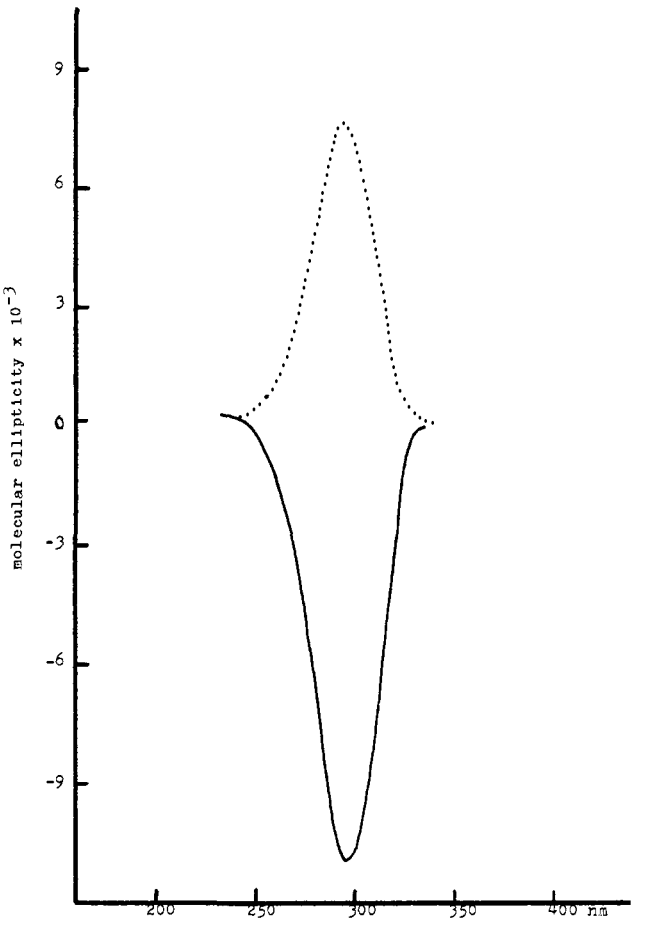


Figure 3. CD curves of PGE_1 (**3**) (——) and **17** (· · ·) in methanol.

hydride reduction[1] of **13** produced 11(*R*),15(*S*)-(+)-**14** and 11(*R*),15(*R*)-(−)-**15**.[19] Also, the 15(*R*) compound **15** was identical with a microbial transformation product obtained from racemic **13** by *Flavobacterium sp.* NRRL B-3874.[20] Hydrogenation of **15** over rhodium on alumina followed by epimerization with potassium acetate[1] afforded (+)-9-oxo-11(*R*),15(*R*)-dihydroxy-(8-*S*,12*S*)-prostanoic acid (**17**).[18,19] As shown in Table IV and Figure 3, the ORD–CD curves of **17** were mir-

Table IV. ORD and CD of PGE_1 (**3**), **16**, and **17** in Methanol[a]

	3	**16**	**17**
ORD n → π^*			
Peak	272 nm	315 nm	315 nm
	+7161	+3764	+3707
Trough	314 nm	273 nm	274 nm
	−6168	−5113	−5630
CD n → π^*	296 nm		295 nm
	−11,100		+7593

[a] The figures are molecular rotation and molecular ellipticity.

ror images of those of natural PGE_1.[21] Likewise, **14** was hydrogenated and then isomerized to **16**,[19] which

(19) Optically active compounds **13**–**17** exhibited 100-MHz nmr spectra in deuteriochloroform identical with those of their racemic modifications; see ref 1 for spectra of the racemates.

(20) M. Miyano, C. R. Dorn, F. B. Colton, and W. J. Marsheck, *Chem. Commun.*, 425 (1971).

(21) For the ORD–CD curves of natural PGE_1, see O. Korver, *Recl. Trav. Chim. Pays-Bas*, 88, 1070 (1969).

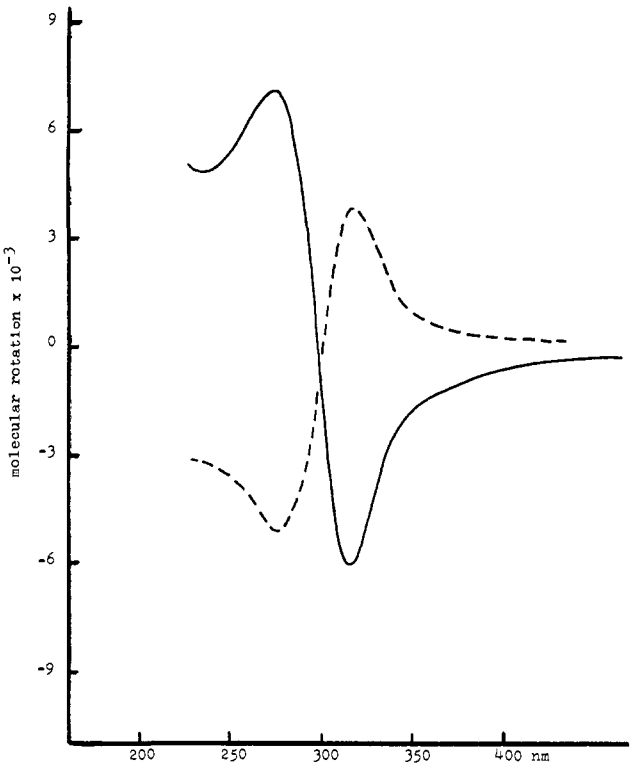


Figure 4. ORD curves of PGE_1 (**3**) (——) and **16** (---) in methanol.

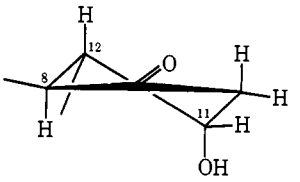
exhibited ORD–CD curves virtually indistinguishable from the curves of **17** and mirror images of those of natural PGE_1 (see Table IV and Figure 4).

The stereochemistry of the racemic modifications of **16** and **17** has been established beyond doubt[1] and the absolute configuration of natural PGE_1 has been demonstrated unambiguously by Dutch and Swedish investigators.[22] Since the C-11 hydroxyl groups of **16** and **17** are axial[1] and the ORD–CD curves of **16** and **17** are the mirror image of PGE_1, their absolute configuration with half-chair conformation must be as depicted in **18** and enantiomeric to natural PGE_1 (**19**).

In cyclopentanones (half-chair), the ring carbon atoms have a first-order effect on the Cotton effect of the carbonyl group, and substituents on the ring carbon atoms a second-order effect.[21,23] A positive Cotton effect was therefore expected for **18** (**20** in general) and was actually observed.

The conclusion drawn from the ORD–CD study was further confirmed by total synthesis of natural PGE_1 from **5a**. Compound **5a** was converted by a known sequence[2b] to 15-dehydroprostaglandin E_1 whose tetrahydropyranyl ether was reduced selectively to give natural PGE_1.[24]

This work establishes an unequivocal link between the absolute configuration of prostaglandins and rethrolones. Thus, the absolute configuration of rethrolones, which had been predicted on somewhat speculative evidence, is ultimately confirmed for the first time.[24a]



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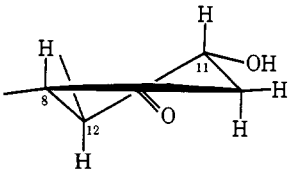

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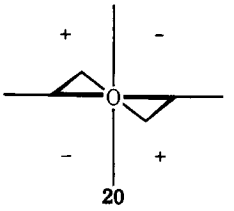

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Experimental Section[25]

(*R*)-(−)-α-Methoxyphenylacetic Acid Esters (5b and 6b). A solution of 5.5 g of racemic alcohol **1**[2b] in 10 ml of dry pyridine was cooled in an ice bath as a solution of (*R*)-(−)-α-methoxyphenylacetyl chloride[6] (prepared from 3.3 g of (*R*)-(−) acid) in 20 ml of benzene was added in one portion. When the exothermic reaction subsided, the mixture was removed from the cooling bath and allowed to stand at 25° for 18 hr. Water (5 ml) was added, and after 30 min the mixture was poured into excess cold aqueous citric acid and extracted twice with ether. The organic extracts were worked up in the usual manner to yield an oily product weighing about 8 g. This material was dissolved in benzene and chromatographed on 800 g of SilicAR CC-4, which was washed with increasing percentages of ethyl acetate. The earlier fractions, obtained upon elution with 15% ethyl acetate, were crystallized from benzene–hexane to afford colorless crystals of the 3-(*S*) ester **6b**: mp 122–124°; ir ($CHCl_3$) 1750, 1710, 1629, 1378 cm^{-1}; uv (MeOH) 325 nm (ε 35,000); nmr ($CDCl_3$) δ 2.87 (d of d, 1, *J* = 19 and 6 Hz), 3.40 (s, 3), 4.80 (s, 1), 6.30 (d, 1, *J* = 6 Hz), 6.78 (d, 1, *J* = 16 Hz), 7.15 (d, 1, *J* = 16 Hz). See Table I for additional analytical data.

Continued elution of the above column with 15% ethyl acetate gave mixtures of **5b** and **6b**, followed closely by **5b**. Crystallization of the latter from benzene–hexane yielded the pure 3-(*R*) ester **5b** as white needles: mp 96–98°; ir ($CHCl_3$) 1750, 1710, 1629, 1378, cm^{-1}; uv (MeOH) 325 nm (ε 36,000); nmr ($CDCl_3$) δ 3.00 (d of d, 1, *J* = 19 and 6 Hz), 3.40 (s, 3), 4.77 (s, 1), 6.13 (d, 1, *J* = 6 Hz), 6.40 (d, 1, *J* = 16 Hz), 6.97 (d, 1, *J* = 16 Hz). For other analytical properties, see Table I.

(*S*)-(+)-α-Methoxyphenylacetic Acid Esters (5c and 6c). These esters were prepared from **1**[2b] and (*S*)-(+)-α-methoxyphenylacetic acid as described above. The spectral properties of **5c** and **6c** were identical with those of **6b** and **5b**, respectively; see Table I for other analytical values.

(−)-Menthoxyacetic Acid Ester (1:1 Complex of 5d and 6d). The alcohol **1**[2b] (7.5 g) was esterified with (−)-menthoxyacetyl chloride[26] as described for the preparation of **5b** and **6b**. The crude product was dissolved in benzene and chromatographed on 1200 g of SilicAR CC-4. Elution with 10% ethyl acetate afforded crystalline material, which was recrystallized twice from methanol or benzene–hexane to give colorless crystals: mp 104–105°; $[\alpha]^{26}D$ −42.1° (1.00% in MeOH); ir ($CHCl_3$) 1755, 1710, 1627, 1372, 1125 cm^{-1}; uv (MeOH) 326 nm (ε 37,200); nmr ($CDCl_3$) δ 2.99 (d of d, 1, *J* = 19 and 6 Hz), 4.18 (s, 2), 6.30 (d of d, 1, *J* = 6 and 2 Hz).

(22) D. H. Nugteren, D. A. van Dorp, S. Bergström, M. Hamberg, and B. Samuelsson, *Nature (London)*, **212**, 38 (1966).
(23) G. Snatzke, *Tetrahedron*, **21**, 413 (1965).
(24) Carried out by Mr. M. Stealey and to be published elsewhere.
(24a) NOTE ADDED IN PROOF. The same absolute configuration was determined almost simultaneously by X-ray crystallography; see M. J. Begley, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1276 (1972).
(25) Unless otherwise mentioned, melting points were determined on Fisher-Johns melting point apparatus and were not corrected. The nmr spectra were recorded on either a Varian A-60 or HA-100 spectrometer using TMS as an internal reference. All uv spectra were taken in 1 mg % methanol solution.
(26) A. W. Ingersoll, *Org. React.*, **2**, 399 (1944).

Anal. Calcd for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.13; H, 8.26.

(+)-7-[2-*trans*-Styryl-3(*S*)-hydroxy-5-oxocyclopentyl]heptanoic Acid (6a). The ester **6b** (630 mg) in 6 ml of tetrahydrofuran was added to an ice cold stirred solution of 85 ml of 0.2% aqueous lithium hydroxide monohydrate containing 900 mg of lithium chloride. After stirring in the cold for 90 min, the mixture was poured into dilute aqueous acetic acid. The semisolid was filtered, washed with water, and taken up in ethyl acetate. The resulting solution was dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization of the residue from ethyl acetate–benzene provided 280 mg of colorless crystals, mp 109–112°. The analytical sample of (+) acid **6a** was obtained by recrystallization from the same solvent pair: mp 113–114°; ir ($CHCl_3$) 3610, 1705 (broad), 1629, 1376, 970 cm^{-1}; uv (MeOH) 325 nm (ϵ 36,000); nmr δ 2.35 (d of d, 1, J = 19 and 2 Hz), 2.89 (d of d, 1, J = 19 and 6 Hz), 5.24 (d of d, 1, J = 6 and 2 Hz). See Table I for additional analytical values.

(−)-7-[2-*trans*-Styryl-3(*R*)-hydroxy-5-oxocyclopentenyl]heptanoic Acid (5a). The (−) acid was obtained from ester **5c** using the conditions employed in the preparation of **6a**. The spectral data of **5a** were essentially the same as those of the enantiomer **6a**; see Table I for additional data.

(+)-7-[2-β-Phenylethyl-3(*S*)-hydroxy-5-oxocyclopentenyl]heptanoic Acid (8a). A solution of enantiomer **6a** (396 mg) in 50 ml of 95% ethanol was hydrogenated in the presence of 30 mg of 5% palladium on carbon at 25° and atmospheric pressure for 90 min. The catalyst was filtered off and the filtrate was concentrated to dryness. The oily residue was dissolved in a small amount of 50% ethyl acetate–benzene and placed on 35 g of SilicAR CC-4 packed in 50% ethyl acetate–benzene; elution was done with the same solvent mixture as fractions of 5 ml were collected. Fractions 35–44 contained 132 mg of material which crystallized slowly from ether–pentane to give colorless crystals of **8a**: mp 53–56°;[27] $[\alpha]^{25}D$ +33.2° (1.00% in MeOH); ir ($CHCl_3$) 3620, 1712, 1648 cm^{-1}; uv (MeOH) 236 nm (ϵ 14,000); nmr ($CDCl_3$) δ 2.87 (broad s, 4), 4.80 (d of d, 1, J = 6 and 2 Hz), 7.26 (s, 5).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.33; H, 7.68.

The semicarbazone was prepared by treating the ketone **8a** with semicarbazide hydrochloride and pyridine in aqueous ethanol at room temperature. Two recrystallizations of the crude product from methanol–ethyl acetate yielded slightly yellow crystals of **8b**: mp 155–158°;[28] $[\alpha]^{26}D$ −86.8° (1.21% in pyridine); ir (KBr) 3480, 3280 (broad), 1710, 1676, 1579 cm^{-1}; uv (MeOH) 268 nm (ϵ 27,000).

(−)-7-[2-β-Phenylethyl-3(*R*)-hydroxy-5-oxocyclopentenyl]heptanoic Acid (11a). Hydrogenation of **5a** followed by chromatography (see preparation of **8a**) furnished the (−)-dihydro compound **11a**: mp 52–56°; $[\alpha]^{25}D$ −30.1° (1.01% in MeOH); spectral properties were the same as those of **8a**.

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.42; H, 7.73.

(27) The corresponding racemate, obtained by either catalytic hydrogenation or lithium–ammonia reduction of **1**, was an oil.

(28) The corresponding *dl* compound melted at 172–174°.

(−)-9,15-Dioxo-11(*R*)-hydroxyprosta-8(12),13-dienoic Acid (13). Aldehyde **12** (3.6 g) was prepared from 4.4 g of **5a** by the known procedure[2b] for the racemic compound and then condensed[1] with triphenyl hexanoylmethylenephosphorane to afford 2.4 g of **13**,[19] $[\alpha]^{25}D$ −55.5° (1.19% in MeOH).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.65.

(+)-9-Oxo-11(*R*)-hydroxy-15(*S*)-hydroxyprosta-8(12),13-dienoic Acid (14) and Its (−)-15(*R*) Isomer (15). An aqueous ethanolic solution of 2.0 g of **13** was reduced with sodium borohydride in the usual manner.[1] The partition chromatographic separation[1] afforded 515 mg of **14** (mp 69.5–72°) and 505 mg of **15** (mp 52.5–58°). Recrystallization from ethyl acetate–Skellysolve B at −10° gave rise to pure **14**:[19] mp 69.5–72°;[29] $[\alpha]^{25}D$ +28.36° (1.00% in MeOH); uv (MeOH) 276.5 nm (ϵ 27,000).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.83; H, 9.06.

Pure **15**[19] was obtained by recrystallization from ethyl acetate–Skellysolve B at −10°: mp 59.5–60.5°;[29] $[\alpha]^{25}D$ −31.3° (1.00% in MeOH); uv (MeOH) 276.5 nm (ϵ 26,000).

(+)-9-Oxo-11(*R*),15(*S*)-dihydroxy-(8*S*,12*S*)-prostanoic Acid (16). Hydrogenation[1] of 154 mg of **14** over rhodium followed by potassium acetate epimerization and chromatography[1] afforded 25 mg of pure **16**:[19] $[\alpha]^{28}D$ +27.5° (1.02% in MeOH). This specimen was used for ORD study (see Figure 4 and Table IV).

(+)-9-Oxo-11(*R*),15(*R*)-dihydroxy-(8*S*,12*S*)-prostanoic Acid (17). Hydrogenation of 220 mg of **15** followed by epimerization in the usual manner[1] gave rise to 30 mg of pure **17**:[19] $[\alpha]^{29}D$ +10.87° (0.506% in MeOH). This specimen was used for ORD–CD study (see Figure 3 and Table IV).

Acknowledgments. Crystalline (+)-pyrethrolone hydrate was generously sent by Dr. M. Elliot, Department of Insecticides & Fungicides, Rothamsted Experimental Station, Harpenden, Herts, who also kindly commented to us on salient problems concerning the absolute configuration of rethrolones. The spectral and optical data presented here were taken by Mr. A. J. Damascus and staff. The elementary analyses were carried out by Mr. E. J. Zielinski and staff. Most of the column chromatography was carried out by Mr. R. T. Nicholson and staff. Hydrogenation was carried out by Messrs. M. G. Scaros and E. Saugstad. The starting materials were prepared by Messrs. M. Stealey, S. Nason and R. Reuter. We express our sincere thanks to those who are mentioned above. We are also indebted to Dr. F. B. Colton, Research Advisor of Searle Laboratories, for several very helpful discussions during the course of this investigation.

(29) The melting point was determined on Thomas-Hoover Unimelt in an open capillary. The corresponding racemic compound was oily.[1]