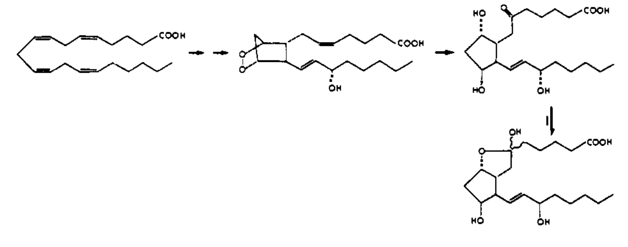
(M − $(CH_3)_3SiOH$), 544 (M − ($(CH_3)_3SiOH + C_5H_{11}$)), 525 (M − (2 × $(CH_3)_3SiOH$)), and 454 (M − (2 × $(CH_3)_3SiOH + C_5H_{11}$)); fragment ions not containing the benzyloxime group were observed at *m/e* 598 (M − C_7H_7O), 508 (M − ($C_7H_7O + (CH_3)_3SiOH$)), 499 (M − (C_7H_7 + (C(1)-C(5) fragment))), 418 (M − (C_7H_7O + (2 × $(CH_3)_3SiOH$))), 413 (M − (C(1)-C(7) fragment) − (2 × CH_3)), 352 (M − ((C(1)-C(7) fragment) + H + $(CH_3)_3SiOH$))), 217, 191, 173, and 115 (base peak above *m/e* 100).

The product derived from PGG_2 had the same R_f value and retention time on gas chromatography. When 5,6,8,9,11,12,14,15-octadeuterioarachidonic acid or PGG_2 was used as substrate, mass spectrometry of the methoxime derivative of the resulting product (**3a**) showed a retention of seven deuterium atoms which were located at positions 5,8,9,11,12,14,15 after comparison of its mass spectrum with that of **2a**. The mass spectrum showed the expected shifts at *m/e* 636 (7 D), 621 (7 D), 606 (7 D), 565 (7 D), 546 (7 D), 545 (6 D), 515 (6 D), 474 (6 D), 455 (6 D), 454 (5 D), 424 (6 D), 419 (6 D), 384 (6 D), 219 (2 D), 192 (1 D), 174 (1 D), and 116 (1 D). The location of the deuterium atoms was further confirmed in the mass spectrum of the benzylhydroxylamine derivative (**3b**). Mass spectral shifts of this compound (first isomer) were observed at *m/e* 697 (7 D), 641 (7 D), 622 (7 D), 621 (6 D), 606 (7 D), 605 (6 D), 550 (6 D), 531 (6 D), 515 (7 D), 505 (6 D), 460 (6 D), 419 (6 D), 219 (2 D), 192 (1 D), 174 (1 D), and 116 (1 D). Similar results were obtained when PGH_2 was used as substrate.

Additional structural support was obtained after catalytic reduction (PtO_2/ethanol) of **2** and **3**. Mass spectra of the hydrogenated derivative of **2a** confirmed the presence of one double bond (M^+ 631). The hydrogenated derivative of **3a** was similarly shifted by two mass units (M^+ 638). The presence of the cis-9,11-dihydroxy function was supported by the formation of a cyclic *n*-butyl boronate (NBB) derivative **4** (retention time 26.6 carbons; $PGF_{2\alpha}$ $MeNBBMe_3Si$ = 25.4 carbons—3% SE-30 on Gas Chrom Q, 240°). Its mass spectrum showed an intense fragmentation pattern characteristic of NBB derivatives of the PGF's[9] namely, *m/e* 551 (M^+), 536 (M − CH_3), 480 (M − C_5H_{11}), and 378 (M − ($(CH_3)_3SiOCHC_5H_{11}$)) [97% intensity]. Other fragment ions in the spectrum included *m/e* 520 (M − OCH_3), 461 (M − ($(CH_3)_3SiOH$)), 449 (M − $C_4H_9BO_2H_2$), 430 (M − ($(CH_3)_3SiOH + OCH_3$)), 418 (M − ($C_4H_9BO_2H + OCH_3$)), 187, 173, and 115 (base peak).

These results demonstrate that arachidonic acid is converted in good yield by rat stomach homogenates into 6-keto-$PGF_{1\alpha}$ via the prostaglandin endoperoxide mechanism (see Scheme I). An interesting feature of this compound, which belongs to the prostaglandin "1" series (i.e., PGE_1 and $PGF_{1\alpha}$), is its formation from a substrate of the prostaglandin "2" series (i.e., PGE_2 and $PGF_{2\alpha}$). Since the isolated product is unreactive to sodium borohydride in methanol, yet reacts with methoxylamine hydrochloride, we propose that the keto group at position 6 must be in the lactol form coupled with the hydroxyl group at position 9. Thus the equilibrium between the open and cyclic forms in methanol heavily favors the lactol form. Further work on the origin of the oxygen atom at position 6 is currently in progress.

Scheme I. Formation of 6-Keto-$PGF_{1\alpha}$ and Its Lactol Form by the Rat Stomach



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(8) The mass spectrum of derivative **2a** was identical with that of 6-keto-$PGF_{1\alpha}$ chemically synthesized by Dr. Udo Axen, The Upjohn Co.
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Regioselective Remote Photocyclization. Examples of a Photochemical Macrocyclic Synthesis with Sulfide-Containing Phthalimides[1,2]

Sir:

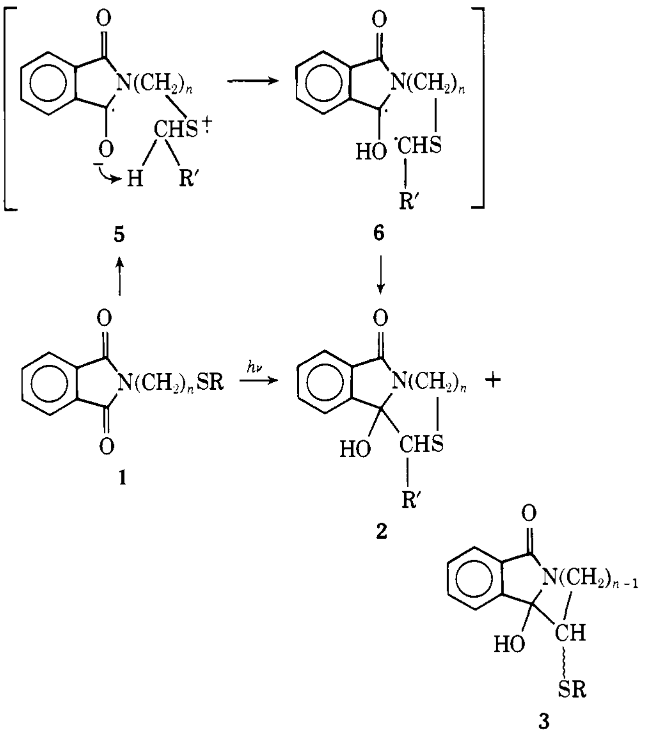
Certain phthalimides (**1**, *n* = 1-3) possessing a terminal sulfide function in their *N*-alkyl side chain undergo photocyclization to give five- to seven-membered azathiacyclols (**2**, *n* = 1-3), probably by way of Norrish type II reactions.[3] We have now extended this type of reaction to an easy synthesis of medium- to large-sized ring systems on the basis of an unusually regioselective remote photocyclization of the sulfide-containing phthalimides.

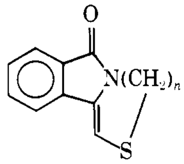
A solution of **1a-d** in acetone (10 mM) was irradiated with a 400-W high-pressure mercury lamp in a stream of argon for 1-2 h. As shown in Table I,[4] in most cases mixtures of nine-membered (**2a-d**) and seven-membered ring compounds (**3a-d**) were obtained, with the former as major products, after preparative TLC in moderate direct yields. In a representative example, the structural assignment for **2a** was based on: (i) the presence of the cyclol moiety[5] ((uv 259 nm, ε 5200), amide (ir 1655 cm^{-1}), hydroxyl (3240 cm^{-1})) and a methylene (instead of methyl in **1a**; NMR 3.15 ppm, s); (ii) the molecular weight and composition of $C_{14}H_{17}NO_2S$ (mass *m/e* 263; elemental analysis); and finally (iii) by analogy with previous cyclizations[3] of **1** in which the number of methylenes in the side chain (*n*) varied from 1 to 3. The substrates further examined represent a homologous series with side chains varying from *n* = 6 to 12 (**1e-i**).[6] In all examples studied, irradiation afforded mainly the expected ring system, up to 16-membered (**2i**), as a result of C-C bond formation between the imide carbonyl and the terminal methylmercapto group.[7] In some cases (**2d**, **3c**) the dehydrated products, such as **4**, were isolated in further support of the postulated cyclol structures. Since it might be suspected that photodimerization has occurred with only the monomer peaks showing in the mass spectra, the molecular weight of, e.g., **2i**, was determined by a vapor pressure method;[8] the value (362) obtained was consistent with that

Table I. Photoproducts from Sulfide-Containing Phthalimides 1[4]

Substrate (1)	n	R	Product ring size (2)	Mp, °C	% yield	Relative efficiency[13]	Product ring size (3)	Mp, °C	% yield
a	5	Me	9	152-153	78		7	145	6
b	5	Et	9	121-123	61		7	Oil	5
c	5	*t*-Bu	9		0		7	165-167	44[a] (27)[b]
d	5	Benzyl	9	169-170 137-138	37 (18)[b]		7		0
e	6	Me	10	153-155	58	1.0	8	Oil	10
f	8	Me	12	151-152	45	0.3	10	201	3
g	9	Me	13	176-177	29	0.3	11		0
h	10	Me	14	167-169	26	0.3	12	198-201	4
i	12	Me	16	115-116	25	0.2	14	136-139	4

[a] Mp cis 149-150; *trans* 144-146 °C. [b] Dehydrated compounds such as **4**.





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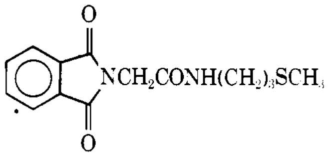

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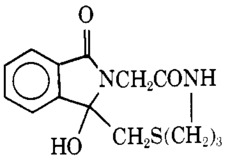

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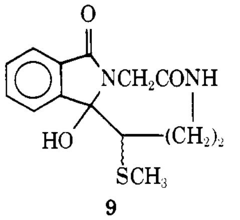

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of the cyclized monomeric structure (calcd 361). The above results demonstrate the universality of this type of photocyclization, by which medium- to large-sized azathiacyclol systems are readily accessible. The photolysis of **1e** was studied in some detail. Quantum yields[9] of the formation of **2e** were 0.07 (acetone), 0.05 (acetonitrile), and 0.08 (*tert*-butyl alcohol), respectively. A Stern-Volmer plot with *trans*-piperylene as a quencher (acetonitrile, ~10 mM) is linear with a slope $k_q\tau = 390\ M^{-1}$.[10]

Although "remote" photoreactions are infrequently encountered, much attention has been recently paid to them with regard to theoretical studies of cyclization[11] and, in general, to reactions of nonconjugated bichromophoric systems.[12] The well-defined examples of such photoreactions are the remote oxidation of long-chain carboxylates by Breslow et al.[11a] in which the reaction sites distribute depending on conformational flexibility of the chain.[11] It is therefore remarkable that in such a flexible system as **1** the medium and large rings are formed with unusual facility and regioselectivity. In view of the fact that relative efficiencies[13] of the cyclization stay on the same order in going to larger rings (Table I), there seems no critical limitation in the size of the macrocycles to be constructed. A special mechanism must be involved in which the sulfur function facilitates the formation of the macrocyclic transition states, because (i) the *O*-methyl analogues fail to undergo the reaction, and (ii) the quantum yields are even increased over, or at least comparable to, those of photocyclizations of usual aromatic imides (0.01 for *N*-*o*-tolylphthalimides)[14] which involve far smaller seven-membered transition states.

Tentatively the remote photocyclization may be rationalized by enhanced proton transfer from the methylmercapto group which would be held close to the imide carbonyl by a postulated charge transfer complex formation in the excited state (**5** → **6**).[15] Such an assumption encourages exploring general application of the "photolysis of donor-acceptor pair system" method[19,20] for various synthetic purposes. With respect to macrocyclic synthesis, since the true cyclizing species are photogenerated and the precursors are ordinarily unreactive in the ground states, preparation of such long-chain starting compounds may be made with less difficulty than that of conventional bifunctional substrates.[21] One direct application of this reaction, for example, may be construction of cyclic peptide models. Thus in a preliminary experiment, irradiation of **5** (14 mM acetone, 40 min) afforded **6** (48%) and **7** (15%), illustrative of the versatility of this approach. The scope, limitation, and mechanism of the remote reaction are under investigation.

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(8) Hitachi–Perkin molecular weight measuring apparatus Model 115; in methanol.
(9) Quantum yield was determined in Pyrex tubes (10 mM) by potassium ferrioxalate actinometry using 313-nm light on a merry-go-round.
(10) The results suggest τ to be ~20 ns for diffusion control quenching, consistent with a triplet state largely quenched intramolecularly, or a singlet state. Thus the problem of the multiplicity involved remains uncertain.
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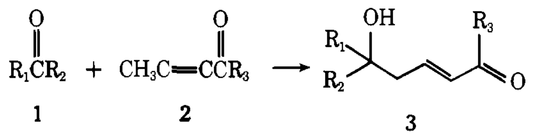
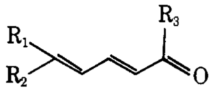
A New Synthesis of Vinylogous Aldols and Polyenones

Sir:

We report here on a new and effective method for the simple introduction of an electrophile such as an aldehyde or ketone on the γ-carbon of an α,β-unsaturated ketone (**1** → **3**). The vinylogous aldols **3** are valuable per se, and also because their easy dehydration provides a convenient access to polyenic ketones **4**, especially since the aldehyde or ketone **1** could itself be unsaturated (vide infra). The difficulty in achieving this transformation stems, of course, from the fact that an α,β-unsaturated ketone such as ethylidene acetone (3-pentene-2-one, **2**, $R_3 = CH_3$) can be transformed either into a kinetic enolate **5**, leading to condensation at the methyl group, or into the (more difficultly obtainable) thermodynamic enolate **6**, which would normally lead to considerable condensation at the 3-position.[1]





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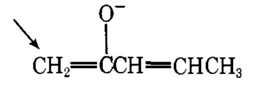

$CH_2{=}\overset{O^-}{C}CH{=}CHCH_3$

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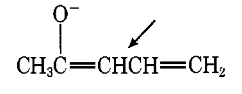

$CH_3\overset{O^-}{C}{=}CHCH{=}CH_2$

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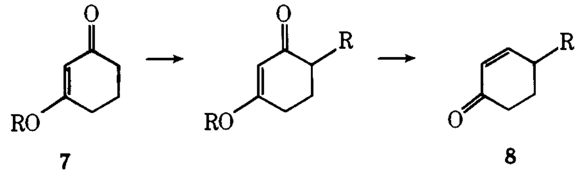
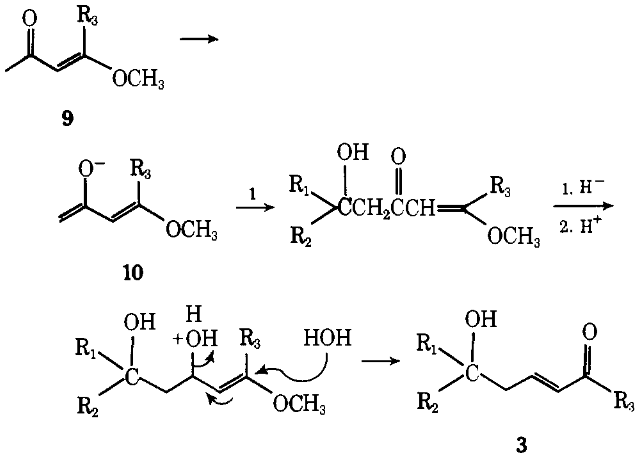
Our solution to the problem is based on the concept we introduced[2] for the construction of γ-substituted cyclic α,β-unsaturated ketones (**7** → **8**).



The vinylogous ester system present in the readily available enol ether of a 1,3-diketone (cf. **9**)[3] gives a kinetic enolate **10**[4] which reacts with aldehydes and ketones to give, after reduction and mild acid treatment, the vinylogous aldols **3**, the formal product of the condensation shown in **1** → **3** above.



The synthesis of vinylogous aldols is illustrated starting with β-ionone (**11**). A solution of 1 equiv of β-ionone in dry tetrahydrofuran was added slowly, at −78°, to a solution of the lithium enolate from 4-methoxy-3-pentene-2-one[5] (**12**), previously prepared by dropwise addition of 1 equiv of **12** in tetrahydrofuran to 1.1 equiv of a 0.5 M solution of lithium diisopropylamide in tetrahydrofuran at −78°, followed by stirring for 10 min. The solution was quenched after 20 min, while still at −78°, by addition 1.1 equiv of acetic acid. Unchanged starting material was removed after workup by bulb-to-bulb distillation under vacuum (85 °C, 0.5 mm), leaving the crude aldol **13**: λ 2.9, 6.3 μ; NMR δ 1.3 (s, $HOCCH_3$), 2.3 (s, $=C(COCH_3)CH_3$), 2.7 (d, $J = 2$ Hz, $CH_2C{=}O$), 3.65 (s, OCH_3), 5.5 (s, $HC{=}C(OCH_3)CH_3$),