attack from the β face favored.

The 13β-H configuration having served its function was inverted to the more stable, natural 13α-H configuration. In the 11-deoxy series, the 13α configuration is only slightly favored (60%),[8] but in the present case, the introduction of the 11α-hydroxy group introduces yet another unfavorable 1,3-diaxial interaction to the 13β-H configuration, and thus, a greater preponderance of the 13α-H material was expected.[14] Diol ketal **8** was hydrolyzed in 80% aqueous acetic acid followed by epimerization of the resulting ketone with aqueous NaOH. A 5:1 mixture of the 13α-H/13β-H ketones was obtained, and pure **9a** (mp 201-202 °C)[11,12,15] was isolated in 67% overall yield from **8**. The diolone **9a** was methoxymethylated to **9b** (mp 90-91 °C) in 89% yield by using (methoxymethyl)triethylammonium chloride[16] in refluxing chloroform; other methods bring about loss of stereochemical purity at C-13.

Completion of the synthesis now required only the introduction of the 16β-acetoxy group and manipulation of protecting groups. Extensive investigation indicated that chemistry at C-16 in **9b** occurs predominantly from the α face and that, once obtained, a 16α functionality could not be successfully inverted. Our strategy thus became to use the α-face selectivity in this series by introducing the oxygen functionality at C-16 *first*, followed by introduction of the C-16 hydrogen. A variety of methods for accomplishing this conversion can be conceived; however, the hydrogenation of Δ^{15}-enol acetate[15,16] seemed particularly appropriate for this system. Trost and co-workers have developed a facile conversion of ketones to α-acetoxy enones,[17] and this chemistry became the key to the completion of the synthesis.

Phenylsulfenylation[17a] of **9b** gave the 16-(phenylthio)ketone[11,13] in 76% yield as a mixture of isomers at C-16, and treatment of this mixture with lead tetraacetate[17b,c] gave **10**[11,12] as predominantly only isomer in 93% yield. Oxidation of **10** to the C-16 sulfoxide was troublesome; however, treatment with MCPBA and pyrolysis of the resulting sulfoxide gave a 32% yield of acetoxy enone which could be hydrogenated in quantitative yield to give **11**[11,13] with none of the 16α-acetoxy compound detectable. Removal of the methoxymethyl protecting groups (4:1:1 CF_3CO_2H-H_2O-THF) gave the 16β-acetoxy-3,11-diol in 57% yield which was identical by NMR, IR, and TLC with material obtained by ozonolysis of dihydrofusidic acid. The diol was converted to the triacetate **3** with Ac_2O/AcOH/TsOH in 63% yield to complete the formal total synthesis of fusidic acid.

A fundamental feature of this synthesis is the use of the shape of the molecule by control of the stereochemistry at centers C-9, C-11, and C-13 to guide reactions to the α or the β face of the molecule.

Acknowledgment. We are greatly indebted to Dr. W. O. Godtfredsen of Leo Pharmaceutical Products, Copenhagen, for the generous supply of fusidic acid which made this study possible.

Registry No. 1, 6990-06-3; **2**, 14253-81-7; **3**, 14185-98-9; **4a**, 79970-95-9; **4b**, 79970-96-0; **5**, 79970-97-1; 9b-**6**, 79970-98-2; 9α-**6**, 80008-82-8; **7**, 5609-46-1; **8**, 79970-99-3; 13α-**9a**, 80008-83-9; 13β-**9a**, 80008-84-0; **9b**, 79971-00-9; 16α-(phenylthio)-**9b**, 79971-01-0; 16β-(phenylthio)-**9b**, 79971-02-1; **10**, 79971-03-2; **11**, 79971-04-3; **11** acetoxyenone, 79971-05-4; 17β-hydroxy-**7**, 80008-85-1; **8** 11-ketone, 79971-06-5; **11** (M^2 = H), 14424-42-1.

(14) This concept has been discussed earlier by Godtfredsen[4b] and on a related compound showed that after simple passage through a column of basic alumina a 1:1 mixture was obtained.

(15) R. Bucourt and M. Legrand (*C. R. Hebd. Seances Acad. Sci.* **1964**, *258*, 3491) have reported a mp of 223 °C for this compound. Their work has been repeated, and the material we obtained was identical in physical and spectral properties with the compound reported in this present study.

(16) The reagent was prepared in analogy to the use by Corey of (methoxyethoxymethyl)triethylammonium chloride for the attachment of MEM groups under mild condition (*Tetrahedron Lett.* **1976**, 809). Subsequently, Teisseire (*Tetrahedron Lett.* **1980**, 2051) also reported the use of the same methodymethyl salt.

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Structural Effects on the Photopolymerization of Bilayer Membranes

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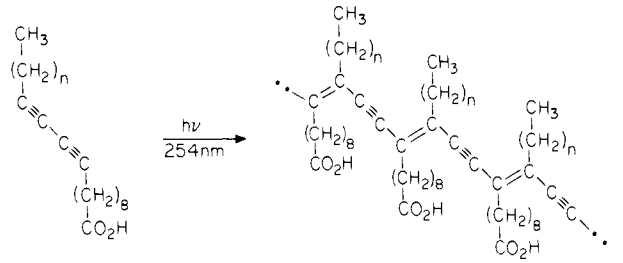
The conformational preference of phosphatidylethanolamines and phosphatidylcholines in bimolecular-layer membranes has been determined by low-angle X-ray diffraction[1] and NMR[2,3] data. In this conformation the glycerol backbone is approximately perpendicular to the plane of the bilayer, and the two fatty acid chains extend unequal distances into the bilayer membrane. In contrast, synthetic bilayer-forming surfactant molecules such as dialkyl dimethylammonium salts, reported by Kunitake and his colleagues,[4] have planes of symmetry which suggest that both chains will penetrate equally into the bilayer membrane.

We wish to report studies on molecules analogous to both the biological and synthetic lipids which contain conjugated diacetylene moieties in the long alkyl chains. These lipid diacetylenes form bilayer structures when suspended in aqueous buffers. The formation of vesicles in sonicated samples has been demonstrated by electron microscopy.[6,7] The ultraviolet-light-initiated polymerization of the diacetylenes in these hydrated lipid bilayers has been described.[5-7] The bilayer structure is retained after polymerization (Figure 1).[6,7] Our studies now demonstrate remarkable differences in photosensitivity which are interpretable in terms of the expected conformational preference of the molecules.



We have prepared samples of lipid diacetylenes based on phosphatidylcholine (**1**),[7] a dialkyl dimethylammonium salt (**2**),[8] and a dialkylphosphate (**3**).[8] The photosensitivity of each membrane was evaluated under conditions of maximum sensitivity,

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(2) (a) Haberkorn, R. A.; Griffin, G. A.; Meadows, M. D.; Oldfield, E. *J. Am. Chem. Soc.* **1977**, *99*, 7353-7355. (b) Yeagle, P. L. *Acc. Chem. Res.* **1978**, *11*, 321-327.

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(4) (a) Kunitake, T.; Okahata, Y.; Tamaki, K.; Kumamaru, F.; Takayangi, M. *Chem. Lett.* **1977**, 387-390. (b) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3860-3861. (c) Kunitake, T.; Okahata, Y.; *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1877-1879.

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(8) Compound **2** was prepared by the reaction of the acid chloride of 10,12-tricosadiynoic acid with bis(2-hydroxyethyl)dimethylammonium chloride using 4-(dimethylamino)pyridine as catalyst. The product was purified by gel permeation and silicic acid chromatography followed by recrystallization from acetone: NMR ($CDCl_3$) δ 0.9 (t, 6 H, CH_3C), 1.4 (br s, 56 H, CH_2), 2.2 (m, 12 H, CH_2CO, $CH_2C{\equiv}$), 3.5 (s, 6 H, CH_3N), 4.2 and 4.6 (m, each 4 H, CH_2O and CH_2N); IR (CCl_4) 1737 and 1260 (CO_2R), 2300, 2400 (w, C≡C) cm^{-1}. Compound **3** was prepared from 10,12-tricosadiyn-1-ol and phosphoryl chloride by a method similar to that of Kunitake et al.[4c] The crude crystalline material was recrystallized from hexane at 0 °C: NMR ($CDCl_3$) δ 0.9 (*t*, 6 H, CH_3), 1.3 (br s, 50 H, CH_2), 2.2 (br t, 8 H, $CH_2C{\equiv}$), 3.7 (br s, 4 H, CH_2O); IR (film) 3400 (br, w, OH), 1230 (P(=O)OH) cm^{-1}.

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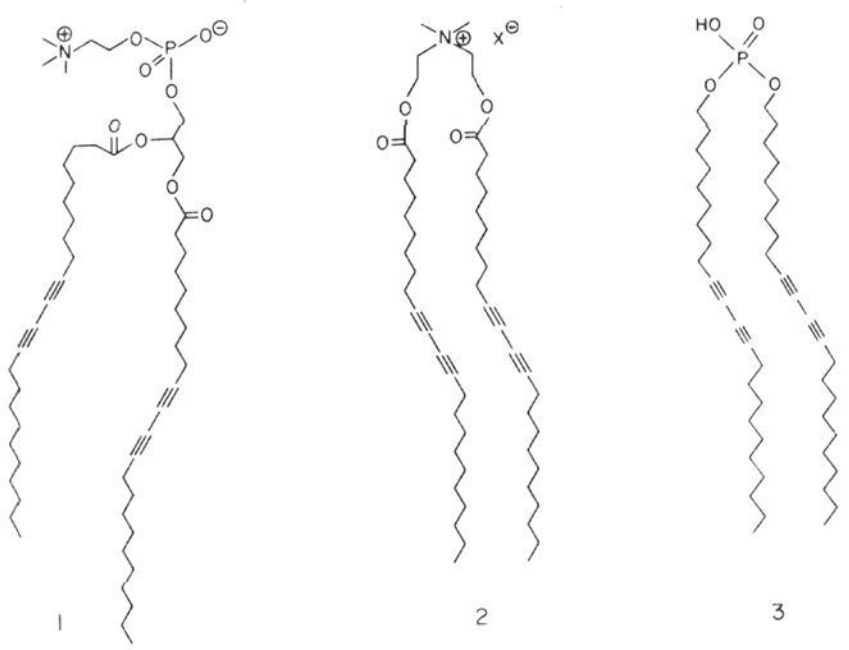
that is at temperatures below the lipid transition temperature and for samples of large vesicles or hydrated bilayers. As previously reported,[7] bilayer membranes of the phosphatidylcholine diacetylene **1** can be photopolymerized to yield a reddish polymer with absorption maxima at 525 and 485 nm. The photopolymerizations of the bilayer membranes of the symmetrical species **2** and **3** are dramatically more efficient. On the basis of estimates of photoproduct extinction coefficients, the quantum yield for photopolymerization of **2** is ~6500 times as great as for **1**.[9] The photoreaction of **3** is comparable to **2**. Furthermore, the photopolymers from **2** and **3** are blue (λ_{max} 644 nm; Figure 2), suggesting a longer and/or a more ordered polymeric structure for these polymers than for poly **1**.[10] On warming, both poly **2** and poly **3** yield red polymers (λ_{max} 540 nm) in a manner consistent with the behavior of poly(diacetylenes) in the solid state.[11]

The photopolymerization of diacetylenes proceeds as a 1,4-addition reaction to give a fully conjugated structure as shown. The reaction is topotactic,[11] and its efficiency depends on the correct alignment of the monomeric units. It has been observed in the solid state,[11] monolayers,[12] and bilayers.[5-7] Bilayers of **1** are photopolymerizable only if the hydrocarbon chains are in a regular, rigid lattice such as that found at temperatures below the lipid transition temperature;[7] polymerization is inhibited above this transition.



The stereochemical requirements of the polymerization suggest that the reaction should be sensitive to the lipid structure and conformation. If the phosphatidylcholine diacetylene **1** molecules exist in a conformation similar to that deduced for other hydrated phospholipids, the diacetylene groups on the α and β chains of **1** cannot simultaneously be in the proper stereochemical arrangement to allow either intramolecular or intermolecular α to β chain reaction. The diacetylene groups in **1** can polymerize only with suitable oriented diacetylene groups in adjacent molecules,

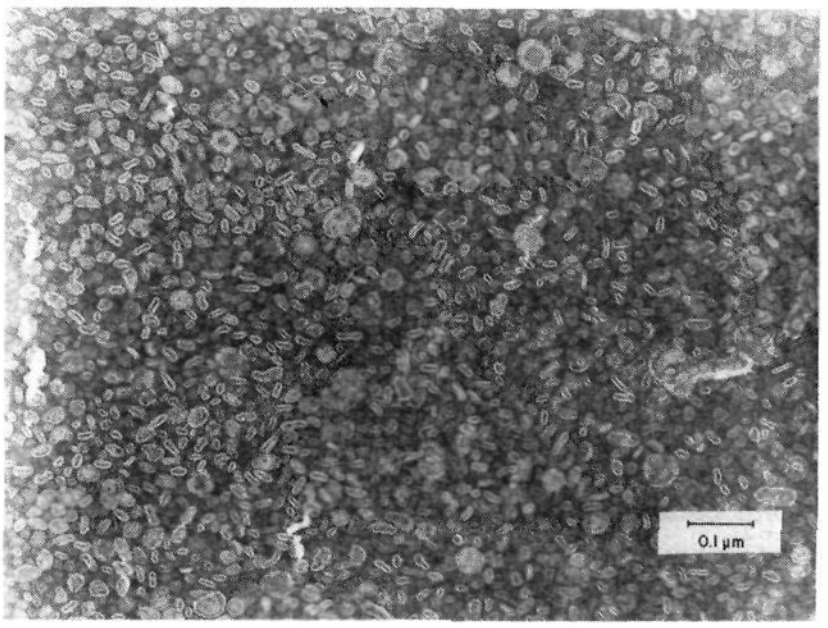


Figure 1. Electron micrograph of negatively stained (ammonium molybdate) membrane vesicles of **1** after photopolymerization.

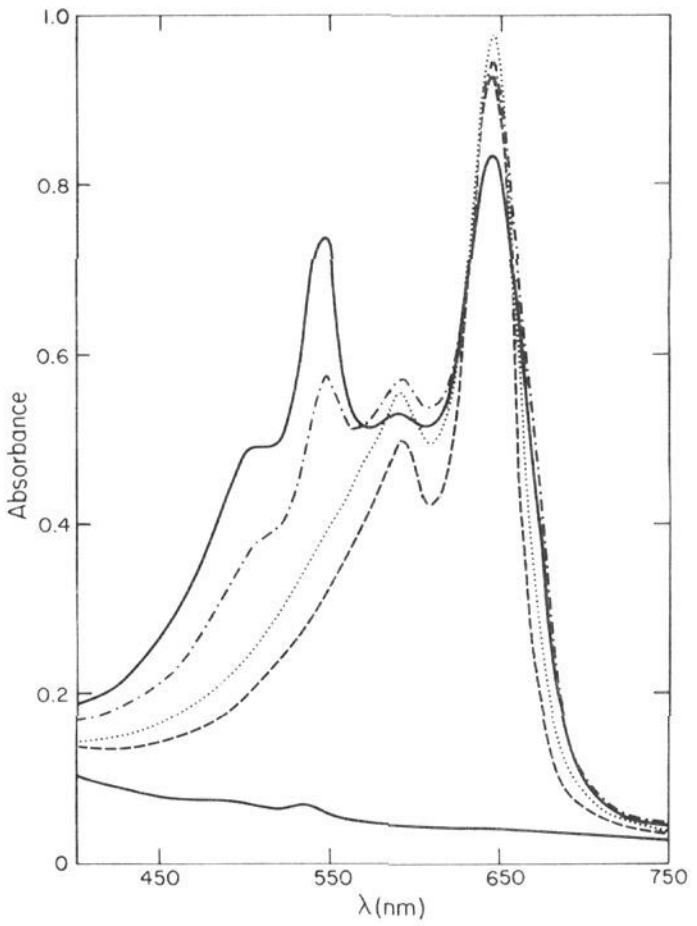


Figure 2. Absorption spectra of membrane vesicles of **2** in aqueous buffer, pH 7.0, in a 1-mm cuvette before exposure to a low-pressure mercury lamp: lower curve —. After exposure times of 5 s, - - -; 10 s, ···; 20 s, -·-·-; 30 s, —.

α to α and β to β. Since polymerization is initiated by light absorption by either an α- or a β-diacetylene chromophore, the polymer formed by a given excitation is expected to be either an α-chain or a β-chain polymer in that microregion. The growth of this polymer will probably decrease the ability of the other chain diacetylene to attain the proper stereochemical arrangement for polymerization.

In contrast, the symmetry of **2** and **3** allows both of the diacetylene groups to be properly oriented for efficient topotactic polymerization. This accounts for the enhanced efficiency of formation of poly **2** and poly **3**. The quantum efficiency of polymer formation from **2** was estimated by ferrioxalate actinometry[13] to be 60, which compares favorably to estimates of the efficiency of polymerization of diacetylenes in the solid state.[14]

This effect of lipid structure on the topotactic polymerization of lipid diacetylenes is consistent with the suggested conformational preferences of phospholipids. The polymerization is sensitive to

(9) The relative efficiencies were determined by irradiation of samples of the hydrated lipid bilayers (~5 mM in lipid) at 20 °C with a calibrated low-pressure mercury lamp (253.7 nm) for selected periods of time. The initial ultraviolet absorption characteristics of **1**–**3** were the same in solution (MeOH) or hydrated bilayers. Each shows maxima due to the diacetylene chromophore at 253, 239, 225 and 214 nm, with smaller peaks at 282 and 266 nm. The samples for irradiation had the same absorbance at 254 nm (±10%). The samples were flushed with argon, and the measured rates were maximum values after purging. The apparent difference in the rates of product formation from **1**, **2**, and **3** are corrected for the extinction coefficients of the products. The photoproducts of **2** and **3** are the blue form of the diacetylene polymer, which has an extinction coefficient of 2.4×10^4 L mol^{-1} cm^{-1}, and the photoproduct of **1** is the red form of the diacetylene polymer, which has an extinction coefficient of 1.7×10^4 L mol^{-1} cm^{-1}. These values were determined by R. Searle and S. Y. Farid, respectively, of the Kodak Research Laboratories.

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lipid structure, to the temperature of the vesicles relative to their phase transition,[17] and to the thermal history of the vesicles.[7] We have also observed that the reaction is sensitive to the size of the lipid bilayer structure. Small sonicated vesicles of lipid diacetylenes are less sensitive to light than vesicles of larger radius or extended bilayers of lipid diacetylene. Since the reaction is very sensitive to the lipid chain order, these preliminary observations suggest that the lipid chains in small sonicated vesicles of lipid diacetylenes are more disordered and support the interpretation of the NMR spectra of sonicated lipid vesicles, which suggest that lipid chain disorder is increased as a result of the increased surface curvature of the vesicles.[15]

Registry No. 1, 75898-24-7; **2** (X = Cl), 80028-58-6; **3**, 80028-59-7.

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Measurement of Relative Rates of Type I Photolysis by Chemically Induced Dynamic Nuclear Polarization[1]

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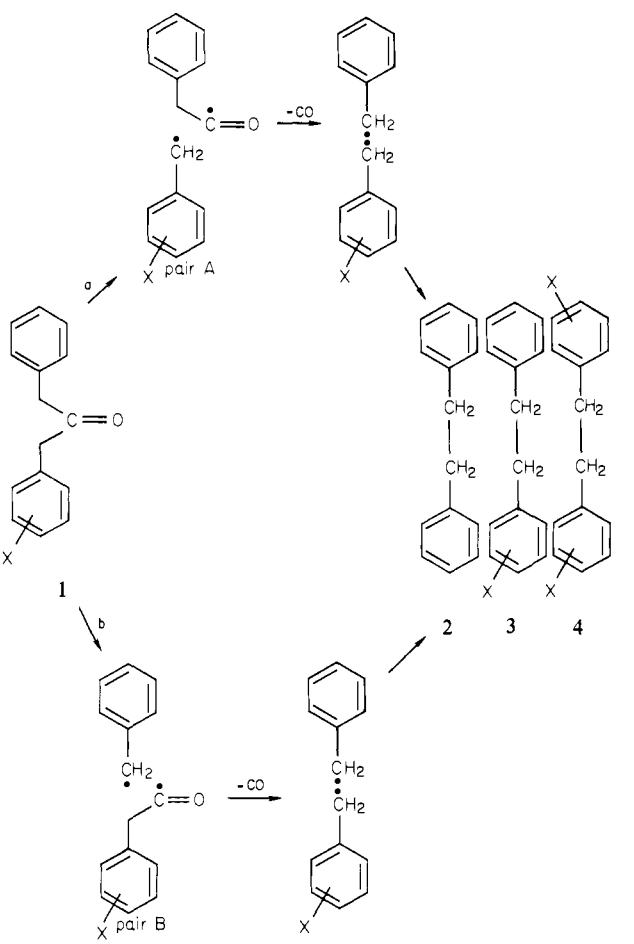
The rate of α cleavage of triplet dibenzyl ketones (Type I photolysis) has been estimated to be at least 10^{10} s^{-1}.[2,3] While we were investigating the behavior of radical pairs on a silica gel surface in comparison with that in solution and micelles,[4] an opportunity presented itself to measure directly the relative rates of the type I reaction. These rates have been correlated with the Hammett equation by using σ^+. The technique of chemically induced dynamic nuclear polarization (CIDNP) was especially well suited for this investigation, the results of which we now wish to report.

The stepwise homolytic α cleavage as well as the nature of the excited precursor in the photolysis of the parent dibenzyl ketone has been clearly demonstrated from CIDNP effects by Fischer et al.[5] These authors observed the methylene protons in strong emission for the starting material and in enhanced absorption for the decarbonylation product, dibenzyl. When a monosubstituted dibenzyl ketone is photolyzed, the possibility of two competitive α cleavages, a and b (Scheme I), exists although the same three final coupling products (dibenzyls **2**–**4**) may result, as indicated. When the photolysis was carried out in the high magnetic field of an NMR spectrometer,[6] the absorptions of the methylene protons of all starting materials (**1a**–**e**) were converted into emission but to different extents. In Figure 1, we show the results obtained from *p*-methoxydibenzyl ketone (**1a**). The *p*-methoxybenzyl methylene protons exhibit a much stronger emission than do the unsubstituted benzyl methylene protons, thus indicating the nonequivalent properties of these two different methylene groups. However, the distribution of dibenzyl products **2**, **3a**, and **4a**, obtained in the ratio of 1:2:1 expected from the statistical coupling of the free benzyl and *p*-methoxybenzyl radicals, fails to indicate the possibility of selective α cleavage. The CIDNP nonequivalence of the methylene protons can, thus, be related to

Scheme I



a, X = *p*-MeO
b, X = *p*-Me
c, X = *p*-F
d, X = *p*-Cl
e, X = *m*-Cl
f, X = H

two different radical pairs, A and B, generated from the two possible competitive α cleavages.

The CIDNP emissive character of the methylene protons of the starting materials is fully accounted for by the Kaptein rule:[7] that is, pairs A and B are generated from a triplet state ($\mu > 0$), the recombination is a cage process ($\epsilon > 0$), the methylene protons of the benzyl radicals have negative hyperfine coupling constants ($A_H < 0$), and the *g* factors of benzyl radicals (2.0025) are larger than those of acyl radicals (2.0007) ($\Delta g > 0$). Since the parameters affecting the CIDNP effects for pair A and pair B are almost the same,[8] we interpret the different signal intensities as being derived from a larger concentration of radical pair A, resulting from a preferred cleavage at the methoxybenzyl–carbonyl bond. A similar interpretation has been put forward by Hutton

(1) Publication No. 000 from the Photochemistry Unit, London, Ontario.
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(6) CIDNP experiments were performed on a Varian XL-100A NMR spectrometer with a Photochemical Research Associates light source (a 200-W Hg–Xe lamp with an ellipsoidal mirror).
(7) Kaptein, R. *J. Chem. Soc., Chem. Commun.* **1971**, 732.
(8) The diffusion behavior, the recombination probability, and Δg of pair A and pair B may be considered to be identical. There is a slight variation in hyperfine coupling constants of methylene protons of benzyl radicals (*p*-MeO, −15.93 G; *p*-Me, −16.07 G; *p*-F, −16.43 G; h, −16.34 G; *p*-Cl, −16.08 G. Neta, P.; Schuler, R. H. *J. Phys. Chem.* **1973**, *77*, 1368). The β protons of the phenylacetyl radicals ($a_H \sim 1$ G; $\Delta g < 0$) can induce a CIDNP effect of the same direction, but this is smaller than that induced by benzylic methylene protons. It is interesting to note that the hyperfine interaction of nuclei other than the methylene protons, particularly those of the ortho and para hydrogens of the benzyl radicals, the paramethyl hydrogens, and the para-fluorine atom, is expected to have a minor influence on the amplitude of the methylene polarization. This is because the present CIDNP effect is basically a Δg effect and because the effect of the hyperfine interactions of other nuclei are averaged to null as far as the polarization of the methylene protons is concerned.

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